THE RELATIONSHIP BETWEEN PREMENSTRUAL SYMPTOMS AND THE OVARIAN CYCLE

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CONTENTS

DECLARATION

Except where acknowledgment is made by reference , the studies described in this thesis were the unaided work of the author , with the assistance of Dr. John Bancroft in their design and inspiration . The creatinine assays were performed by the staff of the NHS Reproductive Endocrinology Laboratories in Edinburgh .

No part of this work has been previously submitted for any other degree , nor is any part of it being concurrently submitted for another degree.

Anne Walker
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ABSTRACT

The majority of women of reproductive age experience physical and / or emotional changes during the week to ten days before menstruation . In a proportion - probably 3 - 5 % - these changes are severe , and constitute the Premenstrual Syndrome (PMS) . The occurrence of these changes in the premenstrual phase has caused many theorists to postulate an aetiological link with the female reproductive cycle . The purpose of this research is to investigate the relationship between premenstrual symptoms and the ovarian hormones .

A review of the literature suggests that previous research has been inconclusive for largely methodological reasons . These studies have focussed on PMS and normal cycles , attempting to delineate endocrinological differences between women with and without the syndrome. Inconsistencies have arisen in the definition and diagnosis of PMS and the frequency and type of assessment of ovarian activity . The occurrence of symptoms in anovulatory or otherwise abnormal menstrual cycles has received little attention . In this research , it was hypothesized that a link between premenstrual changes and ovarian hormones would be demonstrated by a change in symptomatology if the menstrual cycle were naturally or artificially abnormal . Hence , the focus in these studies is on premenstrual symptoms and their degree of change between cycles rather than on the diagnosis of PMS .

Two studies were designed to investigate the hypothesis . The first involved the observation of naturally occuring abnormal menstrual cycles , comparing them symptomatically with normal cycles in the same individual . The second approach involved the comparison of women whose menstrual cycles had been artificially manipulated by the long term use of low-dose oral contraceptive (oc) pills , with matched women experiencing natural cycles . In both of these studies, symptoms were assessed by daily subjective ratings of eight physical and emotional variables using visual analogue scales . In the first study , ovarian activity was assessed by the analysis of daily , early morning urine samples for the major ovarian hormone metabolites - oestrone-3-glucuronide and pregnane- diol-3α-glucuronide . In the second study , various components of the ovarian cycle were assessed by the comparison of combined oc's having a constant dose regime with oc's designed to mimic the normal cycle . In both studies daily

ratings were continued for at least two complete cycles , and frequently longer. The data were analysed in several ways , taking cognisance of the inadequacy of conventional inferential statistical methods in this area .

Clear evidence emerged from these studies to show that neither ovulation nor adequate luteal function are necessary for premenstrual symptom occurrence . A relationship did emerge between the symptom of breast tenderness and luteal hormones in approximately half of the women studied . Absolute hormone levels did not seem to be involved in this effect , suggesting a potential role for some other endocrine or biochemical factor associated with luteal function .

The conclusions drawn from the study were that several different aetiological mechanisms may be involved in the manifestation of premenstrual symptoms . The relationship between symptoms and the ovarian cycle would appear to be purely temporal in the majority of cases . However , some symptoms , i.e. breast tenderness , may be more closely related to luteal function in some women .

INTRODUCTION

INTRODUCTION

The picture normally painted of the Premenstrual Syndrome (PMS) is of a combination of symptoms ranging from irritability , tension and depression to breast tenderness , body swelling and migraine headaches which occur regularly before menstruation and cause untold havoc to marriages , family life and society in general . Although many studies have attempted to describe and define exactly which symptoms constitute the Syndrome , when they occur and how common they are , little success has been achieved . The reasons for this are largely vested in the degree of variability of symptom experience between women , and potentially between menstrual cycles . This has led to the postulation of a number of different definitions of PMS and hence a variety of estimates of its prevalence . A general consensus would appear to be that the majority of women experience some changes in well-being premenstrually , which achieve a level of severity meritting clinical attention in about 2 - 4 % .

The causes of both " normal " premenstrual symptoms and the "abnormal" Premenstrual Syndrome remain obscure . Many different mechanisms have been postulated with greater or lesser validity . The common theme of all of these theories however , and the most widely held belief about PMS , is the relationship between the occurrence of symptoms and the events of the female reproductive cycle . Symptoms have been observed to occur regularly in the second half of the menstrual cycle , the luteal phase , and to be absent from the first half , the follicular phase . This has led to the widely hald assumption that the presence , timing and severity of symptoms is related in some way to an endocrine factor present in the luteal phase but absent from the follicular phase . The most obvious candidate for this being the hormone progesterone , which is only present in the luteal phase of normal ovulatory cycles . Further to this belief is the assumption that symptoms cannot occur in the absence of progesterone, i.e. in the follicular phase or in anovulatory cycles . This assumption is so widely held that some studies cite premenstrual symptoms as evidence of ovulatory cycles (e.g. Magyar, Boyers, Marshall & Abraham 1979) .

Scientific evidence relating premenstrual symptoms to specific events of the hormonal cycle , and particularly to the presence or absence of progesterone, is limited however , partly by incompatabilities between studies in the definition of PMS used and partly by technical inadequacies in the measurement of hormone levels . Accurate studies of this kind are

however crucial to the further understanding of the nature and aetiology of premenstrual symptoms and how the Premenstrual Syndrome should best be approached clinically . Such a study is the subject of this thesis . The assessment of any relationship is however restricted by the level of knowledge of its constituent parts . Hence , in the first part of this thesis , consideration will be given to the nature of both premenstrual symptoms and the ovarian cycle seperately before previous studies of the relationship between them are discussed . The design , analysis , discussion and implications of the studies which constitute this research will then follow .

CHAPTER ONE
PREMENSTRUAL SYMPTOMS AND THE PREMENSTRUAL SYNDROME

1.1 DESCRIPTION OF THE PREMENSTRUAL SYNDROME

" I can only describe my feelings before a period as ' bottled up '.I get more and more uptight and irritable as the week goes on . The minute my period starts it feels as if a cork is released and all the tension floods away "

" I feel very lethargic and disinterested in things around me . I want to be alone , not talk to anyone either on the 'phone or face-to-face . I can't bear being touched . Physical contact (even by my children) annoys me intensely"

" The symptom I feel and fear the most is the violent one . I don't actually do anything violent - but I feel so pent-up like a dam ready to explode . "

" The most severe symptom is general fluid retention . Apart from grossly swollen stomach and very painful breasts , I often experience pain and numbness in my hands and arms . "

" The thing I find most difficult to cope with is the feeling of hopelessness . In the ten days prior to my period I feel as if there is no point in living . I hate my job,I hate my boyfriend , I hate where I live and I hate myself . Then when my period arrives I feel great - it's as if a huge weight has been taken off my shoulders ."

" For about ten days prior to a period I become a compulsive eater - I never feel full ! Also I get a raging thirst . "

" I get so angry and worked up with my husband and children for no reason. Stupid things start me off like leaving the top off the shampoo . I know I am doing these things but I cannot stop myself . I then feel guilty at doing this to my family , I make their life hell . They do try and understand most of the time but sometimes it gets too much for them . "

" Apart from generally feeling bad about myself /tension/depression in the few days before my period starts (and this will happen even if my period is unexpectedly early) and a bad headache just before it begins , the most pronounced pre-menstrual feeling I have is a strong desire to tidy up/pay bills / file /tie up loose ends . "

" PMS .....its like wanting to crawl into a corner away from everything but at the same time not knowing what you want to go into the corner for . "

" I undergo a complete personality change . From a capable , efficient , able secretary and housewife I become withdrawn , ultra-clumsy and accident prone . I normally have a lively , bubbly personality but premenstrually I lack confidence , feel old and fat and prefer to be alone . I get everything out of perspective and have at times become paranoid and obsessional . "

" It astonishes me how much better I feel once my period has arrived . The physical symptoms may be worse perhaps with backache and fatigue

particularly for the first three days , but at least the irrational anger and distorted and depressed view of reality evaporates . "

These extracts are all taken from letters submitted to a national women's magazine " Woman " in August 1985 . The women wrote in response to a questionnaire survey on menstrual health which attracted 7,500 replies . The results of the questionnaire are reported elsewhere (Bancroft & Warner: unpublished). They are all describing symptoms which they experience in the week or ten days before a menstrual period and provide a fairly typical picture of what has recently become known as the "Premenstrual Syndrome " (PMS) . The symptoms of the syndrome are many and various ranging from depression and irritability to painful breasts and skin disorders. Moos (1969) identified over 150 different symptoms from a review of the literature , although this was reduced to 47 by eliminating redundancy (see Table 1.1) .

The first user of the term " Premenstrual Tension " was R.T.Frank (1929, 1931) . He described the condition as :-

" . . . . . a feeling of indescribable tension from ten to seven days preceding menstruation . . . . . These patients complain of unrest , irritability , " like jumping out of their skin " , and a desire to find relief by foolish and ill-considered actions . . . . . Within an hour or two after the onset of the menstrual flow complete relief from both physical and mental tension occurs ."

(Frank1931)

The discussion following the paper makes it clear however that Frank's observations were by no means unique . Dr. Josephine Kenyon , for instance says :-

" . . . . . any suggestion of other ways to combat the depression and emotional tension *so commonly seen* will be of value . "

(Kenyon 1931- my italics)

In fact disturbances of one sort or another associated with menstruation have been recognised throughout history and usually considered to be normal and worthy of little comment (Norris 1987) . For instance Hamilton (1813) in his description of menstruation states that:-

" It continues for a certain number of days , different in different individuals, and its approach is generally preceded by certain feelings of oppression or deviation from the ordinary state of health , which warn the individual of what is to happen . There is in particular , a sensation of fulness about the lower part of the belly and of relaxation about the uterine system . . . . . "

(Hamilton 1813 p.25)

TABLE 1.1

SYMPTOM SCALES MADE UP FROM MENSTRUAL , PREMENSTRUAL , INTERMENSTRUAL AND WORST SYMPTOM FACTOR ANALYSIS

(From : Moos 1969)

1. PAIN
Muscle stiffness
Headache
Cramps
Backache
Fatigue
General aches and pains

2. CONCENTRATION
Insomnia
Forgetfulness
Confusion
Lowered judgement
Difficulty concentrating
Distractible
Accidents
Affectionate

3. BEHAVIOURAL CHANGE
Lowered school or work performance
Take naps ; stay in bed
Stay at home
Avoid social activities
Decreased efficiency

4. AUTONOMIC REACTIONS
Dizziness , faintness
Cold sweats
Nausea , vomiting
Hot flushes
Blind spots , fuzzy vision

5.WATER RETENTION
Weight gain
Skin disorders
Painful breasts
Swelling

6.NEGATIVE AFFECT
Crying
Loneliness
Anxiety
Restlessness
Irritability
Mood swings
Depression
Tension

7. AROUSAL
Orderliness
Excitement
Feelings of well-being
Bursts of energy/ activity

8. CONTROL
Feeling of suffocation
Chest pains
Ringing in the ears
Heart pounding
Numbness tingling

9 . CHANGE IN EATING HABIT

In a section discussing " hysterical complaints " he describes symptoms including :-

" violent sudden fits of crying and laughing . . . . . often followed by stupor and faintings . . . . . in many cases a violent pain in the head " which occur " most frequently about the time of the periodical evacuation "

(Hamilton 1813 p. 47)

Even the Greeks and Romans had observed the phenomenon Hippocrates wrote that :-

". . . . . the blood of females is subject to intermittent 'agitations ' and as a result the ' agitated blood ' finds its way from the head to the uterus whence it is expelled "

(Chadwick & Mann 1950 p. 267)

Soranus of Ephesus (quoted by Symonds 1981) stated that :-

" . . . . . the menses are about to occur when a woman feels somewhat uneasy on walking , when a feeling of heaviness appears in the loins . Some develop a torpor , yawning and pondiculation while others develop nausea and a loss of appetite "

(Symonds 1981)

So there is nothing new about the phenomenon of menstrually related changes in mood and behaviour . However for several reasons the premenstrual syndrome has received much attention and even notoriety in recent years .

Firstly menstruation has " come out of the closet " as it were . Women and men are now able to discuss such issues openly - at least in scientific circles. Secondly - the female reproductive lifespan in the Western World is now longer than ever before (i.e. from puberty to menopause) and interrupted by fewer pregnancies . Hence many more episodes of menstruation are experienced allowing correlations to be drawn . Thirdly - since the Second World War , women, and particularly middle class women, have been involved in paid work outside the home much more than in previous generations . This third reason , together with the general controversy about the role of women in society raised by the Women's Movement and their opponents - has led to concern about possible increases in absenteeism rates or reduced work efficiency in relation to female biology i.e. the menstrual cycle . This concern has shown itself by a flurry of research and media activity into the effects of the menstrual cycle on various aspects of women's health and social functioning . In this thesis however the major concern is the " Premenstrual Syndrome " , rather than dysmenorrhea or other menstruation- related phenomena , hence a

consideration of the social impact of PMS is appropriate in order to establish reasons for studying the phenomenon and the difficulties inherent in such research .

1.2 THE IMPORTANCE OF RESEARCH INTO PMS

The description of PMS given above has several potentially critical implications . If it is in fact the case that some proportion of women in Western Society suffer debilitating symptoms in a regular cyclical manner , and that these changes are outwith their control , then the effects in the home , workplace , courtroom and political arena could be far-reaching .

1.2.1 THE CRIMINAL LAW AND PMS

The research and discussion in this area can be divided into two sections, attempting to answer two seperate but interdependent questions . Firstly - do more crimes committed by women occur during the premenstrual phase of the cycle ? Secondly - can a medical diagnosis of PMS be used as a legal defence to , or mitigation of , a crime which was committed in the premenstruum ?

a) Do more crimes occur in the premenstruum ?

Evidence for a link between the premenstrual phase of the cycle and crime comes in the most part from the work of Katharina Dalton . (eg Dalton 1961 , 1980) . She showed that of 156 regularly menstruating women admitted to a London prison , having committed their crimes within the last 28 days , 49% were in the "paramenstruum" at the time of the crime. (The paramenstruum is defined as the four days immediately preceding and the first four days of the menstrual flow .) (Dalton 1961). However , not all of these women were PMS sufferers . By her own definition only 27% of the total (43 women) suffered from PMS of " incapacitating severity ", of whom 63% (27 women) offended during the paramenstruum . At first sight this would appear to be fairly impressive evidence that there is a link between the paramenstruum and the commission of crimes - however , three points must be made about the research . Firstly - no account is taken of the possible effects that the stressful events surrounding the commission of the crime and subsequent capture may have had upon the onset of menstruation (Parlee 1973 ; Sommer 1978). Secondly - no differentiation was made in this study

between impulsive and/or violent crimes , which might be expected to result from the symptoms of PMS , and premeditated or organised crimes . The women in Dalton's study had been involved in offences as diverse as shoplifting , embezzlement and prostitution . No data are given , either , about whether the women were " first - offenders " or habitual criminals. Thirdly - the comparisons used by Dalton to test the significance of her results can be argued to be inappropriate . Sherif (1980) , for instance , argues that the correct methodology to assess the relationship between crime and the pre- or paramenstruum would be to compare the proportion of paramenstrual women committing crimes for all women committing crimes with the number of paramenstrual women not committing crimes for all women not committing crimes in the same time interval i.e.

$$\frac{\text{Number of PM offenders}}{\text{Number of offenders}} \quad \text{vs} \quad \frac{\text{Number of PM non-offenders}}{\text{Number of non-offenders}}$$

Research in the United States by Morton et al (1953) provides support for this evidence with their findings that of 42 women sentenced for crimes of violence , 62 % had committed the offence during the premenstrual week . However this study is also methodologically flawed (Parlee 1973 ; d'Orban 1983) . A study by Epps (1962) of 200 shoplifters in the same prison did not uphold the relationship between crime and PMS since only 27 (13.5 %) of her sample suffered from PMS and they did not tend to commit their crimes more frequently when premenstrual than at any other time . D'Orban & Dalton (1980) in a more detailed study of 50 consecutive admissions to a female remand prison showed that 22 of the offences (44 %) occurred in the paramenstruum . In this sample 17 women (34 %) suffered from PMS but they did not show any significant tendency to offend in the paramenstruum . In fact of the 22 women who offended premenstrually - only 5 (23 %) had premenstrual symptoms . This is particularly interesting since all the crimes in this study were violent ones against either property or people .

Hence it would appear that the data in this area is inconclusive about the relationships between crime , PMS and the premenstruum . It would seem that more violent crimes tend to be committed in the premenstrual phase (d'Orban 1983) - however there is no established link between a past or present diagnosis of PMS and a premenstrual crime . This adds weight perhaps to the hypothesis that the stressful events leading up to the crime

together with subsequent imprisonment etc. may have caused a premature onset of menses . Perhaps the assumptions should be changed from menstruation causing the crime to crime causing the menstruation.

b) Can PMS be used as a legal defence ?

The use of PMS as a legal defence has been a highly controversial area . To date three British trials have accepted PMS as mitigation of sentence . Two of the cases involved a murder charge , whilst the third was attempted murder , and all three resulted in non-custodial sentences (Regina v Craddock 1981 , Regina v English 1981 ,Regina v Smith 1982 reviewed by Boorse 1987) . In each case the offence was committed in the paramenstruum and evidence given showed that the women were PMS sufferers . The basis of the defence or mitigation was that their legal responsibility was diminished by the Premenstrual Syndrome . However the use of this type of defence is hotly debated and still has not gained credence in the United States for instance . In law , the use of PMS as a defence depends upon whether the sufferer is considered to be responsible for her actions when premenstrual . Responsibility for actions can be broken down into two major components - " causation responsibility " and " liability responsibility " (Houlgate 1987) . The difference between the two being the absence or presence of the intention to cause the event . It is the intention to commit the crime which is the crucial part of the defence . The insanity and automatism defences are based on two implied conditions of " liability responsibility " - namely i) *mens rea* - literally " evil mind " but usually interpreted to mean the absence of the necessary mental element to cause or intend to cause the particular event to happen by virtue of mental disease or handicap etc. This is the basis of the " insanity defence " ; and ii) *Actus rea* - literally " evil action " - this means performing an action under the influence of some external agent , for instance , under compulsion from another person , during an epileptic attack , whilst sleepwalking etc. This is the basis of the "automatism defence " and does not imply any long-term mental instability .

There are arguments for the use of PMS as a complete defence on both of the above grounds - as a mental disease or as a physical illness causing temporary automatism . However much of this depends upon the definition of PMS , its incidence in the general population (it would be meaningless if 90 % of the female population were considered to suffer from PMS) and the

relationship between PMS and the commission of crimes - evidence for which is weak at present (see section 1.2.1(a)) . Boorse (1987) argues that knowledge of this latter criterion is essential before PMS can even be considered in a legal respect. He says :-

" . . . such correlations may show a weak causal influence i.e. that premenstrual changes contribute to antisocial behaviour in some women . But mere contributory causation cannot be sufficient for legal compulsion or loss of control . Many mental , physical and environmental factors favour criminal behaviour . Similar or stronger correlations exist between crime and weather , time of day , level of fatigue , hunger or satiety , sexual tension etc."

(Boorse 1987 p.101)

He then goes on to suggest several potential syndromes which might account for the above conditions e.g. " MDS - Meteorologic Decompensation Syndrome " to account for murder on a hot day !

However it is possible that PMS is valid as a partial defence or mitigation resulting in a reduction of the charge from murder to manslaughter for instance . The " *mens rea* " defence also allows for mental abnormality as well as insanity resulting in a plea of " diminished responsibility " or diminished capacity for responsibility for actions rather than loss of capacity for responsibility (Boorse 1987).

Evidently the whole area of PMS , crime and legal responsibility is controversial . On the one hand there are those who argue that a woman with PMS is not responsible for her actions and should be absolved of any guilt (e.g. Dalton 1977) whilst on the other hand there are those who suggest that PMS may become a " bandwagon " defence allowing women to do anything they like and blame it on PMS (e.g. Holtzman 1984 in Boorse 1987) .

Further and more detailed information is needed on the definition , diagnosis and incidence of PMS as well as the precise relationship between crime , PMS and the menstrual cycle before its status as a legal defence can be debated and decided .

1.2.2 PMS AND THE WORKPLACE

Many reviews of the PMS literature begin by justifying research on the basis of the potential costs of PMS in terms of work disruption , absenteeism etc. (e.g. Reid & Yen 1981) . Symptoms of PMS such as loss of concentration , impaired motor coordination , irritability etc. might be

expected to cause decreased work efficiency whilst symptoms such as depression , tension or physical changes might be expected to lead to an increased absenteeism rate. Parker (1960) reports that :-

" . . . . . in large factories employing 1500 or more women , as many as one-third have been found to take sedatives , analgesics or both premenstrually"

(Parker 1960)

However he gives no information about the effects of this on the quality of the womens' work - whether they made up for any losses at other times of the cycle for instance - or how many of them were dysmenorrheic . Dalton (1966) showed a greater than expected absenteeism rate in days 1-4 of the menstrual cycle - however this may be due to physical period pain rather than emotional symptoms since the incidence in the days immediately preceding menses is no more than expected . Texas Industries , who rely on accuracy in the assembly of electrical components showed a reduction from the normal production rate of 100 components per hour to 75 components per hour during the paramenstruum of their female employees (Dalton 1977). Whether or not these women were PMS sufferers is unknown . Smith (1950) studied absenteeism in three different factories - aircraft , parachute and garment manufacturers. He found increased absenteeism premenstrually in the aircraft and parachute - making industries , but lower than expected absenteeism during menstruation . However in the garment factory the position was reversed (i.e. low premenstrual absenteeism and high menstrual absenteeism) . The suggested reason for this is socio-economic differences between the factory employees . The most likely explanation however would be an age difference between the employees - if the garment workers were younger they might be expected to display a higher incidence of dysmenorrhea resulting in more menstrual absences . No diagnosis of PMS was used in this study hence no conclusions can be drawn from it about the effects of PMS *per se* on absenteeism . A recent study of absenteeism rates in Swedish insurance statistics (Hallman & Georgiev 1987) suggested that women with severe PMS are more inclined to be absent from work and were likely to be diagnosed in the " mental disorders " category during these absences than were women with no or mild premenstrual symptoms . It was not apparent from this study whether such women were absent regularly in the premenstrual phase , or were prone to lengthy absences due to depression for instance . Since the diagnosis of severe PMS was made on the basis of a large retrospective

menstrual health survey , the possibility exists that the women selected were those most likely to complain , or have an external locus of control , rather than that women with severe PMS are more prone to mental disorders or absenteeism .

Studies which have attempted to show specific objective cognitive deficits in the premenstrual phase of the cycle have generally been inconclusive (see Sommer 1973) . In 81 performance tests , carried out by 35 independent research groups , and reviewed by Sommer (1982) only 14 showed any evidence of menstrual or premenstrual changes . However , there may be reasons which account for this lack of findings . For instance , Redgrove (1971) argues that on simple reaction time tasks women may be working harder in the premenstrual phase to compensate for the lack of concentration they feel , thereby reducing any performance deficit . She suggests that cyclical decrements in performance will only be seen when subjects are working at their limits . This over compensation effect would explain the lack of evidence of cyclical change on simple reaction time tasks (e.g. Loucks & Thompson 1968 ; Kopell et.al 1969; Zimmerman & Parlee 1973 ; Little & Zahn 1974 etc.) as compared to studies which involve batteries of tests or more demanding test combinations (e.g. Wuttke et.al 1973 ; Gamberale et.al 1975; Jensen 1982 etc.)

Although a number of studies have looked at changes in various performance measures across the menstrual cycle - few have attempted to objectively assess the reported performance changes in PMS sufferers . Jensen (1982) studied two groups of women - a " distress " group who had high to severe levels of PMS (on the Moos Menstrual Distress Questionnaire) and dysmenorrhea , and an asymptomatic group . The study showed significant premenstrual performance deficits on a pursuit-tracking task . These deficits were independent of distress group . On the other hand performance on a choice reaction time task seemed to be influenced by both cycle phase and distress group as well as variables such as task load , time on task , signal frequency etc. So it would appear that there may be a difference between PMS sufferers and controls on some tasks but not others. Since " distress " was based on retrospective reports and was a global diagnosis , not discriminating between premenstrual depressives for instance and women who suffer physical symptoms, no conclusions can be drawn about the potential effects of specific PMS symptoms on performance. Possibly if subtypes of PMS were defined more explicable results would be

obtained . A recent study has found that women with PMS show lower performance on the Crawford Small Parts Dexterity Test - Part II, a measure of fine motor coordination, in the luteal phase compared to the follicular phase . This contrasted with asymptomatic controls who performed better in the luteal phase . No differences were found between the groups on any of the other functional tests assessed . (Posthuma,Bass,Bull & Nisker 1987).

It would appear therefore that menstrual cycle variables may be involved in absenteeism rates and loss of performance on certain specific tasks . However , the relative contributions of PMS and dysmenorrhea to these rates is not known . Some evidence suggests that there may be an increase in cortical arousal premenstrually (Asso 1978) causing better performance on boring , repetitive tasks but poorer performance on tasks involving high levels of concentration .

In a review of the effects of menstruation on work Harlow (1986) points out that the quoted figures of absenteeism due to menstruation in the United States for 1979 represent only 3 hours per woman per year , in fact the greatest cause of lost work time is influenza . In this field too , further research on the exact nature of PMS and its effects , beneficial or otherwise on task performance and the workplace needs to be done before sweeping statements about its potential effects can be made .

1.2.3 PMS AND THE FAMILY

The reported symptoms of PMS (see Section 1.1) would suggest that implications for marital harmony and family life might be severe . Lever , Brush and Haynes (1979) describe a vicious circle of wifely moodiness and husbandly misunderstanding , supported by anecdotal evidence but no data. They also state that :-

" . . . . . nobody knows how many divorces or seperations PMT has occasioned because no research has been done to find out . "

(Lever , Brush & Haynes 1979 p.85)

Some research has been done however on the relationship between maternal menstrual cycle phase and child battering or child ill-health . Dalton (1966) showed in a survey of 100 mothers attending her surgery with children suffering minor ailments , 54 % were in the paramenstruum . In a similar study of mothers whose children had been admitted to hospital as

emergencies , 49% were in the paramenstruum at the time of admission (Dalton 1970) . There may be several reasons for this - an inability of the mother to cope with her child being even slightly ill when she is premenstrual (Lever et al 1979) , an increase in maternal accident-proneness resulting in injuries to the child (Dalton 1977) and an increase in " baby-battering " as a result of premenstrual irritability (Dalton 1975) . An alternative view is that menstruation was precipitated by worry over the child's health (Parlee 1973) . No evidence is given of the type of malady the children were suffering - although accidental or non-accidental injury may logically be attributable to the pre or paramenstruum, illnesses in the child e.g. appendicitis etc. would be more difficult to ascribe to the effects of the maternal menstrual cycle . No evidence is given of whether the mothers in these studies were PMS sufferers.

To date there is little evidence of the often cited drastic effects of PMS on family life and personal relationships (e.g. Sharma1982 ; Chakmakjian 1983; Shreeve 1983 ; Brush 1984 etc.) . Although these effects may be difficult to document and demonstrate their presence or absence is very important . Dalton (1975) for instance suggests that up to 50 % of mothers who batter their babies could suffer from PMS , a fact the truth of which could obviously influence legal decisions on mothers accused of injuring their children .

Rome (1986) has discussed this aspect of PMS in detail , considering its implications for the role of women . She argues that PMS symptoms cause conflict about the traditional wife and mother role and that the work of Dalton and others like her , whilst reflecting the social atmosphere at the time , serves only as an attempt to reinforce the stereotyped roles of women . She argues :-

" It becomes painfully clear that Dalton's goal is to help women function more smoothly in their traditional stereotypical role , subordinate to men . She wants to help women do what they " ought " : function as housewives and mothers in an uncomplaining , cheerful way . "

Rome (1986)

Rome argues that justifying PMS treatment on the basis of its potential effects on family life is making assumptions about the social status of women which are no longer relevant .

However , as with other aspects of PMS , the lack of an agreed definition and delineation of the syndrome hampers research - it may be that only a subtype of PMS leads to a greater vulnerability to baby battering or marital

disharmony . Basic research is needed before sweeping statements can be made about PMS in this respect .

1.2.4 PMS AND PSYCHIATRIC DISORDERS

a) Suicide and the menstrual cycle

The type of symptomatology associated with PMS e.g. depression , violent feelings etc. might be expected to lead to a higher rate of suicides and suicide attempts during the paramenstruum in women who suffer from it. The literature in this field is difficult to interpret however due to the inherent experimental design limitations of both PMS research and suicide research (see Clare 1982). Studies of completed suicides provide little data about the menstrual history of the women concerned although the precise cycle phase at the time of death can be determined (e.g. Mackinnon et al 1959) . These studies also usually require the consent of the next of kin introducing some bias in subject selection on religious , economic or social grounds (Wetzel & McClure 1972) . Studies of attempted suicides (e.g. Wetzel , Reich & McClure 1971) may involve a different group of people from those actually committing suicide - the 'cry for help ' phenomenon - and those who contact a suicide prevention service may not be representative of suicide attempters as a whole . Problems of definition of cycle phase and PMS are also involved here . Overall, in both the case of completed and attempted suicides several studies have shown an increased risk in the paramenstruum (e.g. Mackinnon et al 1959 ; Ribeiro 1962; Tonks et al 1968; Wetzel et al 1971) . However , these studies are all methodologically flawed and give little information about whether their subjects suffered from PMS . Birtchnell & Floyd (1974) in a study of 76 consecutive attempted suicides found no significant differences between the observed and expected numbers of paramenstrual women when the expected frequency was calculated with an allowance for cycle irregularity . They also point out that suicidal behaviour may be associated with a woman knowing or fearing that she is pregnant . Thirteen young unmarried women in their sample were either pregnant or beyond the expected date of their next menstrual period at the time of the suicide attempt supporting the proposition that premenstrual suicides may occur because of a late period and fear of pregnancy (i.e. social reasons) rather than physiological PMS reasons . In a later study (Birtchnell & Floyd 1975) the incidence of attempted suicide in

the group admitting to "premenstrual emotional disturbance " was not significantly different from those who did not . However a high proportion of these women were beyond the expected date of menstruation suggesting further support for a fear of pregnancy motivation .

Hence there is very little sound evidence to link PMS or the paramenstruum *per se* with suicide or attempted suicide . This does not of course rule out suicides committed by PMS sufferers at other times of the cycle as a result of guilt about their repeated premenstrual behaviour - however no data is available in this area .

b) PMS and affective disorders

The nature of PMS symptoms has led researchers to hypothesize that PMS sufferers are more vulnerable to mental ill-health in general (e.g. Clare 1983) or that PMS might be an appropriate model for other psychiatric disorders. To date several studies have been undertaken assessing either the rate of occurence of affective disorders in women diagnosed as PMS sufferers (e.g. Wetzel , Reich , McClure & Wald 1975 ; Schukit , Daly , Herrman & Hineman 1975 ; Mackenzie,Wilcox & Baron 1986; Hart, Coleman & Russell 1987) or the rate of occurence of PMS in women suffering affective and/or personality disorders (e.g. Coppen 1965 ; Diamond , Rubinstein Dunner & Fieve 1975 ; Hurt, Friedman , Clarkin , Corn & Arnoff 1982 ; Halbriech & Endicott 1985) . In some of these cases the whole syndrome of PMS was discussed , involving physical symptoms as well as psychological , whereas in others only a " premenstrual affective syndrome " (PAS) is considered based on diagnostic criteria outlined by Kashiwagi et al (1976) (see Table 1.2) . However , whatever the diagnostic criteria of PMS or PAS there generally appears to be a trend linking premenstrual depression with a lifetime diagnosis of a major depressive disorder . For instance in a study of 558 freshmen and sophomores (Wetzel et al 1975) who were assessed for PMS on the basis of the Kashiwagi et al criteria at the start of their college careers , 20 % of those diagnosed having PMS visited a psychiatric clinic during their four year course compared to only 14 % of those diagnosed as not having PMS . When these figures were further broken down - 75 % of the clinic attenders without a PMS diagnosis were given an affective disorder diagnosis compared with 89 % of the PMS suffering clinic attenders . Wetzel et al then conclude that a diagnosis of premenstrual affective disorder can predict the subsequent seeking of

TABLE 1.2

CRITERIA FOR PREMENSTRUAL AFFECTIVE SYNDROME (PAS)

(From : Kashiwagi , McClure & Wetzel 1976)

1. At least one of the following behavioural symptoms :-
   - a) Sad , blue or depressed
   - b) Tense or nervous
   - c) Cry easily
   - d) Decreased energy
   - e) Increased mood or energy

2 . At least one of the following somatic symptoms :-
   - a) Swelling of legs
   - b) Swelling of abdomen
   - c) Tenderness of breasts
   - d) Weight gain

3. Subjective rating of symptoms as moderate or severe

4 . Objective recognition of symptoms as moderate or severe

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psychiatric care for affective disorders (It should be borne in mind here that 80 % of their PMS positive women made no visits to the psychiatric clinic so that their conclusions seem somewhat overstated . It would be fairer to say that a previous diagnosis of PAS might be considered a contributory factor in an affective disorder diagnosis during their college careers in young women). Similarly a high prevalence of PMS or PAS is often found in women with a current or lifetime diagnosis involving a major depressive disorder (MDD). Halbriech & Endicott (1985) showed that 57 % of their sample of 110 women with a lifetime MDD diagnosis met the criteria for premenstrual depression set out in the PAF (Premenstrual Assessment Form) . This compared to a rate of 14 % in a group of 37 women who were "never mentally ill " .

Overall it would appear that about 50 - 65 % of women with affective disorders experience premenstrual depression or premenstrual exacerbation of a current depressive episode . The proviso should be added

that the majority of studies involving psychiatric patients or ex-patients are retrospective and make no comment on whether this group of people are more or less likely to complain in response to such instruments than are the general population . It would also seem that women who suffer regular premenstrual depression are more likely to have had or to develop an affective disorder than their asymptomatic sisters . Hence some researchers have argued that PMS - and particularly premenstrual depression - could be useful as a model to study the various concomitants of clinical depression (Rubinow & Roy-Byrne 1984 ; Halbriech & Endicott 1985) - or possibly could be related to manic-depressive illness (Coppen 1965; Kashiwagi et al 1976). This latter phenomenon has recently been suggested to have a genetic basis in some populations (Egeland et al 1987) but as Stone (1982.) points out - isogenic conditions need not always be isophenic, the possibility being that PMS and recurrent affective disorders are different phenotypic expressions of a common genetic source . If this were the case then treatments shown to be effective in manic-depressive illness might be expected to be therapeutic in PMS . Sletton & Gershon (1966) report positive results in 8 cases of PMS who were given lithium carbonate , an effective treatment in manic depression. However no quantitative data were given to substantiate this report . Subsequent studies (Mattson & von Schoultz 1974 ; Singer , Cheng & Schou 1974 ; Steiner , Haskett , Osmun & Carroll 1980) have failed to demonstrate any consistently beneficial effect of lithium carbonate as compared to placebo in PMS. This does not rule out the possibility that different phenotypic expressions of the same genetic disorder may not respond to the same treatment , however some doubt must be cast upon the relationship between PMS and cyclical affective disorders .

This still leaves the possibility of an aetiological link between dysphoric PMS and endogeneous depression on the basis of the literature reviewed above (for a full exposition of this point of view see Halbriech & Endicott 1987). Steiner & Haskett (1987) argue that PMS is not a model for endogeneous depression (ED) since the typical dysfunction of the hypothalamo-pituitary-adrenocortical axis seen in patients with ED cannot be demonstrated in patients with PMS . It is known that some depressed patients secrete ACTH (Adrenocorticotrophic hormone) , and hence cortisol in a different way to the normal population , and that this secretion of cortisol is not abolished by normal negative feedback mechanisms . This can be demonstrated by giving dexamethazone as a challenge . Approximately

50% of hospitalized depressed patients will suppress their cortisol levels in response to dexamethazone whereas virtually all non-depressed people will (Green & Costain 1981 p.56) . Steiner & Haskett measured 24 hour urinary free cortisol levels in 38 women with PMS , before and after giving the dexamethazone suppression test (DST) , in the follicular and the late luteal phases of their menstrual cycles . None of the women showed evidence of hypersecretion of cortisol before DST on either occasion and none of the women showed an abnormal response to DST on both occasions . Four women gave abnormal DST results in the follicular phase and 3 in the luteal phase but there was no trend towards abnormal results in either phase . Despite the absence of control groups of depressed patients with or without PMS and non-depressed women without PMS, they argue that PMS does not appear to be a model for ED and that hypothalamo-pituitary- adrenocortical activity is not a neuroendocrine marker for PMS . However there were clearly individual differences here - and since only 50% of patients with ED show abnormal DST results , some caution should be used in the interpretation of this study .

So it would seem that the relationship between PMS and affective disorders and the possible importance of PMS as a model for the study of clinical depression is more controversial than first thought . As in most areas of PMS research , lack of concordance between studies about the definition of PMS and the selection of subjects makes the data easy to criticize and difficult to interpret.

1.2.5 SUMMARY OF SECTION 1.2

The existence of a cyclical pattern of mood and behaviour in women associated with the menstrual cycle has been established by folklore and case history reports . Studies of the effects of the menstrual cycle and subsequently PMS on various aspects of women's social functioning have produced what at first sight appear to be dramatic associations between the premenstrual and menstrual cycle phases and antisocial behaviour with the resultant implication that if women could only be treated so as to behave as if they were always in the follicular phase then all would be right with the world . Media " panic " about the influence of hormones on women's behaviour and the attendant implications for women's role in society has led

to a flurry of research activity in the field .

Closer inspection of the studies in all the fields reviewed above reveals major methodological flaws in experimental design and lack of consensus between research studies about exactly what is meant by the term PMS . Further research is needed in order to discover precisely what proportion of the female population suffer premenstrual symptoms and just what it is that they are experiencing before conclusions about the causes and effects can be drawn .

1.3 PREVALENCE OF PREMENSTRUAL SYNDROME

Attempts to establish the prevalence and incidence[1] of occurence of premenstrual problems in the general population have produced inconclusive results when considered as a whole . The large number and variety of symptoms associated with the premenstruum has led to a lack of terminological concordance between questionnaire studies and the variability in symptom severity between individuals and between cycles has led to possibly erroneously high prevalences of PMS being reported . Pennington (1957) for instance reported that 95 % of a sample of 1000 mostly high school and college girls , suffered at least one premenstrual symptom . However , no indication of the severity of these symptoms was given and the age group studied may not be representative of PMS sufferers in general . Other studies (e.g. Woods , Most & Dery 1982) have avoided giving prevalence rates for PMS but rather have reported on individual symptoms such as irritability or breast pain . These studies give lower prevalence rates for each symptom , but little indication of the proportion of women suffering symptom combinations . Still other studies (e.g. Moos 1968; Rouse 1978 ; Abraham & Hargrove 1980) concentrate on symptom categories or clusters which may be clinically useful but provide little comparison with other studies.Some of the symptoms commonly assessed for prevalence are described in tables 1.3 - 1.8. The differing terminology in different studies , means that tension for instance has been omitted . Only studies reporting data for specific single symptoms have been included to

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[1] The distinction should be made here between prevalence - the proportion of a population affected by a disease at any one time - and incidence , the number of new cases diagnosed within a particular time period (Barker & Rose 1979) . Although studies of PMS often discuss " incidence " , the data they present is actually describing prevalence rates .

give some degree of comparability . It would appear from this summary that depression , irritability , breast pain and abdominal swelling are fairly common premenstrually and show a reasonably consistent prevalence rate across all the samples studied. Those studies which have assessed premenstrual symptom severity (e.g. Moos 1968; Woods , Most & Dery 1982 ; Andersch et al 1986) are consistent in finding a very small proportion of the sample indicating severe symptoms . This latter group is arguably the one to which the label PMS should be assigned giving a prevalence rate of about 2 - 12 % of the general population depending on symptom . The generally accepted belief that premenstrual symptoms are relieved at the onset of menstruation does not seem to be borne out in those studies which have assessed menstrual symptoms . Possibly these figures represent a different group of women , however the only symptom showing any consistent trend is "period pain " which not surprisingly increases during menstruation .

The studies outlined above can all be criticized on several counts. Firstly - the use of a retrospective questionnaire to assess premenstrual symptoms may introduce response bias (Parlee 1973) . Prospective studies of prevalence tend to give lower rates generally supporting the idea that cyclical psychological change is a relatively common phenomenon and that a small percentage suffer a clinical syndrome (Slade 1984 ; Taylor et al 1986) . Secondly - many studies only asked about premenstrual symptoms . Since the symptoms may also be present during menstruation either as a continuation of PMS or as a seperate 'syndrome ' - some confusion may exist in subjects ' minds leading to excess symptom reporting . Thirdly - littleaccount is taken of the possible effects of oral contraceptives (oc 's) on premenstrual symptoms . Rouse (1978) showed that as a rule women taking oc's reported fewer premenstrual and more menstrual symptoms than women not taking oc 's . However effects of the length of time for which the oc has been used or of being an ex -oc user have not been assessed. Fourthly - few studies assess symptom prevalence intermenstrually , hence the possibility of premenstrual exacerbation of underlying symptoms is ignored . Finally - few studies take into account the woman's cycle phase at the time of questionnaire completion . Although Moos (1968) and Rouse (1978) show no cycle effects on symptom reporting on the MDQ , this was based on a comparison between a group of " premenstrual " women and a group of "midcycle " women not on a repeated measures design within an

TABLE 1.3

STUDIES OF PMS PREVALENCE

STUDY	SAMPLE	SYMPTOMS ASSESSED
Pennington 1957	N = 1000 95% High School & College girls	17 symptoms 12 physical 5 mood perimenstrual
Kessel & Coppen 1963	N = 465 / 500 randomly selected from 5 GP practices Age 18 - 45 yrs	5 symptoms 3 physical : 2 mood worst PM/Mens/Other
Sutherland & Stewart 1965	N = 100 students N = 50 nurses All nulliparae	37 symptoms Yes/No/Occasionally
Moos 1968	N = 839 Wives of graduate students Mean Age 25.2 yrs	Moos MDQ6 point scale PM/Mens/Inter Most recent cycle
Timonen & Procope 1971	N = 748 students Age 20 - 27 yrs	17 symptoms 12 physical : 5 mood PM/Mens Sev/not sev
Janiger , Riffenbergh & Kersh 1972	N = 135 Housewives & outpatients	33 symptoms No/Mild/Mod/Sev
Sheldrake & Cormack 1976	N = 2542 non oc N = 756 oc Students	9 symptoms 6 physical : 3 mood PM / Mens
Rouse 1978	N = 196 oc,176 non oc FPC attenders Age 15 - 55 yrs	Moos MDQ 6 point scale PM/Mens/Postmens
Woods, Most & Dery 1982	N = 179 Respondents to phone call to all homes in 5 districts	Moos MDQ 6 point scale PM /Mens/Postmens
Friedman & Jaffe 1985	N = 384 " Volunteers "	147 symptoms 4 point scale PM
Mao & Chang 1985	N = 84 Student nurses Age 18 - 20 yrs	9 symptoms 6 physical : 3 mood PM
Andersch , Wendestam Hahn & Ohman 1986	N = 913 Random selection from census 5 age groups	6 symptoms 3 physical : 3 mood 4 point scale PM
Taylor, Alexander & Fordyce 1986	N = 530 Random sample from 5 GP's Age 20 - 40 yrs	Symptoms from van Keep 1983 Pm/Mens/Postmens
Boyle, Berkowitz & Kelsey 1987	N = 520 In/Outpatients	5 symptoms 4 physical : 1 mood PM

Key :- PM - premenstrual ; Mens - during menstruation ; Postmens - after menstruation
oc - oral contraceptive user , sev - severe .

TABLE 1.4

STUDIES OF PREMENSTRUAL IRRITABILITY PREVALENCE

STUDY	Premenstrual		Menstrual		Postmenstrual	
	Mild	Severe	Mild	Severe	Mild	Severe
Pennington 1957	47 %				-	
Kessel & Coppen 1963	42 %		8 %		2 %	
Sutherland & Stewart 1965	69 %		-		-	
Moos 1968	39 %	13 %	40 %	8 %	9 %	1 %
Timonen & Procope 1971	70 %		-		-	
Janiger, Riffenbergh & Kersh 1972	70 %		-		-	
Sheldrake & Cormack 1976	32 %		22 %		-	
Woods , Most & Dery 1982	44 %	12 %	38 %	11 %	14 %	4 %
Mao & Chang 1985	52 %		-		-	
Andersch et al 1986	72 %	3 %	-		-	
Taylor, Alexander & Fordyce 1986	65 %		37 %		3 %	
MEAN	58.4 %		32.8 %		3.0 %	
RANGE	32 % - 75 %		8 % - 49 %		2 % - 18 %	

TABLE 1.5

STUDIES OF PREMENSTRUAL DEPRESSION PREVALENCE

STUDY	Premenstrual		Menstrual		Postmenstrual	
	Mild	Severe	Mild	Severe	Mild	Severe
Kessel & Coppen 1963	38 %		10 %		1 %	
Sutherland & Stewart 1965	63 %		-		-	
Moos 1968	33 %	10 %	28 %	7 %	7 %	2 %
Timonen & Procope 1971	43 %		-		-	
Janiger, Riffenbergh & Kersh 1972	58 %		-		-	
Sheldrake & Cormack 1976	31 %		15 %		-	
Woods, Most & Dery 1982	30 %	7 %	30 %	5 %	17 %	2 %
Friedman & Jaffe 1985	56 %	14 %	-		-	
Mao & Chang 1985	86 %		-		-	
Andersch et al 1986	34 %	2 %	-		-	
Taylor, Alexander & Fordyce 1986	43 %		22 %		4 %	
MEAN	46.1 %		23.4 %		8.2 %	
RANGE	31 % - 70 %		10 % - 35 %		1 % - 19 %	

TABLE 1.6

STUDIES OF PREMENSTRUAL BREAST SYMPTOM PREVALENCE

STUDY	Premenstrual		Menstrual		Postmenstrual	
	Mild	Severe	Mild	Severe	Mild	Severe
Pennington 1957	18 %				-	
Sutherland & Stewart 1965	40 %		-		-	
Moos 1968	28 %	7 %	23 %	5 %	4 %	1 %
Timonen & Procope 1971	47 %		-		-	
Janiger, Riffenbergh & Kersh 1972	56 %		-		-	
Woods, Most & Dery 1982	28 %	8 %	25 %	5 %	8 %	2 %
Friedman & Jaffe 1985	67 %	17 %	-		-	
Mao & Chang 1985	42 %		-		-	
Andersch et al 1986	56 %	3 %	-		-	
Taylor, Alexander & Fordyce 1986	54 %		21 %		4 %	
Boyle, Berkowitz & Kelsey 1987	41 %		-		-	
MEAN	49.3 %		26.4 %		6.1 %	
RANGE	25 % - 84 %		21 % - 30 %		4 % - 10 %	

TABLE 1.7

STUDIES OF PREMENSTRUAL ABDOMINAL SWELLING

PREVALENCE

STUDY	Premenstrual		Menstrual		Postmenstrual	
	Mild	Severe	Mild	Severe	Mild	Severe
Pennington 1957	2 %				-	
Kessel & Coppen 1963	43 %		7 %		1 %	
Sutherland & Stewart 1965	52 %		-		-	
Moos 1968	30 %	5 %	31 %	4 %	4 %	1 %
Timonen & Procope 1971	49 %		-		-	
Janiger Riffenbergh & Kersh 1972	63 %		-		-	
Woods, Most & Dery 1982	39 %	5 %	34 %	5 %	9 %	2 %
Friedman & Jaffe 1985	73 %	13 %	-		-	
Mao & Chang 1985	27 %		-		-	
Andersch et al 1986	72 %	2 %	-		-	
Taylor , Alexander & Fordyce 1986	60 %		26 %		4 %	
Boyle , Berkowitz & Kelsey 1987	81 %		-		-	
MEAN	55.7 %		26.8 %		5.2 %	
RANGE	27 % - 86 %		7 % - 39 %		1 % - 11 %	

TABLE 1.8

STUDIES OF PREMENSTRUAL PERIOD PAIN PREVALENCE

STUDY	Premenstrual		Menstrual		Postmenstrual	
	Mild	Severe	Mild	Severe	Mild	Severe
Pennington 1957	62 %				-	
Kessel & Coppen 1963	13 %		35 %		1 %	
Sutherland & Stewart 1965	25 %		54 %		-	
Moos 1968	12 %	2 %	36 %	11 %	4 %	1 %
Timonen & Procope 1971	53 %	13 %	25 %	55 %	-	
Janiger, Riffenbergh & Kersh 1972	59 %		-		-	
Sheldrake & Cormack 1976	21 %		44 %		-	
Woods, Most & Dery 1982	25 %	6 %	36 %	17 %	10 %	3 %
Taylor, Alexander & Fordyce 1986	41 %		55 %		4 %	
Boyle, Berkowotz & Kelsey 1987	67 %		-		-	
MEAN	37 %		50 %		6 %	
RANGE	13 % - 67 %		35 % - 75 %		1 % - 14 %	

individual . It therefore seems illogical to conclude that the individual cycle phase at the time of questionnaire completion has no effect on the individual responses to the questionnaire .

Correlational analyses of various social and personal factors and their relationship to premenstrual symptoms has been undertaken in several prevalence studies . Age has been shown to be negatively correlated with dysmenorrhea (Kessel & Coppen 1963 ; Woods , Most & Dery 1982 ; Boyle, Berkowitz & Kelsey 1987) however premenstrual mood symptoms show no clear pattern . Some studies cite no correlation between age and PMS (Kessel & Coppen 1963 ; Boyle , Berkowitz & Kelsey 1987) . Andersch et al (1986) showed increases in premenstrual anxiety and peripheral swelling with age and Rouse (1978) showed overall MDQ score increases with age. However Woods, Most & Dery (1982) showed a decrease in premenstrual irritability,crying and napping in older subjects . No effects of marital status have been reported , except for Kessel & Coppen 's (1963) report of increased premenstrual irritability in married women . Andersch et al (1986) demonstrated increased anxiety and abdominal swelling in divorced women. Parity seems to have a similar effect to age on premenstrual and menstrual cramps - the effect remaining significant when the confounding factor of age is removed (Kessel & Coppen 1963 ; Woods , Most & Dery 1982 ; Andersch et al 1986 ; Boyle , Berkowitz & Kelsey 1987) . However no correlation with psychological symptoms has been shown . Woods,Most & Dery (1982) and Boyle , Berkowitz & Kelsey (1987) suggest that race may be an important factor , with white women generally reporting more premenstrual changes and black women more menstrual changes (except for cramps) . Cross-cultural prevalence studies , however tend to show fairly similar premenstrual symptoms across different cultural groups with variations in the frequency and severity of symptoms (Janiger, Riffenbergh & Kersh 1972 ; W.H.O. 1981; Mao & Chang 1985) . Friedman & Jaffe (1985) suggest an association between lifestyle and PMS , with housewives and less well educated women in their sample consistently reporting higher scores on fluid retention , autonomic and negative affect scales . Cycle regularity does not appear to be correlated with premenstrual symptoms or dysmenorrhea , but oral contraceptive use does have an effect on menstrual symptoms , particularly cramps and skin disorders, and a slight effect on premenstrual symptoms , although this may become more marked after prolonged use (Sheldrake & Cormack 1976 ; Rouse 1978 ; Woods, Most &

Dery 1982) . The effects of being an ex-oc user are not assessed in any study .

Overall then it would seem that the incidence of PMS *per se* is difficult to assess due to definitional problems . However the symptoms of it have been assessed both retrospectively and prospectively, suggesting that a large number of women experience some symptoms to some degree premenstrually. The number apparently suffering severe symptoms is small - about 2-12 % and this figure may give a reasonable estimate of PMS prevalence . Although dysmenorrhea is significantly correlated with such factors as age , parity and oc use , no consistent correlations have emerged for premenstrual mood symptoms . These findings have led some researchers to describe premenstrual mood changes as a physiological rather than a pathological process and possibly independent of physical changes . (Sutherland & Stewart 1965 ; Taylor, Alexander & Fordyce 1986).

1.4 DEFINITION AND DIAGNOSIS OF PREMENSTRUAL SYNDROME

The above description and discussion of PMS forms the rather untidy picture of the syndrome as a mixture of symptoms occuring with some temporal relationship to the menstrual cycle in some proportion of the female population. The concept has attracted the attention of the media as well as the medical / scientific fraternity resulting in many hypothetical claims being made on the basis of very little sound evidence about the phenomenon . A plethora of studies have been undertaken mostly within the medical / treatment framework, using a variety of diagnostic criteria for PMS and instruments for its assessment, and producing conflicting results . Few of these studies can withstand methodological criticism resulting in even more confusion about the exact nature of PMS . This has led several reviewers (e.g. Ginsberg 1987 ; Clare 1982 etc.) to the conclusion that little progress will be made in the field in the absence of a universally acceptable and meaningful definition of the syndrome . This conclusion is easy to draw but less easy to act upon . The assumption that it is possible to define PMS as a clinical entity may prove to be unfounded .

It would appear from a consideration of the nature of definitions (see Appendix One) , that the term " Premenstrual Syndrome " may be difficult to define , or even practicably indefinable . However , before dismissing the

concept as such , some of the known parameters of PMS should be discussed to give some idea of the current ' convention ' on the subject .

1.4.1 THE NATURE OF PMS

Although there may be little agreement between studies on the precise criteria upon which to select PMS sufferers - there does seem to be some general consensus about the constituents of the syndrome . The major features are : -

i) A large number of possible symptoms .

ii) Individual differences in the number and type of symptoms reported .

iii) Inter-cycle differences in the number and type of symptoms within an individual .

iv) Symptom onset during the " premenstrual phase " ranging from 3 days before menses to 3 weeks before menses and varying between individuals and between cycles .

v) Symptom relief at some time during or immediately after menses , varying between individuals and betwen cycles .

vi) Variable symptom severity between individuals and between cycles .

vii) Premenstrual exacerbation of underlying chronic conditions e.g. affective disorder .

viii) Effects of other life events e.g. bereavment , heavy workload ,etc. on experience of premenstrual symptoms .

ix) Lack of knowledge about aetiology .

To include all of these factors in a definition conforming to the rules outlined in Appendix 1 , would give a rather unwieldy and ambiguous result. In response to this , researchers have concentrated on specific aspects of PMS which they have defined to their satisfaction . For instance , Halbriech , Endicott & Lesser (1985) postulate a "premenstrual affective disorder " which involves only depression based symptoms . They make little specification about the the symptom timing but insist upon particular symptom clusters . On the other hand Dalton (1977 etc.) emphasizes that symptoms must occur in the week before menses with complete remission during the first day of menstrual flow . Hence in this definition , timing of symptoms is the crucial factor .

In this case it is necessary to go back to one of the basic premises and limitations of any definition i.e. " it is not possible to define concepts - only linguistic phenomena " . The problem here is that by giving a name , "PMS", to the observed phenomena of cyclical changes in women , researchers have attempted to create a linguistic phenomenon from what is essentially an open concept . Simply giving something a name does not change the essential nature of the "something " . In fact naming a phenomenon which we do not understand can have dangerous consequences . In this case the label Premenstrual Syndrome has aetiological implications i.e. the syndrome is caused by some parameter of the menstrual cycle or even menses *per se* which may be misleading .

There are two possible solutions to this problem . Either :-

i) The phenomenon known as PMS is not a single entity but rather many different entities or syndromes which have been " lumped together " because of a coincident correlation with the menstrual cycle .If this is the case , then the subtypes of other syndromes occuring premenstrually need to be isolated and defined before aetiological work can progress . If we assume that there is at least one syndrome for each of the currently recognised symptoms i.e. approximately 50 , in each of their temporal possibilities and add to that all the possible interactions with each other both symptomatically and temporally the total number of syndromes is practically infinite . Or :-

ii)The phenomenon known as PMS is not an entity at all but could be better described as the extreme of a continuum of premenstrual symptoms .

1.4.2 PMS AS THE EXTREME OF A CONTINUUM

Many human attributes form a continuum in the population . One of the most obvious examples is height ,which is normally distributed . This pattern however can be subject to environmental pressure - for instance in countries deficient in dietary Vitamin D , bone problems may cause an excess of people at the shorter end of the spectrum i.e. the distribution may become skewed . A problem arises however when we wish to define " tall " . If we assume a normal distribution of height (fig. 1.1a) where is the dividing line between " tall " and " not tall "? The same argument could apply to PMS . If the x-axis is relabelled number/severity/timing of premenstrual symptoms then it is conceivable that the women at the extreme right of the curve might

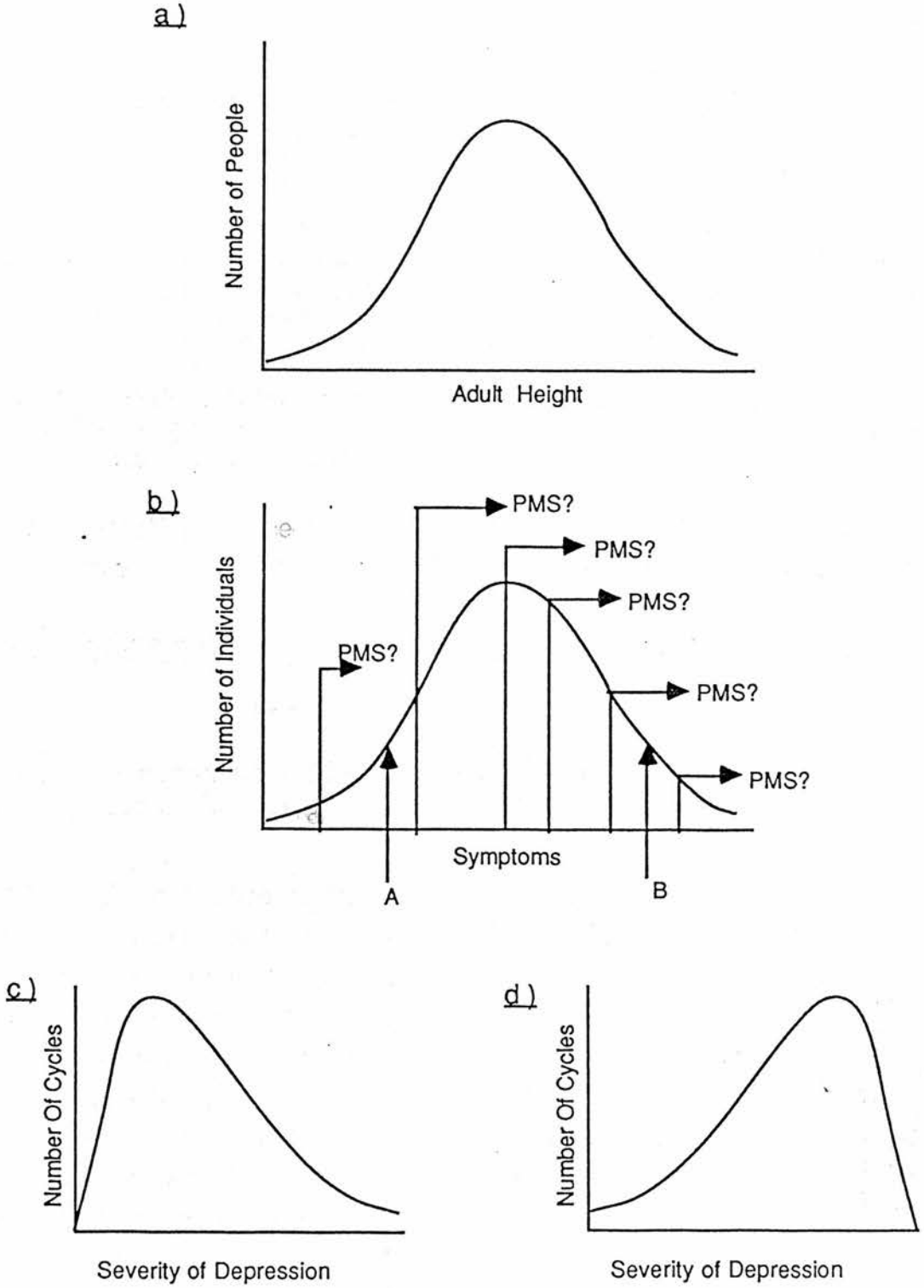

Figure 1.1 Graphical Explanations of PMS as a Continuum

a) The Normal Distribution Curve

b) The Definition Of PMS

c) Lifetime Symptom Profile Of Woman A

d) Lifetime Symptom Profile Of Woman B

complain of premenstrual syndrome . The question is where to put the dividing line . If this hypothesis of an underlying normal distribution of premenstrual symptoms is true - then generally they are no more of an illness than height is . However in this respect premenstrual symptoms are better likened to intelligence. Women whose symptom severity , for example, falls at the right hand end of the continuum are undoubtedly suffering and need help in the same way that people falling at the left hand end of the intelligence continuum need help . The different criteria used in different research studies have assigned different cut-off points for PMS explaining why , for instance , there is a lack of consensus in studies of incidence (see fig. 1.1b) . The picture is further complicated if we take into account variability between cycles in each individual woman . It is possible to hypothesize that each individual also experiences symptoms on a continuum skewed according to how she fits into the general population If a woman with an overall symptom severity of A (fig. 1.1b) is considered then her lifetime profile of , for instance, premenstrual depression would probably be a skewed distribution as in figure 1.1c. Whereas if a woman with overall severity B (fig. 1.1b) were chosen her distribution might be skewed in the opposite direction as in figure 1.1d. This hypothesis explains the variation between and within individuals,and has quite important implications for aetiological studies . If PMS is just a name given to symptoms at the end of a continuum , then searching for some factor present or absent in women with PMS and not in women without PMS would be fruitless. The implication is an underlying predisposition whose expression may be dependent on both biological and environmental factors (cf. intelligence) . It is possible that certain environmental factors may cause an upward or downward shift in the whole distribution in particular populations . It may be that in our Western culture either the menstrual symptom curve has become skewed to the right as a result of some environmental pressure or the subjective threshold for symptom reporting has shifted to the left as a result of media exposure , meaning that there is a preponderance of women with symptoms at the severe end of the scale . If this is the case then the argument for symptomatic treatment is advocated . However it may be that although a normal distribution curve is obtained , an individual woman does not stay at the same point on the curve for the whole of her reproductive life . Certain events in her life e.g. pregnancy , oral contraceptive use , bereavment etc. may cause her to switch from position A to position B for instance (fig. 1.1b). If

that were the case then some manipulation might be possible to cause a shift downwards in severe sufferers .

This analysis is purely hypothetical and raises as many questions as it answers . However it is eminently testable - simply by longitudinal studies of normal unselected women and by large epidemiological studies .

1.4.3 SUMMARY OF SECTION 1.4

One of the major problems of research into PMS is the lack of an adequate definition . The reason for this may be that PMS is an open concept rather than an entity and as such will not fit into any practicably definable category. There are two possible solutions to this problem , either PMS is a blanket term subsuming many other syndromes occuring premenstrually , all of which are entities in their own right and definable ; or PMS represents the extreme of a continuum of menstrual symptoms and as such is virtually indefinable . The latter position is favoured for two reasons :-

i) If PMS is a blanket term then the number of sub-syndromes and the interactions between them approaches infinity , making their delineation and interpretation a practical impossibility .

ii) The continuum theory is a more flexible explanation of the observed phenomenon and involves few inherent assumptions about it .

1.5 THE AETIOLOGY OF PREMENSTRUAL SYNDROME

The diverse and elusive nature of PMS has led to nearly as many aetiological theories as there are potential symptoms . These theories range from the genetic to the psychological and none can be proven beyond doubt. The most obvious candidate for a syndrome correlating with the menstrual cycle is a malfunction of the ovarian hormone system which regulates the female cycle . Although the evidence for this is controversial most of the physiological theories of PMS assume that the substance in question e.g. dopamine or prostaglandin is producing systemic and/or central effects in response to ovarian hormones and as such shift the burden of guilt as it were back on to oestrogen and progesterone. The nature and role of the ovarian hormones is a major part of this thesis and will not be discussed in detail here . However a brief resume of the alternative

hypotheses is outlined below .

1.5.1 THE GENETIC HYPOTHESIS

Recent evidence of a genetic linkage in some affective disorders (e.g. Egeland et al 1987) is suggestive that there may be some genetic influence in PMS (Clare 1985) . There is very little evidence to support or deny such a theory. Dalton (1977) dogmatically states that a familial tendency for the syndrome exists and that mothers and daughters are likely not only to both experience PMS but to exhibit the same premenstrual symptom cluster .Two surveys of premenstrual symptoms (Widhlolm & Kantero 1971 ; Chern, Gatewood & Andersen 1980) have reported significant relationships between mothers , daughters and sisters on various cycle parameters including "premenstrual tension " - although these results could easily have explanations other than genetic , especially if the women were living together . A study by Paulson (1961) found that 58% of the mothers of a group of "high premenstrual tension" sufferers also experienced premenstrual and menstrual symptoms , compared to only 27% of a " low premenstrual tension " group . He argues that maternal feelings and attitudes predispose later premenstrual problems in their daughters . However the explanation could equally as well be a genetic predisposition rather than a sociocultural one . To date no good data exists from studies of dizygotic or monozygotic twins . Dalton (1987) reports such a study in progress whose preliminary results support the hypothesis , however all such studies will require very close scrutiny and careful replication before conclusions can be drawn .

It could be argued that since PMS only affects women (as far as we know) it is essentially a genetic condition in the same way that menstruation is a genetic condition , and that the underlying genotype can be influenced by the environment to cause variable phenotypic expression (see Section 1.4.2). This argument is suggesting , not a genetic malfunction or genetically carried disease - such as Down's syndrome , but rather a normal underlying genetic predisposition whose expression can be influenced by the environment . If this were the case then traditional genetic studies of twins would reveal nothing more than studies of sisters who had shared the same early environment .

An alternative view of this is that offered by sociobiology . Rosseinsky &

Hall (1974) argue that PMS - or at least premenstrual hostility - may have evolved in order to repel male advances at a time of the menstrual cycle when the female is likely to be infertile - thus intensifying male ardour during the next fertile phase , optimizing the chances of conception . If the female does not conceive then repeated bouts of premenstrual hostility may cause the breakdown of an infertile pair-bond . They answer the criticism that the thwarted male need only turn to another female to satisfy his sexual needs by citing evidence of menstrual cycle synchronicity in cohabiting females (McClintock 1971) . They then go on to state:-

" The primary corollary to the thesis is that PMT is intrinsic and ineradicable although symptomatic treatment may be appropriate "
(Rosseinsky & Hall 1974)

Hence the theoretical possibility of a genetic basis for PMS is accepted but little evidence to support or deny the theory is available .

1.5.2 THE MONOAMINE NEUROTRANSMITTER HYPOTHESES

a) Catecholamines

The three catecholamine neurotransmitters are dopamine (DA) , norepinephrine (NE) and epinephrine . The first two of these (DA & NE) have been implicated in the expression of various mood states and psychiatric disorders (Schildkraut & Kety 1967 ; Stein & Wise 1971) , although the exact nature of the involvement is unclear and remains controversial . The catecholamines have also been implicated in the control of the reproductive cycle, and particularly of LH release in the rat (Meyerson & Sawyer 1968 ; Schneider & McCann 1969 ; Kamberi 1970 ; Kalra & McCann 1973) . Oestrogen and progesterone have been shown to be effective in modulating uptake and passive effux of NE and DA from synaptosome (Janowsky & Davis 1970) and in altering absolute levels of NE and turnover rates of NE and DA in rat brain (Janowsky , Berens & Davis 1973 ; Pfaff & McEwen 1983) . In these respects oestrogen and progesterone appear to have opposite effects . Three major areas of evidence suggest a possible link between catecholamines and the menstrual cycle in humans:-

i) Increased levels of urinary NE in the luteal phase (Wiener & Elmadjian 1962 ; Feichtinger et al 1979 ; Goldstein, Levinson & Keiser 1983). Measures of total urinary NE include amine from both central and peripheral

sources. However a study of urinary 3-methoxy-4-hydroxphenyl -glycol (MHPG) purported to be the major urinary metabolite of central NE found elevated levels in the late luteal phase followed by a rapid drop two days premenstrually and rebound elevation during menses (DeLeon-Jones, Steinberg , DeKirmejian & Garver 1978) .

ii) Decreased Dopamine-ß-Hydroxylase (DBH) in the premenstrual / menstrual phases (Lamprecht , Matta , Little & Zahn 1974) This enzyme converts DA to NE and a decrease suggests an alteration in the synthetic pathway of NE and a reduction in NE levels .

iii) Increased sensitivity to tyramine premenstrually (Ghose & Turner 1977). Tyramine is a measure of NE receptor sensitivity and this increase suggests reduced NE activity .

So , in the immediate premenstruum there would appear to be a reduction in NE activity possibly leading to psychological disturbance . This may be in response to levels of oestrogen and progesterone , or it may be causal, or both may be mediated by other factors .

A recent study of urinary MHPG levels in carefully diagnosed PMS sufferers and controls has suggested that women with PMS excrete higher levels of MHPG throughout the cycle (Schrijver , Louwerse , Bruinse & Van den Berg 1987) . In this study , no cyclical changes in urinary MHPG were seen - however, levels were only assesed at five points during the cycle and hence , subtle variations may have been missed . The levels seen were comparable to those suggestive of depression , hence the authors argue that it is tempting to view PMS as a manifestation of an affective disorder .

b) Indoleamines

The major indoleamine is serotonin (5-hydroxytryptamine ;5HT) . This has been implicated in major theories of depressive illness (Lapin & Oxenkrug 1969; Curzon 1969) and is responsive to progesterone withdrawal (Hackman, Wirz-Justice & Lichtsteiner 1973 ; Ladsisch 1977) Several studies have demonstrated cyclicity of 5HT action by measuring appropriate indices e.g. tryptophan levels (Wirz-Justice , Puhringer , Hole & Menzi 1975); platelet 5HT uptake (Wirz-Justice & Chappius-Arntt 1976 ; Taylor et al 1982); urinary 5-HIAA levels (LerdodeTejade etal 1978) [N.B. 5-HIAA , 5 hydroxyindole- acetic acid , is the major metabolite of 5HT however only a small fraction of urinary 5 HIAA originates from the CNS , therefore such studies should be treated with caution (Green & Costain 1981 p.67)] .

These studies suggest that platelet uptake of 5HT is decreased premenstrually . Taylor et al (1982) correlated platelet uptake negative affect and cognitive deficit , showing a strong positive correlation , lower platelet levels being associated with lower mood levels .

Ladsisch (1977) suggested that 5 HT levels drop in response to progesterone withdrawal as opposed to low progesterone levels *per se* , leading to increased reactivity to stress premenstrually . Labrum (1983) argues that serotonin values fall in response to oestrogen withdrawal - the higher the relative oestrogen level in the early luteal phase , the more pronounced the withdrawal effect on 5HT and the worse the PMS symptoms.

One of the cofactors involved in the synthesis of 5HT from tryptophan (and dopamine from tyrosine) is pyridoxal phosphate , derived from pyridoxine (Vitamin B6) in the diet . A relative deficiency of this vitamin has been noted in oral contraceptive (oc) users (Green , Bloomfield , Woods & Seed 1978) and has been related to oc induced depression (Adams , Rose, Folkard , Wynn , Seed & Strong 1973) . On the same basis pyridoxine has been prescribed for PMS , although its therapeutic efficacy has not been fully demonstrated (Stokes & Mendels 1972 ; Winston 1973 ; Hagen, Nesheim & Tuntland 1985 ; Williams , Harris & Dean 1985) . This does not of course rule out a part for serotonin in PMS . Labrum (1983) argues for possible interactions between oestrogen , serotonin and other factors e.g. α MSH or ßendorphin whilst Rausch & Janowsky (1982) suggest that the serotonin hypothesis may bear some relation to the mineralocorticoid theory.

1.5.3 OTHER ENDOCRINE HYPOTHESES

a) Prolactin

Prolactin is a pituitary hormone and is involved in milk synthesis and breast development . Some studies have shown variations in prolactin across the menstrual cycle (e.g. Halbriech , Assael , Ben-David & Bernstein 1976) whilst others have shown no overall change (McNeilly , Evans & Chard 1973; Epstein , McNeilly , Murray & Hockaday 1975) . Whilst some of these discrepancies may be related to experimental method and diurnal variation in prolactin secretion , most of the confusion is explained by large individual differences . Although some women show little variability , others

have clear mid-cycle and late luteal elevations . (McNeilly & Chard 1974 ; Steiner & Carroll 1977) .

Horrobin (1973) reports an experience of PMS like symptoms (fluid retention, irritability and depression) after an injection of prolactin and suggested that elevated levels in the late luteal phase might explain the premenstrual syndrome. Studies of prolactin levels in PMS sufferers have not demonstrated any clear difference between women with PMS and those without (Benedek- Jaszman & Hearn-Sturtevant 1976 ; Assael , Ben-David & Bernstein 1976 ; Carroll & Steiner 1978) . An alternative way of testing the hypothesis is by use of bromocriptine - a dopamine antagonist and prolactin suppressant . However although some results have been encouraging (Benedek-Jaszman , Lequin & Sternthal 1975;Cole,Evered,Horrobin, Manku, Mtabaji & Nassar 1975; Benedek-Jaszman & Hearn-Sturtevant 1976; Elsner,Buster, Schindler,Nessim & Abraham 1980 ; Ylostalo,Kauppila, Puolakka ,Ronnberg & Janne 1982) , careful double blind control trials have failed to show a significant effect over placebo (Andersen, Larsen, Steenstrup, Svendstrup & Nielsen 1977 ; Ghose & Coppen 1977 ; Graham, Harding, Wise & Berryman 1978 ; Steiner,Haskett,Osmun & O'Carroll 1983). The only symptom to consistently show any improvement being breast pain (Kullander & Svanberg 1979 ; Andersch1983).

Although prolactin may be involved in PMS - or cyclical mastalgia (Mansel, Preece & Hughes 1980) it does not appear to have a direct effect on cyclical mood change . The possibility of an effect due to increased tissue sensitivity to prolactin (Horrobin 1983) is discussed later(Section 1.5.5) .

b) Insulin

DePirro , Fusco , Bertoli , Greco & Lauro (1978) have demonstrated cyclicity in the specific binding of 125 I Insulin to circulating monocytes coincident with the menstrual cycle . An inverse relationship exists between insulin binding and levels of 17ß oestradiol , progesterone and 17-hydroxyprogesterone (Bertoli, DePerro,Fusco,Greco,Magnatto & Lauro 1980) . Since other researchers have reported subclinical hypoglycaemia premenstrually (Morton 1950) and the symptoms of PMS are similar to those of transient hypoglycaemia (Clare 1985) ; Rausch & Janowsky (1982) suggested that PMS may be explicable by changes in insulin receptor binding and glucose tolerance in response to ovarian hormones .

A recent study of oral glucose tolerance tests in normal women and

women with PMS and premenstrual hypoglycaemic attacks found no evidence of significant menstrual cycle related differences in glucose metabolism or glucose intolerance in either group of women (Reid, Greenaway & Hahn 1986) . However four of the six PMS women did show manifestations suggestive of hypoglycaemia coincidentally to the glucose nadir , even though this was never low enough to be considered abnormal . Reid et al point out that although these manifestations occured in both the follicular and luteal phases , none of the women complained about them in the follicular phase . They say :-

" . . . . . whether women with alleged PMHA truly experience symptoms only during the luteal phase when cravings for sweets may abruptly increase the amounts of chocolate and refined carbohydrate in their diet , or whether they are merely more aware of symptoms due to the heightened anxiety and tension of Premenstrual Syndrome is not known "

(Reid , Greenaway & Hahn 1986)

c) Melatonin

Melatonin is a hormone secreted from the pineal gland in the brain . Its isolation is fairly recent (Lerner et al 1958) and its role as the major pineal hormone remains controversial . It has been shown to play a part in seasonal breeding in several species (see Lincoln 1984) forming a link between photoperiod and the reproductive axis , in sleep disturbances (Jimerson, Lynch,Post,Wurtman & Bunney 1977) ,and in mood (Carman, Post & Buswell 1976) . Melatonin excretion has also been shown to vary across the menstrual cycle with highest values premenstrually and during menstruation (Wetterburg, Arendt,Paunier,Sizonenko,von Konselaar & Hepden 1976) . This evidence suggests that melatonin may be a candidate for the aetiology of PMS (Rausch & Janowsky 1982) .

Parry,Rosenthal,Tamarkin & Wehr (1987) have recently published a case report of a patient experiencing severe premenstrual depression only during the autumn and winter months . The symptoms were alleviated by high intensity light and inhibitors of melatonin synthesis and release (propanolol and atenolol) . The beneficial effects of light being reversible by exogeneous melatonin administration . The results of this study raise the possibility of an interaction between seasonal and menstrual rhythms , potentially mediated by melatonin . However the results of one case study cannot be generalized to all women , further investigations are required to extend these findings .

d) Androgens

The androgens are the " male " hormones - dihydroepiandrosterone , androstenedione and testerone . In the ovary they are a midway point in the synthesis of oestrogens from progesterone (see Chapter 2) and their function in women is unknown (Baird 1984) . Plasma levels of these hormones generally show a midcycle peak (Judd & Yen 1973) . As a result of this , evidence showing an association between testosterone , sexual drive and aggression (Rose 1972) and reports of premenstrual acne exacerbation (Sutherland & Stewart 1965) Steiner & Carroll (1977) suggested a role for the androgens in PMS .

Studies measuring absolute plasma androgen levels in women with PMS have found no differences when compared to controls or normal ranges (Adamopoulos, Loraine,Lunn,Coppen & Daly 1972 ;Backstrom & Aakvaag 1981 ˙ Backstrom,Sanders,Leask,Davidson,Warner & Bancroft 1983) . However , levels of androgen in women (especially testosterone) are low compared to male levels and relatively difficult to measure on a regular basis . Hence subtle differences between the groups may have been obscured .

e) Gonadotrophins

Coulson (1986) argues that elevated levels of gonadotrophins (LH and FSH) in PMS patients may lead to inteference with the action of parathyroid hormone and a temporary state of hypoparathyroidism .The symptoms of this condition being tension, anxiety , lassitude , inability to concentrate , insomnia and depression .

FSH and LH are excreted in a cyclical fashion reflecting their role in controlling ovarian function . Backstrom, Wide,Sodergard & Carstensen (1976) have shown significantly higher plasma FSH levels in PMS patients but no differences in LH levels . Other studies have shown no difference or even lower than normal LH/FSH levels in women with PMS (Adamopoulos, Loraine,Lunn,Coppen & Daly 1972 ; Backstrom,Baird,Bancroft,Bixo, Hammarback,Sanders, Smith & Zetterlund 1983). Young, Brownjohn, Chapman & Lee (1983) demonstrated abnormal LH responses to a thyrotropin releasing hormone and luteinising hormone releasing hormone challenge in patients with cyclical oedema , suggesting that there may be a disturbance of the hypothalamic-pituitary axis in this condition and hence possibly in PMS . Some studies have reported beneficial results with anti-

gonadotrophic agents such as danazol (Day 1979; Watts , Butt & Edwards 1987) or with LHRH agonist (Muse,Cetei, Futterman & Yen 1984) . However these drugs also remove the effects of the peripheral ovarian steroids . The possibility of an aetiological role for gonadotrophins remains and will be discussed further in Chapter Three.

1.5.4 THE ADRENAL CORTEX HYPOTHESES

The adrenal cortex secretes several hormones , among them aldosterone, cortisol and deoxycorticosterone . These three are involved in the metabolism of water and electrolytes including sodium and potassium ("mineralocorticoid" activity) and the metabolism of carbohydrate and protein (" glucocorticoid " activity) . All three are involved in both of these activities to a greater or lesser extent , and both of the functions have been implicated in PMS .

a) The mineralocorticoid hypothesis

Aldosterone is the most potent mineralocorticoid . It acts in the kidney , gastrointestinal tract , salivary and sweat glands to promote sodium resorption and potassium secretion . Aldosterone itself is produced in the adrenal cortex in response to angiotensin and renin - hence the renin-angiotensin- aldosterone system controls sodium and water levels in the body . Excessive mineralocorticoid activity can lead to increased blood

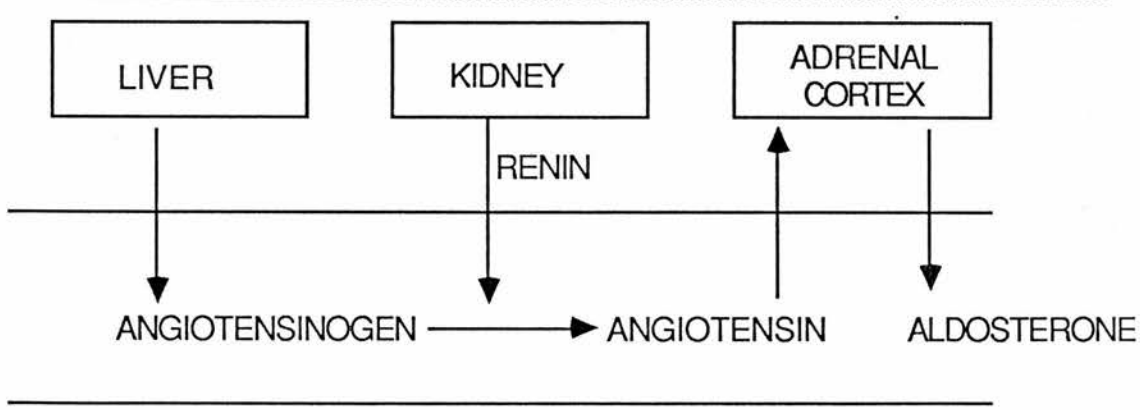

Figure 1.2 Diagrammatic representation of the renin-angiotensin-aldosterone system

(From :- Vander , Sherman & Luciano (1980) p. 382)

pressure , toxic effects on cardiac muscle and decreased excitability of brain tissue . A mineralocorticoid deficiency will have the opposite effects and is known as hypoadrenal corticalism .

Early studies of PMS subscribed to an aetiological model based on fluid retention as the major symptom , all others being the result of it . Thus the syndrome was caused by a cyclical malfunction of the renin-angiotensin-aldosterone system . This in turn was thought to be under the control of ovarian steroids . Greenhill & Freed (1941) wrote :-

" We have postulated that premenstrual distress and premenstrual tension are the result of changes in the electrolyte and water balance of the various tissues of the body which are probably the result of cyclic ovarian activity . Thus , under the influence of certain ovarian steroids , sodium is retained by the tissues with a subsequent increase in extracellular fluid . When this occurs to a significant degree in the brain , headaches develop ; when the gastrointestinal tract is involved , distention occurs ; and when the edema is located in the labia , pruritis may appear . With the subsidence in activity of the ovary coincident with menstruation , the various tissues lose their retained sodium and water and the respective symptoms disappear "

Greenhill & Freed (1941)

This hypothesis was supported by a report of relief of PMS in 34 of 40 sufferers treated with a diuretic , ammonium chloride .

Several assumptions are made by the hypothesis :-

i)The renin-angiotensin-aldosterone system is sensitive to ovarian steroids.

ii) Malfunction of the renin-angiotensin-aldosterone system can lead to psychological disturbance .

iii) All women with PMS retain sodium and water premenstrually and hence gain weight .

A vast body of literature has arisen investigating all of these asumptions and the overall hypothesis , and has been amply reviewed elsewhere (Reid & Yen 1981 ; Rausch & Janowsky 1982) . The results are contradictory and inconclusive (Munday , Brush & Taylor 1977 ; Andersch , Hahn, Andersen & Isaaksson 1978) . The lack of any reports of psychpathology in cases of chronic aldosterone elevation e.g. Conn's Syndrome (Rausch & Janowsky 1982) argues against an aldosterone hypothesis - although changing levels may be the key factor rather than an excess of aldosterone as such .

b) The glucocorticoid hypothesis

Cortisol , the most potent glucocorticoid , has wide-ranging effects

including metabolism of carbohydrates , proteins and nucleic acids , lipids and calcium ; inflammatory and allergic responses ; epithelial cell proliferation ; fluid and electrolyte balance ; gastric secretions ; and resistance to stress . A deficiency in cotrisol can lead to impaired vascular tone and cardiac output ; hypoglycaemia on fasting ; muscle weakness ; decreased ability to excrete water; disturbed gastro-intestinal function ; loss of appetite and increased susceptibility to even minor stresses . The reverse effects are centripetal obesity , fatigue and hyperglycaemia .

Genazzani , Lemarchand-Beraud , Aubert & Felber (1975) observed increases in plasma cortisol ten days after ovulation . However other studies have failed to show such cyclicity (Saxena , Dusitsin & Lazarus 1974 ; Ablanalp, Livingston , Rose & Sandwisch 1977) . Cortisol secretion is abnormal in cases of endogeneous depression and is increased in response to stress . Ablanalp et al (1977) failed to demonstrate any cyclical change in cortisol levels in response to stress at different cycle phases and Steiner & Haskett (1987) have shown that women with PMS do not exhibit responses to the dexamethazone suppression test characteristic of depressed patients (see section 1.2.4) . Hence it seems unlikely that cortisol is implicated in PMS - although further studies are necessary .

1.5.5 THE PROSTAGLANDIN HYPOTHESIS

Interest in the prostaglandins in relation to PMS has arisen from two sources:

i) Recent evidence has implicated the prostaglandin 2 series in the aetiology of primary dysmenorrhea (e.g. Lumsden,Kelly & Baird 1983 ; Abel 1985 ; Lumsden 1985) - although this may not be the case in women suffering premenstrual pain only (Stromberg,Akerlund,Forsling,Granstrom & Kindahl 1984) .

ii) One of the effects of prolactin is the stimulation of prostaglandin E1 formation (Manku,Horrobin,Karmazyu et al 1979) . This appears to control further prolactin secretion by a negative feedback mechanism . Horrobin (1983) has argued that a failure in this feedback mechanism could lead to physiological consequences after even small doses of prolactin - hence the symptoms of PMS - caused not by an excess of prolactin but by increased tissue sensitivity to it as a result of deficient PGE1.Both of these arguments have been tested using appropriate treatment models - either prostaglandin

PROSTAGLANDIN SYNTHESIS

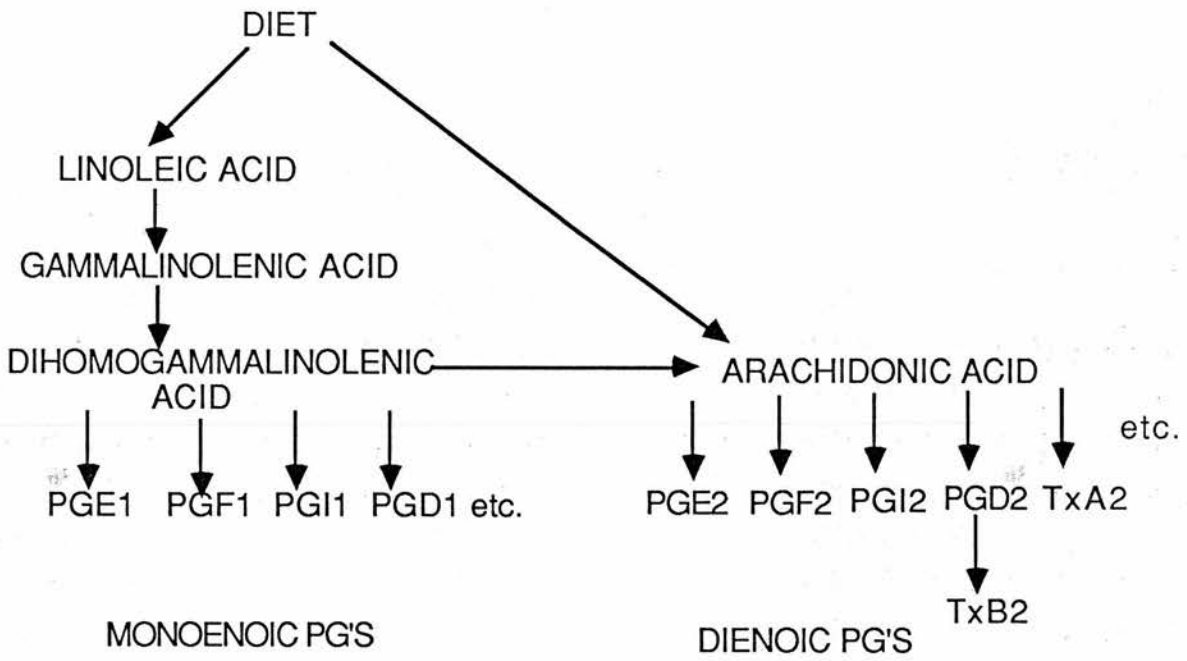

Figure 1.3 Synthetic pathways of monoenoic and dienoic prostaglandins
Key :- PG - prostaglandin Tx - Thromboxane

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synthetase inhibitors e.g. mefenamic acid , or a dietary precursor of PGE1 - gammalinolenic acid .

The first randomized double blind placebo controlled trial of mefenemic acid (Wood & Jacubowicz 1980) showed some efficacy of the anti-prostaglandin on all symptoms except breast tenderness . They did note however that the drug was only effective in those women who only had premenstrual symptoms as opposed to symptoms continuing into the menses. This would fit in with the Stromberg et al observation that premenstrual pain is not associated with excess prostaglandin whereas menstrual pain is . Budoff (1983) reports a single blind randomized placebo controlled crossover study of mefenemic acid in which a significant effect was seen on breast symptoms and other physical parameters but not on any of the psychological or mood symptoms . She argues that the dosage of medication and length of treatment (an average of 2.8 days before the onset of flow until menses) may have been insufficient to affect psychological symptoms . In a study measuring plasma prostaglandins and metabolites as

well as being a double-blind placebo controlled trial of mefenemic acid Jacubowicz , Godard & Dewhurst (1984) , PMS patients were found to have serum prostaglandin levels significantly lower than control subjects in both the secretory and proliferative phases of the cycle . This suggested to Pariser,Stern , Shank , Falko , O'Shaugnessy & Friedman (1985) a possible enhancement of PGI synthesis leading to precursor depletion.

The alternative prostaglandin theory involves the therapeutic use of Evening Primrose Oil . This substance is rich in gammalinolenic acid , an essential fatty acid and precursor of monoenoic PG's .

Horrobin (1983) reports four studies all showing a substantial improvement in PMS symptoms when compared to placebo (N.B. only three of the studies were placebo controlled) . These effects were particularly striking in patients whose primary symptom was cyclical breast pain . He argues that :-

" . . . . . a functional deficiency of essential fatty acids either due to inadequate linoleic acid intake or absorption or to failure of normal conversion of linoleic acid to GLA leads to abnormal sensitivity to prolactin and the features of PMS "

(Horrobin 1983)

These results are supported by a study of fatty acids in total plasma phospholipids of PMS patients (Brush , Watson , Horrobin & Manku 1984) which showed elevated levels of linoleic acid and significantly diminished levels of gammalinolenic acid compared to normal suggesting an abnormality in the metabolic conversion of LA to GLA . This abnormality was present in both follicular and luteal phases - although the women were asymptomatic in the follicular phase .

A recent study (Ylikorkala , Puolakka , Makarainen & Viinikka 1986) has shown no differences between women with PMS and controls in the synthesis of the vasoconstrictory and proaggregatory thromboxane A2 (TxA2) . They also show a beneficial effect of Evening Primrose Oil with accompanying inhibition of TxB2 - generated by platelets in response to TxA2 . Hence they suggest that GLA is acting in two ways - to compensate for the endogeneous defect in the monoenoic pathway and to inhibit the actions of the relative excess of dienoic PG's produced by the body in response to a monoenoic deficit .

The efficacy of prostaglandin synthetase inhibitors may also be due to the reduction of the excess dienoic PG's produced in response to an

abnormality in the monoenoic PG pathway . If this were the case then PMS should be expected to correlate well with primary dysmenorrhea . However Dalton (1977, 1982) remarks that a characteristic of PMS is pain-free menstruation .

In summary - the reasons for studying PG's in relation to PMS are not very clear . PG's are produced locally in the body in response to some stimulus - it is difficult to see which site of origin might lead to the diversity of PMS symptoms . It is possible that PG effects are secondary to some other mechanism e.g. endogeneous opiates or catecholamine systems and hence symptomatic treatment of PG imbalance may be partially helpful . Further careful research is needed to assess the relationship between PG's and PMS.

1.5.6 THE ENDOGENEOUS OPIOD PEPTIDE (EOP) HYPOTHESIS

The possibility of endogeneous substances having morphine like properties was first proposed by Kosterlitz & Hughes (1975) . Since then much work has been done to isolate and characterize these peptides and their neurotransmitter properties . The endogeneous opiates are involved in analgesia , mood and neuroendocrine modulation (Miller 1978) . Evidence has been given that the opioid peptides - and especially ß- endorphin are involved in the neuroendocrine regulation of the menstrual cycle and particularly in the regulation of LH pulse frequency and menstrual cyclicity (Quigley & Yen 1980 ; Blankstein , Reyes , Winter & Faiman 1981 ; Ferin 1984; Ferin , VanVugt & Wardlaw 1984) .

Reid & Yen (1981) proposed a model of PMS utilizing the relationship between the gonadotrophic hormones , EOP's and mood . They suggest that :-

". . . . an aberrant release of or sensitivity to α-MSH and ß-endorphin during the luteal phase may be the central event which triggers a cascade of neuroendocrine changes leading ultimately to the varied manifestations of PMS. "

Reid & Yen (1981)

The suggestion is that β-endorphin levels rise in the luteal phase in response to oestrogen and progesterone , alone or in combination . This increase in EOP activity may lead to activation of inhibitory presynaptic opioid receptors on catecholaminergic systems leading to fatigue and depression . The EOP increase could also account for increased appetite

and constipation through other mechanisms . An abrupt fall in EOP activity ummediately before menstruation leads to classic symptoms of opiate withdrawal - irritability , tension, anxiety , hostile behaviour , GI and vasomotor disturbances . These symptoms are relieved by a return to normal neurotransmission after the withdrawal phase (Reid 1983) . Differing levels of gonadal steroids - and hence differing levels of ß-endorphin from month to month and between individuals can account for the variability seen in symptom manifestation and severity (Reid & Yen 1981) .

This theory is tempting - it accounts for almost all the manifestations of PMS and the observations of other theorists since the EOP's interact with so many other physiological systems e.g. prostaglandin synthesis (Coupar 1978);catecholaminergic systems (Schwartz 1979) ; glucose metabolism (Reid & Yen 1981b) and hypophyseal hormone secretion (Ferin, VanVugt & Wardlaw 1984) . However there is little direct evidence for a role in PMS as yet.

Chuong,Coulam,Kao,Bergstralh & Go (1985) demonstrated lower levels of β-endorphin on day 25 in patients with PMS when compared both to their own day 7 values and to asymptomatic luteal phase control values . This data could fit with the Reid & Yen (1981) hypothesis , suggesting a greater fall in EOP levels immediately before menstruation in women with PMS . However , the intermittent sampling schedule used , and the relative impermeability of the blood-brain barrier to ß-endorphin , disclaiming a relationship between peripheral measures and central nervous system activity , reduce the validity of this study .

Reid , Greenaway-Coates & Hahn (1986) failed to show any effects of naloxone (an EOP antagonist) on glucose , insulin or glucagon responsesto an oral glucose tolerance test at any point in the menstrual cycle in women with or without PMS and premenstrual hypoglycaemic attacks . They suggest that either the naloxone dosage (an infusion rate of 1mg/h for 6h) was insufficient ; the glucoregulatory effect of EOP's is at a receptor site unaffected by naloxone ; or else EOP's do not exert a glucoregulatory effect . There would not appear to be any evidence from this study that EOP's are involved in the carbohydrate craving / hypoglycaemia aspects of PMS.

Tulenheimo , Laatikainen & Salminen (1987) studied plasma ß-endorphin immunoreactivity in twelve women complaining of PMS and fourteen controls. They were unable to demonstrate any cyclical changes in ß-endorphin which could be related to the presence or absence of PMS ,

although the mean plasma level of ß-endorphin was slightly lower in the PMS group . They suggest that PMS may be related to significant changes in central EOP activity which are not reflected in peripheral plasma . They also point out that daily sampling might reveal more than their intermittent samples .

Hence there would appear to be little support for the theory as yet - and few therapeutic applications of it . Difficulties in the measurement of centrally active EOP's and the lack of an appropriate animal model for PMS make research in this area problematic .

1.5.7 THE PSYCHOGENIC HYPOTHESES

The lack of consensus about a physiological aetiology of PMS coupled with an increase in interest in women's health and social position generally has led to a number of psychological hypotheses of aetiology of PMS . Although these are all interlinked they can conveniently be considered under three headings .

a) Personality

The possibility that PMS is a manifestation of an underlying personality maladjustment or neuroticism has been suggested and tested by several authors. Rees (1953) found a higher frequency of PMS in neurotic than normal subjects - although he noted some very neurotic women with no PMS. He concluded that physiological factors were also involved . The majority of studies have shown significant relationships between PMS and particular personality variables (Coppen & Kessel 1963 ; Levitt & Lubin 1967 ; Gough 1975 ; Gruba & Rohrbaugh 1975 ; Halbriech & Kas 1977 ; Taylor 1979 ; Mira , Vizzard & Abraham 1985) . However the instruments used are variable e.g. the MMPI , EPI, California Personality Inventory, 16PF, Taylor MAS , STAI etc. and therefore the results are not strictly comparable . Gannon (1981) points out that some items on standard personality questionnaires e.g. the MMPI are virtually repeated on instruments such as the Moos MDQ . Hence the results of using two such instruments are confounded and significant correlation coefficients are a *fait accompli* . Coppen & Kessel (1963) have provided the only research accounting for this factor by eliminating all the MMPI questions with a periodic component e.g. " Are you sometimes bubbling over with energy and

sometimes very sluggish ? " . Their overall results were however unchanged - premenstrual psychological symptoms correlated significantly with neuroticism . Gannon (1981) also points out the large number of correlational analyses undertaken by most studies in this area - and hence the increased likeliehood of significant relationships occuring by chance . Gruba & Rohrbaugh (1975) for instance found 16 significant correlations from 160 analyses . Asso (1983) echoes these criticisms and draws attention to the fact that most of the subjects in these studies were students . Since PMS is most likely to occur in the thirties - a student population may not be representative of women and PMS sufferers in general . Another source of error is the effect of cycle phase at the time of questionnaire completion . Although personality questionnaires are generally accepted to be stable instruments - this may not be the case for PMS sufferers . Mira , Vizzard & Abraham (1985) showed significant differences between luteal and follicular phase scores on the State Trait Anxiety Inventory (STAI) for PMS sufferers but not for controls . This was true for both the state and trait scales.

Hence early research indicates a link between PMS and personality , particularly neurotic personality . However recent methodological criticisms have cast doubt on the relationship . Whilst the possibility remains that PMS is a manifestation of a particular personality type , it should also be borne in mind that PMS could cause a particular expression of personality or both may be reflections of an underlying mechanism .

b) Attitudes towards menstruation and femininity

This area of research has received much attention from two points of view:-

i) The psychoanalytic approach . The psychoanalytic view of menstruation is of a regular reminder to women of their lack of a penis :-

" The girl's initial high estimation of her body is shattered by her sense of mutilation (castration) when at a time when a child is jealous of all possessions , she finds she has no penis ; this notion of a wound is confirmed by menstruation and defloration "

(Mitchell 1974 p.123)

Hence PMS is a reflection of hostility towards menstruation , which itself is a symptom of conflict about femininity . Horney (1967) links PMS with ambivalent or contradictory attitudes towards motherhood e.g.if a fear of childbirth or fear of coitus is linked with a strong desire for children . PMS

can be seen as one manifestation of underlying penis envy and conflict about the female role resulting from incomplete superego development .

In a careful psychoanalytic study of 15 neurotic patients over 125 menstrual cycles , Benedek & Rubenstein (1939b) showed a correlation between the menstrual cycle and " instinctual tendencies " . The premenstrual phase is characterized by conflicts about femininity and sexuality , fears of pain , mutilation and childbirth . They emphasize that menstruation itself is usually associated with emotional relief - although occasionally a feeling of loss may occur - as if menstruation represented a ' lost child ' . Skultans (1970) implicates the quality of the marital and sexual relationship in women's attitudes towards and level of complaint about menstruation . Differential experiences of menstruation are due to the expression of unconscious emotional attitudes generated by conflict about the female role and reflected in problematic sexual relationships .

ii) The sociocultural approach . The sociocultural view of PMS is also based on conflict about the female role and menstruation . However the sources of the conflict are claimed to be entrenched in society rather than in the individual . (A psychoanalytic theorist might argue that this is just a reflection of individual psychosexual development i.e. society has developed menstrual taboos etc. as a consequence of individual penis envy and fear of mutilation). Society 's attitudes towards women's role and menstruation and the response of women to them have been discussed extensively (e.g. Parlee 1974,1976; Brattesani & Silverthorne 1978 ; Rohrbaugh 1979 ; Ruble & Brooks-Gunn 1979 ; Brown & Woods 1986 etc.) . However evidence of such an interplay is hard to obtain. Several studies have suggested that "traditional " women with high femininity scores indicate more premenstrual distress (Paige 1973; Gough 1975 ; Slade & Jenner 1980) , whilst other studies suggest that ambivalence about female role leads to greater symptomatology (e.g. Berry & McGuire 1972) and still others have found no relationship between sex role and symptoms (Watts , Dennerstein, De & Horne 1980 ; Spencer-Gardner , Dennerstein & Burrows 1983) .

The presence of negative attitudes towards menstruation in Western Society has been substantiated in studies of adolescents (Dunham 1970 ; Brooks-Gunn & Ruble 1982 ; Abraham et al 1985 ; Stoltzman 1986) , men (Parlee 1973; Brooks-Gunn & Ruble 1986) and women in general (Paige 1971;Schneider & Schneider-Ducker 1974 ; Brooks , Ruble & Clark 1977 ;

McKeever 1984 ; Woods 1986 ; Ericksen 1987) . These attitudes have been linked to religious beliefs (Paige 1971 ; Paige-Ericksen 1987) suggesting that the notion of menstruation is associated with the concept of 'pollution ' in most cultures . However PMS as such only appears to be prevalent in the west whilst menstrual symptoms are similar everywhere . Religious beliefs are also important - Catholic women showed an extreme jump in anxiety premenstrually compared to Protestant women who showed little cyclicity and Jewish women who were anxious all the time (Paige 1973) .

Hence attitudes and beliefs about menstruation and conflicts about the female role appear to be involved in PMS . There is insufficient evidence as yet of a causal link in either direction , however these psychological factors should be taken into account when considering other theories .

c) Arousal and Attribution

The cognition-arousal theory of emotion states that an emotional state is the result of an interaction between physiological arousal and cognitions about the arousing situation (Schachter & Singer 1962) . These two components are linked by labelling the arousal in terms of emotional cognitions .In normal situations the cues arousing the person also provide the cognitive labels for that arousal . However this is not always the case . If a case of unexplained physiological arousal occurs without an appropriate emotional label a " cause " must be found by reinterpreting the situation . The theory has been described as the " Juke-Box " theory (Mandler 1962) . To play a juke-box a coin must be inserted and a tune selected . Arousal is analagous to the coin which activates the machine , a physiological condition necessary for emotion to occur but not specifically programmed for any particular emotion . Interpretation of the social situation is analagous to the tune - if others are laughing the tune will be happiness , if others are frowning the tune will be anger .

Koeske & Koeske (1975) suggest that an attribution pattern exists linking negative moods to the paramenstruum . Hence any increase in sympathetic arousal at that point in the menstrual cycle will be attributed to cyclical mood changes and labelled negative e.g. anxiety or irritability . This hypothesis can be tested on several counts :-

i) Social conventions exist linking negative moods to the paramenstruum

ii) Women with PMS experience some degree of elevated physiological arousal in the premenstruum .

iii) Women with PMS will attribute negative mood states to premenstrual arousal .

iv) Women with PMS are more likely to feel that their lives are outwith their own control hence are more likely to use a biological attribution for premenstrual arousal

The first point has been discussed in the previous section (1.5.7 (b)) showing a significant social convention that negative moods are associated with the premenstruum . The second point has been investigated by Doreen Asso (Asso & Beech 1975 ; Asso 1978 ; Braier & Asso 1980 ; Asso & Braier 1982) suggesting raised premenstrual levels of autonomic arousal on some measures but not others in the normal menstrual cycle . The third point has been addressed in a classic study by Ruble (1977) in which women were misled about their cycle phase . Women who thought they were premenstrual reported more symptoms than women who thought they were intermenstrual even though both groups were tested at the same time relative to menses . Rodin (1976) found that premenstrual and menstruating women do attribute task produced arousal and frustration to symptoms of menstruation . However the level to which they do this depends upon the usual severity of premenstrual symptoms , women who usually have strong premenstrual symptoms attribute task-induced arousal to the menstrual cycle whereas women who have mild symptoms usually do not . The fourth point has been investigated by Spencer-Gardner, Dennerstein & Burrows (1983) . They assessed locus of control and found a tendency towards externalization in women with PMS although this did not achieve significance. Harding (1987) has also shown that women with severe premenstrual and menstrual symptoms , especially pain , were less likely to see the locus of control as lying within themselves .

There is some evidence then to suggest that the cognition-arousal theory of emotion may be applicable to PMS . However the theory itself is open to criticism (e.g. Reizenzein 1983) and any derivation from it should be treated with caution .

1.5.8 SUMMARY OF SECTION 1.5

A wide variety of aetiological models have been suggested to account for cyclical changes in well-being . Apart from the methodological inadequacies and diagnostic inconsistencies inherent in studies attempting to test the

various hypotheses , all of the theories outlined above can be criticized on two theoretical or conceptual grounds:-

i) Few of the hypotheses take into account the variability of symptoms, both between women and between cycles . Neither the timing nor the severity of symptoms is considered , nor the possibility that seperate aetiological mechanisms exist for different symptoms or subgroups of symptoms .

ii) Several , potentially important , observations about PMS are rarely taken into account . The first of these is the apparent relationship between premenstrual symptoms , particularly depression , and affective disorders (see section 1.2.4) . The second is the high rate of placebo effects in studies of PMS. This observation , usually dismissed as an experimental " thorn in the side " , may be an important indicator of the psychosomatic nature of some premenstrual symptoms .

In other words , research in this area has tended to assume that a homogeneous cyclical phenomenon known as the " Premenstrual Syndrome" occurs , which , although it may be manifest by a variety of symptoms , has a single physiological cause . As Bancroft & Backstrom (1985) point out , the failure of many models of premenstrual symptom aetiology may be due to their failure to take into account the inherent complexity of the phenomenon , resulting in conflict and confusion . In response to this they propose a "systems model " of PMS (fig 1.4) , suggesting that causation of the syndrome is vested both in a peripheral response to ovarian steroid levels , and in a central mediation of , and response to , ovarian cyclicity and mood change . Factors such as predisposition to affective disorder are included as modifiers of the type of mood change experienced . Possible modifications to the model might include the incorporation of present " stress " , with its potential effects both on emotional experience and ovarian cyclicity (Parlee 1973) , and the addition of personality factors and attitudes towards menstruation as modifiers of the type of mood change experienced .

This type of interactive model is testable by interference and observation at various levels and may prove to be more constructive and instructive about the nature of premenstrual changes and PMS than any of the unitary approaches .

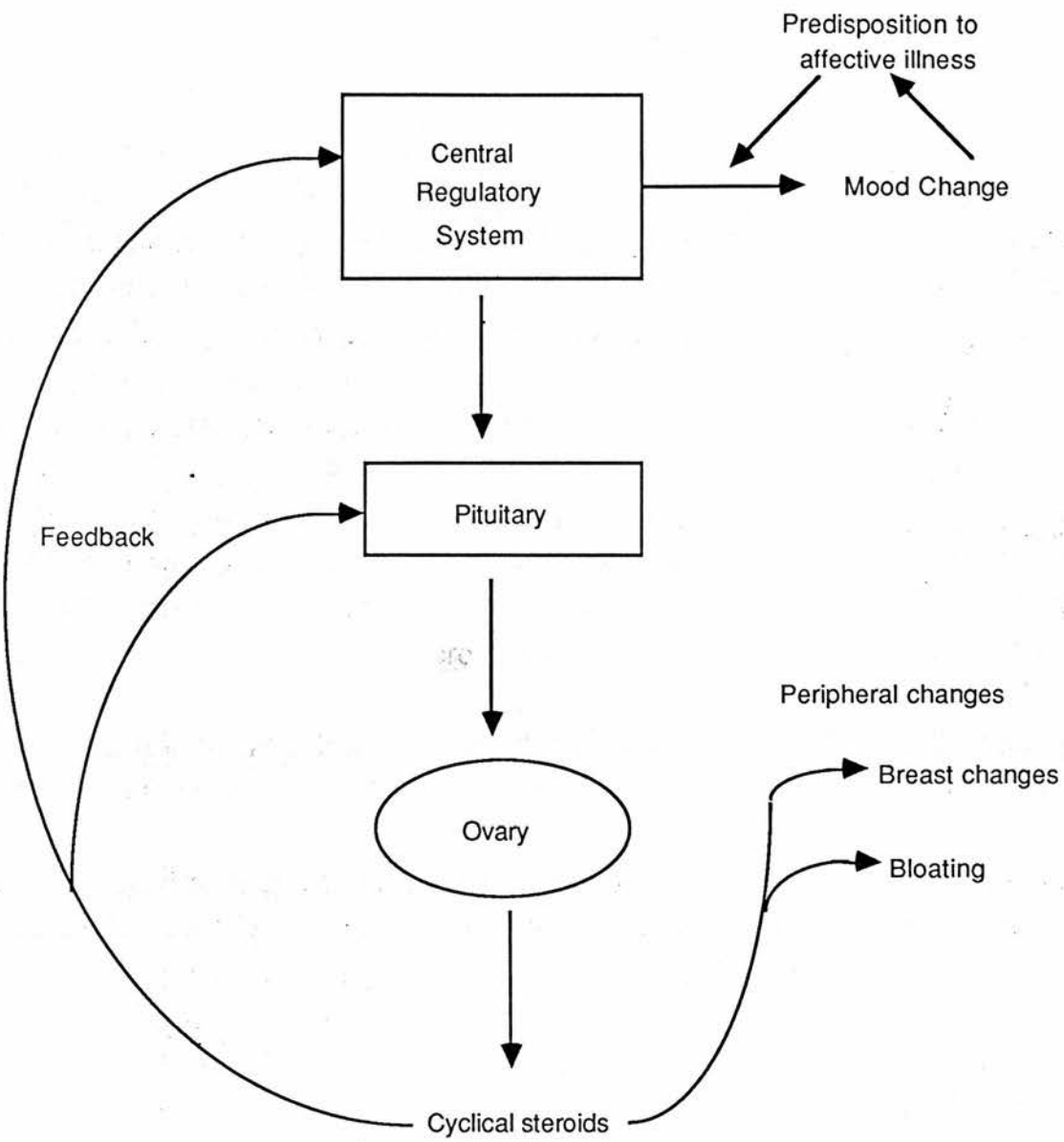

Figure 1.4 Hypothetical " Systems Model " of Premenstrual Symptoms

(From : Bancroft & Backstrom 1985)

1.6 SUMMARY AND CONCLUSIONS OF CHAPTER ONE

This chapter has given an outline of the syndrome under study and its possible social and medical importance . PMS is a complex phenomenon, manifested in many ways . Its prevalence is difficult to assess since the syndrome is either practically indefinable as a single entity or the reflection of an extreme of premenstrual symptoms . The problems of definition have led to a lack of concordance across research studies , some researchers opting for a purely stipulative definition for use in that particular study , offering no comparability with other research - whilst others offer no definition at all . (The problems of PMS assessment will be discussed in Chapter 4). The search for cause and cure of PMS has largely been fruitless . No single biochemical or psychological factor has yet been found to distinguish PMS sufferers from non-sufferers . This may be a reflection of definitional problems and the nature of PMS . The failure of many aetiological models to take into account the complex nature of the syndrome and its relationships with many other factors , has led to an over simplistic view of the phenomenon . Current thinking supports a more interactive , psychosomatic type approach to research , with less emphasis on a unitary underlying mechanism . The label premenstrual has led to the assumption that aetiological factors are inherent in the menstrual cycle or women's response to it . However the possibility of cyclical mood changes, in men and women , whose timing has synchronized about the menstrual clock in women has not been investigated .

The social and political repercussions of a potential cyclic deficit in women's performance together with the more humanitarian desire to relieve suffering means that further careful and thoughtful research is indicated in this field in order to clarify the situation .

CHAPTER TWO
THE HUMAN MENSTRUAL CYCLE : NORMALITY , ABNORMALITY AND DISRUPTION

2.1 INTRODUCTION

" There are a few days each month during which a very high percentage of women cannot become pregnant . These sterile periods as a rule extend from about the twelfth or fourteenth day after the cessation of each menstrual flow to a day or so preceding the next menstruation . "
Sperry (1900) " Confidential Talks With Husband And Wife " p.156

" . . . . . The periodicity of menstruation and ovulation are not however necessarily synchronous . They do not always occur together , though they both occur once in the month . "
Wrench (1916) " The Healthy Marriage " p. 152

" . . . . . for the ordinary " safe period " which comes at the intermenstrual phase . . . . . "
Stopes (1932) " Contraception " p. 95

These quotations give an idea of the amount of confusion and lack of knowledge about the female reproductive cycle and the relationships between ovulation , menstruation and conception which prevailed in popular literature even at the beginning of this century . The anatomy of the female reproductive system has been long characterized - detailed diagrams exist from the fifteenth and sixteenth centuries . However , the functional significance of the various components was not realized until much later . During the nineteenth century , the phenomena of ovulation , menstruation and fertilization were described independently . However , the temporal relationships between them were the subject of many misconceptions. Ovulation was thought to occur either in response to coitus or during menstruation (see Short 1977). This latter view led to the recommendation of the " safe period " , in terms of contraception , as being midway between episodes of menstruation - exactly the time when women are most likely to conceive . It is little wonder that Marie Stopes reports a 100 % failure rate of this method of birth control (Stopes 1932 p.25) - not from an inability to adhere to the proscribed period of sexual abstinence , but from a misunderstanding of the female reproductive cycle .

Knowledge of the menstrual cycle and the manner by which it is controlled , is largely a product of the twentieth century . The development of medical technology has allowed the reproductive system to be visualized and its endocrinology characterized , removing much of the myth and

folklore surrounding it . The story is , however , far from complete . For example , the potential interactions between the female reproductive system and her physical and mental state have been little explored . One manifestation of this possible interaction is the subject of this thesis . However , before an examination of this interaction is undertaken , it is perhaps relevant to discuss the characteristics of the normal menstrual cycle the mechanisms by which abnormalities occur and the manner by which the cycle may be disrupted .

2.2 THE NORMAL MENSTRUAL CYCLE

The normal menstrual cycle is the result of a complex interaction between the central nervous system (CNS) and the ovaries . As Short (1972 et seq) has pointed out - the menstrual cycle is a consequence of infertility and hence the system which modulates it is geared to the optimization of physiological conditions for a possible conception . If pregnancy does not occur , then a series of signals from the ovary to the CNS and back again lead to renewed preparations for another " pregnancy attempt " . Hence the control of the menstrual cycle can be divided into two sections :-

1) Those events which occur in the ovary and are indicated by changes in the peripheral levels of messengers to and from the ovary .

and 2) Those events in the central nervous system which occur in response to , or mediate the transmission of , ovarian messages .

Both of these aspects are essential to ovarian function and fertility and therefore to the control of the menstrual cycle .

2.2.1 OVARIAN EVENTS DURING THE NORMAL MENSTRUAL CYCLE

The ovary essentially has two functions . Its primary role is oogenic , allowing the primitive oocytes , present in the ovary from birth , to mature within ovarian follicles , until they are ripe for ovulation . The second function is as an endocrine gland , providing a suitable environment for follicular growth , supporting the ovum after ovulation and maintaining the reproductive tract and secondary sexual characteristics . These functions can be considered seperately, however they are intimately interconnected and mutually dependent (Baird 1984) . Although the time taken for the ovum to develop is the major determinant of menstrual cycle length , the

endocrine function of the ovary is a more accurate reflection of menstrual cycle control . The ovary secretes a variety of hormones , including the female sex steroids , oestrogen and progesterone . These are the most important ovarian hormones with respect to menstrual cycle regulation and have frequently been measured in human peripheral blood samples (e.g. Landgren , Unden & Diczfalusy 1980) . They are both synthesized from cholesterol (Figure 2.1) within different ovarian structures , the follicle , in which oestrogen alone is produced , and the corpus luteum , which produces both oestrogen and progesterone . These structures are transitory within the menstrual cycle , and hence measurement of peripheral hormones reflects different stages in the oogenic function of the ovary as well as its endocrine function .

Figure 2.2 illustrates the changing levels of the ovarian steroids throughout the menstrual cycle . The rise in oestradiol during the first half of the cycle , the follicular or proliferative[1] phase , reflects its increasing secretion by the growing follicle . This hormone provides support for the growing oocyte and maintains and prepares the reproductive tract , breasts etc. for conception . Oestradiol 17ß , the major form of oestrogen , reaches a peak at about midcycle indicating that the follicle is mature . This peak is shortly followed by ovulation , the release of the ovum from the follicle , marking the end of the follicular phase . The remainder of the cycle is dominated by the actions of the corpus luteum . This structure arises , phoenix-like , from the ashes of the ruptured follicle . It continues to secrete oestradiol throughout the luteal , or secretory [1], phase but also produces another hormone , progesterone . This is essentially a pregnancy hormone . It acts on the oestrogen primed uterine lining in preparation for conception and implantation and is active in the maintenance of pregnancy when it occurs . If pregnancy does not occur , progesterone and oestradiol levels fall in phase with the declining corpus luteum , the falling levels of ovarian steroids , acting directly on the endometrium , being the trigger for menstruation [2] .

1

[1] The terms proliferative and secretory phase refer to characteristics of the uterine endometrium at different menstrual cycle stages

[2] The actual trigger for menstruation remains a controversial issue . Hertz (1986) , for instance , argues that falling steroid levels cause a change in the

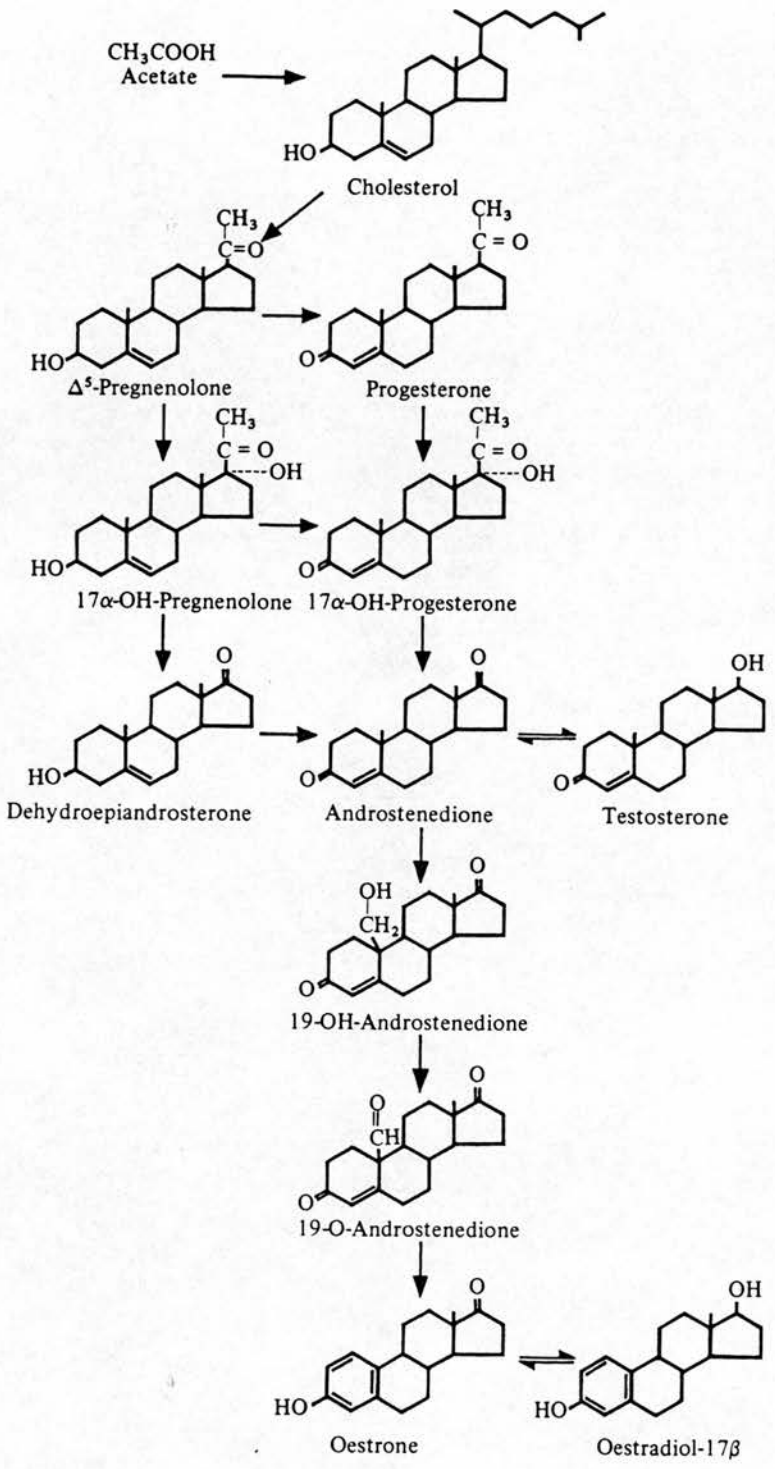

Figure 2.1 The Synthesis of Oestrogen and Progesterone from Cholesterol in the ovary . From Baird (1984) .

autoimmune system resulting in physiological rejection of the endometrium , and hence menstruation .

As mentioned above , the ovary is not an independent organ . An interaction exists between the gonads and the brain , in the form of the hypothalamus and pituitary gland . This latter gland secretes luteinizing hormone (LH) and follicle stimulating hormone (FSH) to act as messengers from the brain to the ovary ,as oestrogen and progesterone are messengers from the ovary to the brain . As can be seen from figure 2.2 , FSH levels are highest at the beginning of the cycle, literally stimulating a follicle to grow and produce oestrogen . When oestrogen reaches a certain level , suggestive that the follicle is now mature , a surge of LH is released which signals the follicle to ovulate . Progesterone and oestradiol from the corpus luteum then in turn signal to the brain that ovulation and/or pregnancy has occured , allowing the cycle to be repeated .

At present , the potential role of FSH in the control of ovulation itself is unclear , as is the potential role of LH in follicular development . It is possible that the two hormones act synergistically rather than independently (Shaw 1978) .

The changes in these four hormones then , characterize the endocrinology of the menstrual cycle at the ovarian level . The more subtle control of the menstrual cycle and the feedback mechanisms involved requires a consideration from the neuroendocrine point of view .

2.2.2 THE NEUROENDOCRINE CONTROL OF THE NORMAL MENSTRUAL CYCLE

In most species , reproduction is not an independent event . If it were , then neural involvement would only be necessary at the most basic level . However , several factors are important in governing when an animal should breed , and hence its reproductive function . For instance , seasonality is important in many species . In order for the maximum number of young to survive the cold and nutritionally sparse winter in a species such as the sheep, they must be born in the early spring to ensure that fat reserves have built up over the summer months. Hence some method of fertility control is needed to allow for this survival factor . Similarly if an animal is itself undernourished , unhealthy or under some other kind of stress , it makes sense for there to be a temporary closure of the reproductive axis . Therefore, a delicate balance must be maintained between ovarian conditions and the status of other physiological systems .

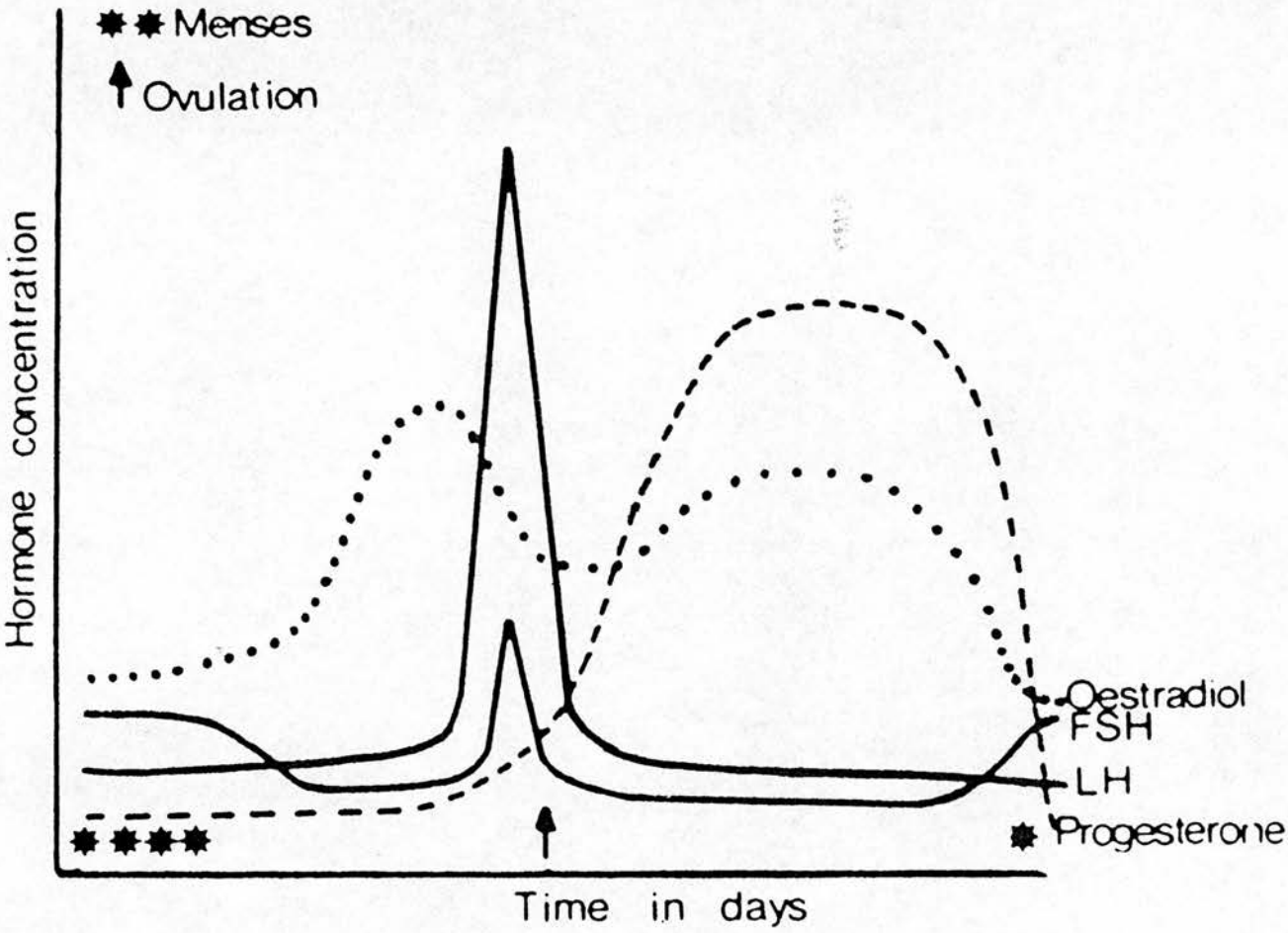

Figure 2.2 Diagrammatic changes in serum levels of LH , FSH , Oestradiol- 17β and progesterone during the menstrual cycle . (From Shaw (1978)) .

This balance is maintained by a complex feedback mechanism between the ovaries , the anterior pituitary gland (adenohypophysis) and the hypothalamus . The release of LH and FSH from the anterior pituitary is under the control of gonadotrophin releasing hormone (GnRH) from the hypothalamus .This structure contains cell bodies which have axonal projections to many areas of the brain allowing for an extremely complex network of neuronal communication between neural and endocrine regulatory centres (see Karsch 1984) . Hence , factors such as day length , nutritional status and so on can influence reproduction through the hypothalamus . GnRH is secreted in a pulsatile fashion from the hypothalamic GnRH pulse generator . GnRH is active in the brain and does not cross the blood-brain barrier to any measurable extent . Hence , attempts to measure GnRH in the peripheral circulation are fruitless . GnRH release can however be inferred by measures of LH , reflecting a pituitary response which is almost instantaneous (Clayton 1987) . The characteristics of LH pulses vary across the menstrual cycle (see Crowley et al 1985) . Thus the follicular phase is characterized by low amplitude pulses of increasing frequency, forming a saw-tooth pattern , which dramatically increase in amplitude at midcycle . After ovulation , the pulses become large and slow , with increased bimodality as the cycle progresses (Figure 2.3) .

Control of the menstrual cycle is not a one-way process . Levels of GnRH and consequently LH and FSH are sensitive to ovarian events by a system of positive and negative feedback of the ovarian steroids . Negative feedback describes a situation in which levels of one hormone lead to an inhibition of release of another . This occurs at the beginning of the cycle when oestrogen levels cause an inhibition of LH and FSH release . This effect appears to be at the level of the anterior pituitary , modulating its sensitivity to GnRH andsuppressing LH pulse amplitude (Goodman & Karsch 1980) . Increasing levels of oestrogen through the follicular phase appear to increase the frequency of GnRH pulses , although the mechanism for this is not yet understood . A point is reached as the follicle matures , by which high levels of oestrogen act on the anterior pituitary by a process of positive feedback , stimulating LH and FSH release . Hence a surge of LH is seen at midcycle which causes ovulation and luteinization of the follicle . Oestrogen and progesterone act synergistically in the luteal phase to inhibit

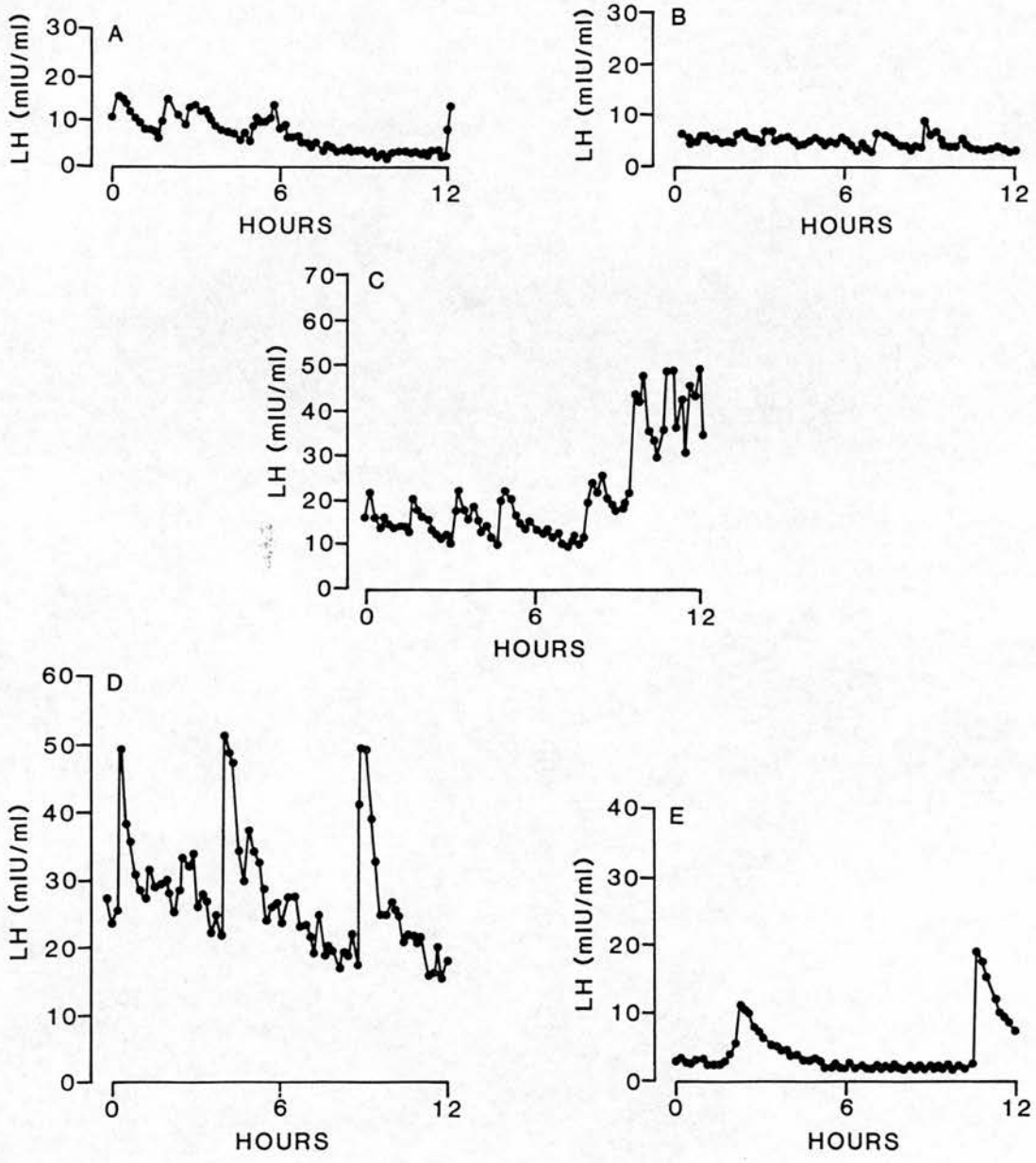

Figure 2.3 Changes in LH pulsatility across the normal menstrual cycle

(From Crowley et al (1985))

A - Early follicular phase (day 2)

B - Mid-follicular phase

C - Late follicular phase (day of LH surge)

D - Early luteal phase (LH surge + 1 day)

E - Mid luteal phase (LH surge + 8 days)

gonadotrophin release . Progesterone would appear to act directly on the hypothalamic GnRH pulse generator , slowing the frequency of GnRH pulses and hence of LH pulses (Soules , Steiner , Clifton ,Cohen , Aksel & Bremner 1984) . Oestrogen , presumably continues to exert its primary action at the pituitary level . Progesterone secretion is also pulsatile in the luteal phase , Crowley (1985) commented that the timing of these pulses correlated well with that of the smaller LH pulses forming the second phase of the bimodal wave pattern . A careful study by Steele , Braund & Judd (1986) however , failed to find any relationship between progesterone pulses and either LH or prolactin secretion . The mechanism producing this pattern of progesterone secretion and its physiological significance remain to be explained . In the absence of pregnancy , the corpus luteum degenerates , oestrogen and progesterone levels fall , reducing gonadotrophin inhibition and thus stimulating a new follicle to grow . This follicle starts to secrete oestrogen , inhibiting gonadotrophins , and the cycle begins again . Thus between puberty and menopause , in the absence of pregnancy , the female reproductive rhythm is a true cycle , with no beginning and no end .

Hence , although our knowledge of female reproductive neuroendocrinology is gradually increasing , we are still a long way from being able to specify the exact control mechanisms involved in the menstrual cycle . The biological importance of hormone pulsatility is not yet understood, nor the trigger factors for menstrual onset . The relative importance of other physiological systems in governing reproduction through the hypothalamus has not been assessed , nor the potential effects of reproductive functions on other systems . The mechanism of selection of one follicle to grow and ovulate in each cycle from a pool of primordiol follicles remains an enigma as do the relative roles of LH and FSH and their , common or diverse , releasing hormone(s) . The potential roles of other ovarian products , for instance prostaglandins , inhibin , testosterone etc. , in menstrual cycle control also remain to be explored .

2.3 THE ABNORMAL MENSTRUAL CYCLE

The complex neuroendocrine control of the menstrual cycle leaves ample scope for disruption . The results of this disruption can be manifest in several ways - for instance , primary or secondary amenorrhea , short or inadequate

luteal phase , polycystic ovary syndrome etc . These abnormalities can however be divided into two categories which are pertinent to this thesis - those states in which ovulation is present and those in which it is absent .

2.3.1 THE ANOVULATORY MENSTRUAL CYCLE

The incidence of anovulatory cycles , that is apparently normal menstrual cycles in which ovulation is absent (as opposed to amenorrhea in which both ovulation and menstruation are absent) , varies across the reproductive lifespan . This type of cycle is most common in the early and late menstruating years , after childbirth and in response to stress (Doring 1969 , Vollman 1977, Metcalf & MacKenzie 1980 , Metcalf 1983) . Two types of anovulatory hormonal patterns have been described (Newton 1972) . The first type consists of a constant low excretion of oestrogen and progestagens , in the absence of a midcycle LH surge. The second type shows cyclical changes in oestrogen levels but constantly low levels of progesterone.

In puberty , it would appear that the positive feedback mechanism by which oestrogen induces the LH surge does not mature as quickly as the rest of the reproductive axis . Hence although follicles may grow and become mature , they cannot ovulate and hence become atretic .The subsequent fall in oestrogen levels may be sufficient to cause menstruation . Hence the second type of cycle mentioned above is seen . Gradually through adolescence the feedback mechanism becomes operational and the cycles become ovulatory (see Figure 2.4) .This pattern also occurs in the higher primates , e.g. chimpanzees , and may have some adaptive significance (see Short 1984) . The neuroendocrine mechanism , although speculative , suggests that maturation of the GnRH pulse generator is independent of the gonadal steroids (Clayton 1987) and is a reflection of the changing pattern of neural control over the hypothalamus . Hence although follicles may be stimulated to grow in the ovary , the pulse generator is unable to evoke an appropriate GnRH response to the oestrogen they produce . This proposed mechanism requires further assessment . Hypothalamic maturation may also be confounded by the presence of other factors e.g. low body weight , having different effects on the reproductive axis.

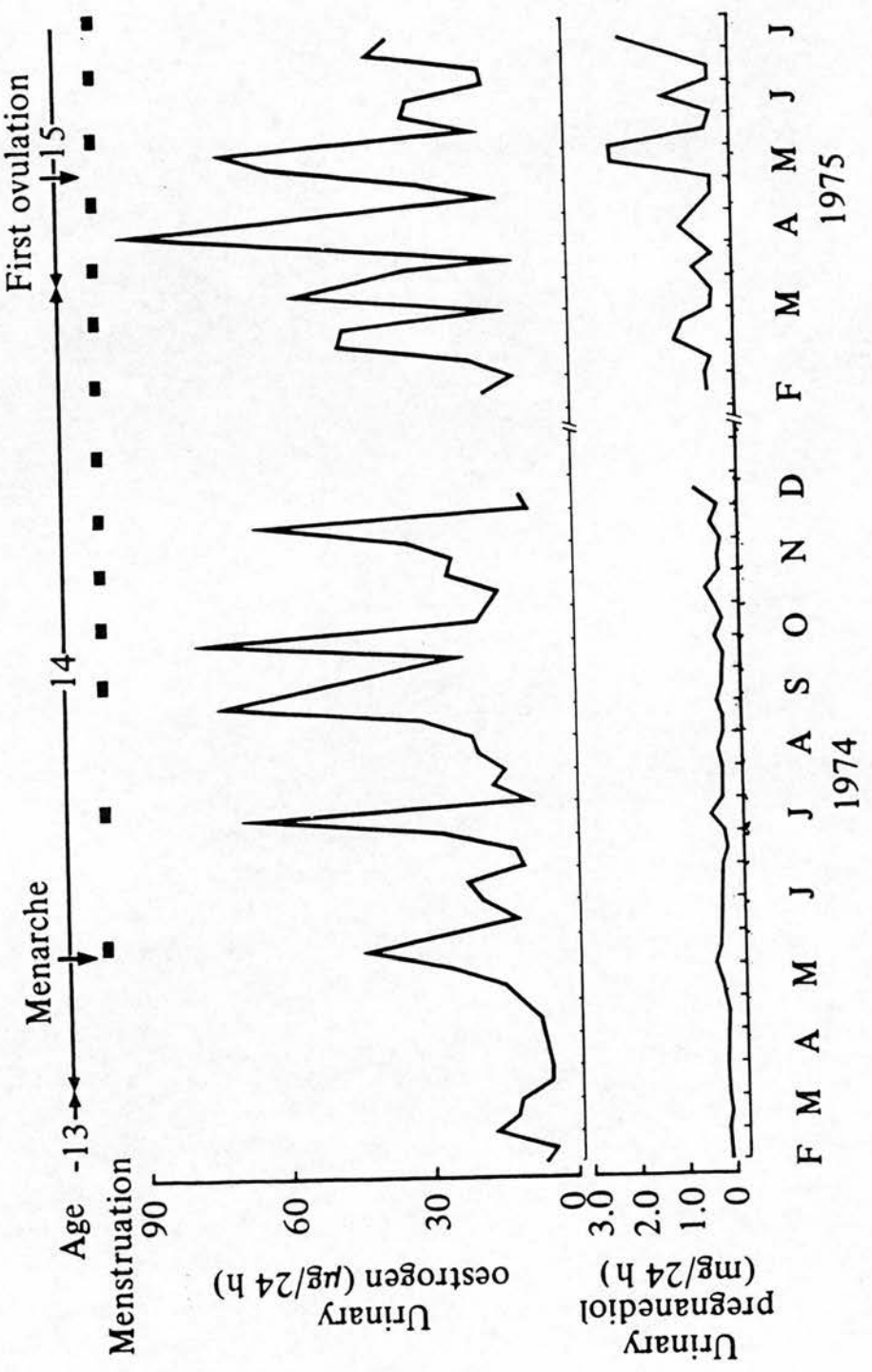

Figure 2.4 Urinary oestrogen and pregnanediol excretion in a girl going through puberty. (From Short (1984)).

At the opposite end of the reproductive lifespan , the perimenopause , anovulatory cycles are also common . At this stage the hormonal milieu tends to be characterized by rising LH and FSH levels (Adamopoulos , Loraine & Dove 1971 ; Sherman , West & Korenman 1976) reflecting changes in pituitary gonadotrophic function and an alteration in feedback mechanisms . The primary cause of anovulation is , however , probably ovarian . A shortage of viable oocytes may lead to insufficient follicular development and hence lower than normal levels of follicular phase oestrogen . As above a follicle may begin to grow , but produce insufficient oestrogen for positive feedback to occur , hence no LH surge and no ovulation . As the follicle becomes atretic , falling oestrogen levels , although slight , may be enough to cause menstruation . As in puberty , cycles are seen with cyclical oestrogen levels but no progesterone .

Post-partum anovulatory cycles usually follow a period of lactational amenorrhea . Ovarian activity resumes gradually during lactation in direct proportion to suckling frequency and hence prolactin levels (Howie , McNeilly , Houston , Cook & Boyle 1982b) . Only about one -third of breast-feeding mothers ovulate before their first post-partum menstruation (Howie, McNeilly, Houston, Cook & Boyle 1982 a) . Even after the first menstruation , cycles may be anovulatory or exhibit a luteal phase deficiency , although this effect is variable (Howie et al 1982b) . The neuroendocrine mechanism of this effect is unknown . Although differences have been demonstrated in LH pulsatility between amenorrheic lactators and subsequent normal cycles (Glasier, McNeilly & Howie 1984) , and the hypothalamic-pituitary axis of post-partum women has been shown to be hypersensitive to the negative feedback effects of oestradiol (Baird, McNeilly,Sawers & Sharpe 1979) , little investigation has been conducted of the anovulatory cycles following lactational amenorrhea. These cycles probably reflect an inter-individual variability in adaptation from the post-partum state to normal . Lactational amenorrhea itself appears to be the result of two potential actions of prolactin . Firstly , a direct block of LH action at the ovarian level , and , secondly , an inhibition of the ability of the hypothalamic-pituitary axis to maintain pulsatile LH secretion in response to oestrogen negative feedback (Glasier , McNeilly & Howie 1984). This latter effect is unlikely to be operational in anovulatory post-partum cycles since Glasier et al (1984) showed normal LH secretion in such cycles . However

the block of LH action at the ovarian level may still be present in the later anovulatory cycles . Hence , adequate follicular development cannot result in ovulation or adequate corpus luteum formation . Falling oestrogen levels from the atretic follicle would then lead to a withdrawal bleed . Present knowledge of the action of prolactin on the ovary (eg Baird 1984) do not allow this theory to be any more than speculative .

Metcalf & MacKenzie (1980) demonstrated a remarkably high incidence of anovulatory cycles in the 20 - 24 years age group of their sample , with only 62 % of 254 women showing consistently ovulatory cycles over a three month period , lower than any other age group . This phenomenon appeared to be related to the living conditions of the women . Those who lived in flats or hostels , as opposed to living with their families , were less likely to be ovulatory (only 45% of the group were consistently ovulatory compared to 76 % of the family living group) . This suggests that the ovary is sensitive to stresses at that time of life . Another example of the effects of a different kind of stressor is the common phenomenon of amenorrhea and anovulation in anorexia nervosa sufferers . In this latter case , loss of body weight has had a suppressive effect on the hypothalamic-pituitary-ovarian axis (see Halmi 1982 for review) . The precise mechanisms by which these factors exert their effects are unknown , although they are likely to be supra-hypothalamic , hence suppressing the GnRH pulse generator itself rather than acting by a disruption of ovarian feedback. Menstrual cycle disruption is also often seen in air hostesses , whose internal " clock " is frequently out of synchrony with the outside world (e.g. Iglesias , Terres & Chavarria 1980) , and in athletes , where strenuous exercise seems to have a similar effect to anorexia (e.g. Shangold,Freeman,Thysen & Gatz 1979 , Prior 1985)[1],[2] . Hence ,

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[1] Cumming & Rebar (1985) point out that athletes , particularly young runners , gymnasts and ballet dancers tend to be preoccupied with their own body image . Hence their eating habits tend to be frugal and sporadic . The apparent effect of exercise may actually be due to malnutrition.

[2] Borghi et al (1976) observed that ovarian disruption had occurred before weight loss in one-third to one-fifth of anorexics . This led Halmi (1982) to postulate a subgroup of women whose hypothalamus is " vulnerable " to environmental stress during the late teens and early twenties . The age range of poor ovulators due to stress observed by Metcalf & Mackenzie (1980) above , adds weight to this idea . Is this " vulnerable " hypothalamus also reflected in the numbers of young women who react badly to oral

anovulatory cycles can occur in a variety of physiological situations due to suppression of the reproductive axis . This suppression can either be from external sources acting directly on the hypothalamus or from inadequacies within the axis itself .

2.3.2 THE ABNORMAL LUTEAL PHASE

This section deals with those abnormalities of the menstrual cycle in which ovulation has occurred . In this case , there is a deficiency in the second half of the cycle , the luteal phase .

The definition of ovulation depends upon the index used to asses the menstrual cycle . This may be basal body temperature (BBT) , endometrial biopsy, cervical mucus changes , plasma or urinary progesterone measurements or LH measurements . All of these , except LH measurements , are progesterone dependent [1] .

Abnormalities of the luteal phase can fall into two categories - the short luteal phase (SLP) and the inadequate luteal phase (ILP) (Moszkowski , Woodruff & Jones 1962 ; Sherman & Korenman 1974 a,b) . These terms reflect the possibilities of abnormalities in both the duration of progesterone secretion (SLP) and the amount of progesterone secretion (ILP) from the corpus luteum . Coutts (1985) points out that a major problem in the evaluation of the abnormal luteal phase is the precise definition of a normal luteal phase in terms of the minimum requirement for maintenance of a conception . Hence , definitions are usually made with reference to some normal range . The normal luteal phase is itself variable in length both between cycles and between different assays . Basal body temperature studies suggest an average length of 12.7 (± 1.7) days (Doring 1966 quoted in Friedrich & Kemeter 1979) and a median of 11.8 days (Vollman 1977) ; intermenstrual pain studies suggest a median of 14.3 days (Vollman 1977) ;

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contraceptives ? - or thosee who are predisposed to PMS or post-natal depression ?

[1] Any assay of ovulation using a measure of progesterone secretion runs the risk of Type II errors due to the possibility of a " luteinized unruptured follicle " (LUF) . In this case , although luteinization occurs , the ovum is not released . Hormonally , a LUF cycle may be indistinguishable from a normal cycle - Kerin et al (1983) found a LUF frequency of 4.9 % in a series of otherwise normal cycles studied laparoscopically . A high incidence of LUFhas however been found in patients with luteal insufficiency (Hamilton, Evers & DeHaan 1987) suggesting that this may be one cause of apparent luteal inadequacy .

whilst studies of cervical mucus suggest median lengths of 16 days (Vollman 1977) or an average of 13.5 (±2.8) days (WHO 1983) . Lenton , Landgren & Sexton (1984) studied 327 luteal phases from overtly ovulatory cycles by daily blood sampling for LH . The mean normal luteal phase length was 14.13 ±1.41 days with 95 % confidence limits of 11.3 to 17 .0 days [2] . A subpopulation of short luteal phase cycles was found with an average length of 9.21 ± 1.41 days . All luteal phases of ≤ 9 days were found to be abnormal on the basis of endometrial biopsy as well as 74 % of those lasting 10 days and 22 % of those lasting 11 days . Hence they defined a short luteal phase as one of 11 days or less . Other studies have however used different criteria . Coutts (1985) , for example , recommends a cut-off point of 10 days whilst Sherman & Korenman (1974) advocate an 8 day maximum for a diagnosis of SLP . The definition of inadequate luteal phase is dependent upon the method of assay . However usually , values lying consistently below a normal range are described as inadequate . A diagnosis of ILP is often made on the basis of a single midluteal progesterone value . The pulsatile nature of progesterone secretion in the luteal phase (Healy , Schenken , Lynch ,Williams & Hodgen 1984 ;Steele , White & Judd 1985; Steele , Braund & Judd 1986) suggests that this diagnostic criterion may be susceptible to both false positives , due to the sample being taken at the nadir of a normal pulse and false negatives , the apex of a pulse from an inadequate luteal phase may be within the normal range . Hence studies using such a diagnostic tool should be treated with caution . A luteal phase, then , can fall into one of four categories :-

a) Normal length and adequacy
b) Normal length and inadequacy
c) Shorter than normal and adequate
d) Shorter than normal and inadequate

The latter three of these could be described collectively as defective luteal phases .

Defective luteal phase cycles tend to occur during puberty and the perimenopause , and during resumption of ovarian cyclicity post partum , post abortion or after discontinuance of oral contraceptives . They are also

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[2] Luteal phase length is defined as the number of days after , but not including , the day of maximum LH up to and including the day before menstrual bleeding . Midnight was used as the dividing point between days .

common in patients with recurrent miscarriage , hyperprolactinaemia , hypothyroidism , hyperstimulation of the ovary , " unexplained " infertility , hyperandrogenism and women who undergo strenuous athletic conditioning or have been treated with clomiphene citrate (Lee 1987) . In the context of the effect of exercise on the menstrual cycle , Shangold (1985) describes an orderly progression of dysfunction resulting from any insult to the female reproductive axis ; from luteal phase defects through anovulatory cycles and euoestrogenic anovulatory oligomenorrhea to hypoestrogenic amenorrhea . This progression , although not proven , possibly reflects an increasing suppression of the hypothalamo-pituitary- gonadal axis .

The endocrine profiles of patients with defective luteal phases have been the subject of several studies (e.g. Sherman & Korenman 1974 a, b ; Lenton,Adams & Cooke 1978 ; Lenton,Lawrence,Coleman & Cooke 1983 ; Smith, Lenton & Cooke 1983 ; Lenton,Landgren & Sexton 1984 etc.) . However the aetiology of the phenomenon remains obscure .

Adequate follicular maturation in the preovulatory phase would appear to be an important determinant of corpus luteum function . Sherman & Korenman (1974) found low follicular phase FSH and oestradiol-17ß in cycles which had simultaneously short and inadequate luteal phases . Hence they suggest that corpus luteum adequacy is dependent on follicle adequacy .This finding is supported by Wilks,Hodgen & Ross (1979) who show abnormal follicular phase FSH and LH levels in defective luteal phase cycles of rhesus monkeys , and by Stouffer & Hodgen (1980) who report luteal phase deficiencies in rhesus monkeys treated with porcine follicular fluid (pFF) in the early follicular phase (pFF selectively suppresses monkey FSH levels without changing serum LH) . However , Lenton , Adams & Cooke (1978) in a study of infertile women with normal length but inadequate luteal phases , found no differences in follicular plasma LH , FSH or oestradiol levels when compared to a control group .

An alternative view of luteal phase adequacy is offered by Lee (1987). The corpus luteum consists of " large " and " small " cells derived from the granulosa and theca cells of the follicle respectively . As corpus luteum function progresses , the large cells degenerate and the small cells become larger , forming practically the entire functional CL during pregnancy . The granulosa cell of the follicle responds to the LH surge at ovulation in a non-reversible fashion . Hence after luteinization , the LH receptors of the

large CL cells are blocked . These cells produce large quantities of progesterone during the early luteal phase , but degenerate since they are unresponsive to LH , and become non-functional by about day 10 of the luteal phase . The theca derived small cells produce small amounts of progesterone in the early luteal phase , but are responsive to LH stimulation , grow and are ready to assume the major secretion of progesterone in conception cycles . Lee (1987) suggests that luteal phase inadequacy is caused by a deficiency in the response of granulosa cells to the LH surge . The entire progesterone production of the CL is then the responsibility of the small cells - resulting in a physiological shortfall . This theory is however untested .

The short luteal phase is a similar enigma . Smith , Lenton & Cooke (1983) have shown that short luteal phase cycles have higher progesterone levels at menstrual onset than control cycles , this finding being true in both adequate and inadequate luteal phase cycles . This suggests that mechanisms which initiate menstrual bleeding may be different in short luteal phase cycles rather than any follicular or corpus luteum defect . Other studies have suggested that prolactin levels may be involved in short luteal phase cycles . Corenblum , Pairaudeau & Shewchuk (1976) observed short luteal phases in women with galactorrhea , an expression of excess prolactin levels. After bromocriptine therapy , both prolactin levels and luteal phase length normalized . Seppala , Hirvonen & Ranta (1976) also found short luteal phases in women with elevated prolactin levels who later became galactorrheic and amenorrheic . Elevated prolactin levels are often seen in runners and athletes after exercise (e.g. Russell , Mitchell , Musey & Collins 1984 ; Cumming & Rebar 1985) . This effect may be related to the type and amount of exercise undertaken as well as subjective fitness beforehand (Howlett 1987) , and does not seem to cause sustained hyperprolactinaemia (Shangold 1985) . However , luteal phase defects , and especially short luteal phase are common amongst athletes (Prior 1985) . Defective and short luteal phases are also seen in the gradual resumption of fertility post-partum , another occasion in which prolactin may be active (Howie ,McNeilly , Houston , Cook & Boyle 1982 b) . Little solid evidence exists however linking prolactin with the short luteal phase , and both would appear to be able to exist independently as for instance in the perimenopause when short luteal phase cycles are common but there is little

evidence of hyperprolactinaemia . A deficiency in the ovarian or hypothalamo-pituitary response to normal prolactin levels cannot of course be ruled out , neither can the possibility of a third factor causing changes in both luteal function and prolactin levels . The mechanism by which prolactin might produce the short luteal phase is as yet unknown .

Although little is known about the endocrinology , aetiology or implications for fertility of the deficient luteal phase cycle , it can be said that they tend to occur under similar conditions to anovulatory cycles . Inadequate luteal phases also appear to be consistent within women . The assumption has been that this correlation of incidence implies a common aetiology i.e. partial suppresion of the hypothalamo-pituitary-gonadal axis , however endocrinological studies have not consistently supported this hypothesis . The problems of definition and diagnosis of both short and inadequate luteal phases and the frequent confounding of these two variables leads to confusion in the interpretation of endocrinological data . Whether the short and inadequate luteal phase have the same or diverse aetiologies is unknown , and will remain so until studies are more specific about the type of defects observed in any particular group .

2.4 ARTIFICIAL DISRUPTION OF THE OVULATORY CYCLE

In section 2.3 a variety of " natural " events were seen to disrupt the normal female reproductive cycle . A similar number of pharmacological interventions can also cause disruption , either deliberately or inadvertently , to a greater or lesser extent . The most common and reliable deliberate intervention is the oral contraceptive . The history of the development of the modern oral contraceptive (oc) has been thoroughly reviewed elsewhere (e.g. Drill 1966 ; Greenblatt 1980) . They have become one of the most widely used drug groups in Western society , the subject of much controversy about their ethical and long-term medical significance .

The effects of oral contraceptives on a varietry of physiological systems have been extensively studied (see Greenblatt 1980) , however their precise effects on the reproductive axis , especially in the case of the newer "low-dose " oc's are perhaps less well characterized . The overall mechanism of action of oral contraceptives, and the potential residual activity of the ovary despite this , are the subjects of this section .

2.4.1 ORAL CONTRACEPTIVES AND THEIR MECHANISM OF ACTION

Two major classes of oral contraceptives are currently available in this country - the combined oral contraceptives , containing an oestrogen and a progestagen , and the progestagen -only contraceptives (British National Formulary 1987) . A subgroup of combined oc's is also available containing a phased formulation of oestrogen and progestagen , designed to mimic the natural hormonal cycle . The combined oc's are usually administered on a " twenty-one day on - seven day off " schedule , a withdrawal bleed occuring during the pill free week to mimic normal menstruation . The progestagen only pills are administered continuously , and bleeding patterns are usually erratic.

Several varieties of combined oral contraceptives exist , containing different doses of synthetic oestrogens and progestagens . The synthetic oestrogens most commonly used are mestranol (ME) and ethinyloestradiol (EE). These compounds have similar oestrogenic effects , although mestranol is metabolized to ethinyloestradiol before it becomes active . A wider variety of progestagens are used at different doses (Table 2.1) . These compounds differ both in their progestational effects and in the degree to which they are oestrogenic and / or androgenic . For instance , the progestagen used in Enovid™ , the first oc , norethynodrel, is slightly oestrogenic but not androgenic , whereas norethindrone used in Ortho-Novum 10 ™ was slightly androgenic but not oestrogenic (Drill 1966) . Some progestagens are highly anti-oestrogenic , for instance norgestrel, one of the most widely used modern progestagens (Upton 1980) .

The mechanism of action of all combined preparations is essentially similar . They were originally thought to act directly on the pituitary gland to inhibit LH and FSH release , utilizing the negative feedback effects of ovarian steroids (Drill 1966) . Recent evidence has suggested that they may also be active at the hypothalamic level , suppressing GnRH release (Mishell,Kletzky, Brenner,Roy & Nicoloff 1977 ; Fraser & Jansen 1983) . However , the relative amounts of hypothalamic and pituitary suppression may be variable , both between individuals and between dose regimen . The varying doses of steroids in the phased oc's do not imply a differential mode of action , but only an attempt to provide the reproductive system with a more " realistic " hormonal milieu .

The progestagen - only pill (P-O-P) utilizes the negative feedback effects of progesterone on the hypothalamus and pituitary to suppress ovarian activity . However , without the synergistic actions of oestrogen , the degree of ovarian suppression is incomplete and unpredictable (Landgren & Diczfalusy 1974 ; Elstein, Briston,Hewitt,Kirk & Miller 1976) . Peripheral effects of progestagens on cervical mucus , endometrium and possibly tubal function are therefore likely to play a large part in the contraceptive efficacy of these drugs (Fraser & Jansen 1983) .

Mishell (1982) has pointed out that the oral contraceptives have many other physiological functions than the disruption of ovulation . Those progestagens with anti-oestrogenic actions may reduce the proliferative effects of oestrogen on the endometrium and breast tissue . Hence , lighter menstrual bleeding and reduced levels of benign breast disease can be beneficial side-effects of oc use . Effects on carbohydrate metabolism , liver function , blood pressure, plasma lipid levels and tendencies to blood clotting have also been observed (Greenblatt 1980) . This latter aspect has received much attention in the lay press after reports of increased risks of thromboembolic disease and myocardial infarction amongst pill users (Vessey, McPherson & Johnson 1977) . Use of the pill has also been linked with the development of various types of cancer , for instance endometrial cancer (Silverberg & Makowski 1975) , however incidence rates of other types of cancer , e.g. ovarian cancer have revealed protective effects of oc use (Casagrande,Pike, Ross,Louie,Roy & Henderson 1979) .

Hence , the oral contraceptives , and particularly the combined oral contraceptives , are widely used and widely studied inhibitors of ovulation and / or reproductive function .

2.4.2 RESIDUAL OVARIAN ACTIVITY IN COMBINED ORAL CONTRACEPTIVE USERS

Worries about the long term effects of oral contraceptive administration , particularly with respect to oestrogen levels , have led to reductions in the dosages of both oestrogen and progestagen and the introduction of formulations phased to mimic the normal menstrual cycle . The new " low-dose " brands of oc are defined on the basis of their oestrogen content i.e. $\leq$ 35 μg per tablet . This introduces the possibility that suppression of the hypothalamo- pituitary-ovarian axis is incomplete in users of these brands .

Since the subject of this thesis is the relationship between cyclical mood changes and ovarian steroid levels , and a large part of the experimental data is concerned with users of low-dose oc's , an understanding of the hormonal fluctuations experienced by such users is essential to the interpretation of later results .

Two main areas of query arise here :- Firstly - what are the endocrinologic sequelae of the pill free week (pfw) ? - and secondly - how much ovarian activity is present during the period of pill ingestion ?

The placebo or pill free week was introduced when oc's were first marketed since it was thought that the total absence of menstruation would be unacceptable , to reduce the possibility of troublesome " breakthrough bleeding" and to guard against potentially deleterious endometrial side-effects (Drill 1966). The current data on endocrine activity during the pfw has been amply reviewed elsewhere (Fraser & Jansen 1983 ; Guillebaud 1986) . Follicular development can occur during the pfw in users of low-dose pills such as Microgynon™ or Trinordiol™ (Molloy, Coulson,Lee & Watters 1985) - with atresia of the follicles occuring by the seventh day of pill taking . Guillebaud (1986) cites a study of 120 women scanned ultrasonically on the seventh day of the pfw . 23 % of them had follicles greater than 10mm in diameter , suggestive of substantial follicular development . It would appear that a significant rise in FSH occurs during the pfw , followed by a small but significant rise in oestradiol , suggestive of follicular growth (Fraser & Jansen 1983) . A dose dependent effect of oestrogen would seem to be involved . Dericks-Tan,Krog,Akteries & Taubert (1976) found that pituitary suppression to a 50μg ethinyloestradiol based oc lasted up to two weeks after discontinuance , the length of this suppression being greatly reduced for the lower dose pills and non-existent for the progestagen only brands .

The amount of follicular activity and hypothalamo-pituitary suppression during the course of the low dose oral contraceptives has been studied in several ways . Firstly , indices of ovulation and corpus luteum activity have been assessed e.g.cervical mucus changes , basal body temperature and luteal phase plasma progesterone levels . Secondly - assessments of the relative involvement of pituitary and hypothalamic factors in gonadal supperession have been measured by pituitary stimulation tests . Thirdly - measures of ovarian and follicular activity have been made using

ultrasound, and fourthly - measures of peripheral plasma or urinary gonadotrophin and steroid levels have been made to assess follicular endocrine function . Several factors have led to confusion in the literature about the levels of residual ovarian activity in low-dose oc users :-

1) The variety of synthetic oestrogens and progestagens used in contraceptive formulations , whilst all being effective in terms of ovulation inhibition , also all have differing potencies and , in the case of progestagens, oestrogenic or androgenic properties .

2) The absolute dose of oestrogen and progestagen varies even within the " low-dose " category . Perhaps more importantly , the ratio of E to P varies between brands .

3) Individual differences in the absorption rates of and sensitivity to exogeneous hormones .

4) The length of time the particular oc has been in use

5) Technical differences in the administration of the pituitary stimulation test .

6) The absence of a suitable control group or baseline measurement in many studies .

Hence , some studies suggest that there is no ovarian activity during low-dose oc use (e.g. Elstein,Morris,Groom,Jenner, Scarisbrick & Cameron 1976; Schneider,Spona & Matt 1974 ; Colau et al 1983) whilst others suggest that there is (e.g. Dericks-Tan,Krog,Akteries & Taubert 1976 ; Spellacy,Kalra, Buhi & Birk 1980 ; VanderVange,Bruinse,Tweel,Coelingh-Benink & Haspels 1985) and still others show individual variation in response (e.g. Scott,Kletzky, Brenner & Mishell 1978 ; Spona,Schneider & Lachnit-Fixson 1980)

Few studies have yet been undertaken of the biphasic and triphasic oral contraceptives . These drugs were formulated with the objective of lower overall oestrogen levels and more naturalistic cycle control (Greenblatt 1980; Upton 1980) . Their efficacy in terms of ovulation inhibition , subject tolerance and compliance , and side effects is comparable with that of the low dosed monophasic oc's (Spona, Schneider & Lachnit-Fixson 1980 ; Woutersz, Butler, Cohen,Korba & Canavan 1987) . A recent study by Smith,Kirkman, Arce, McNeilly,Loudon & Baird (1986) suggests that follicular activity is maintained ar a greater level in triphasic pill users than in monophasic pill users , and that ovarian activity is restored more quickly

after triphasic use . However , only the first treatment cycle was considered in this study . The question of whether long term triphasic users experience cyclical follicular activity to a greater extent than comparable monophasic users remains unanswered . The possibility remains , as mentioned above , that a subgroup of women exist whose reproductive axes are less adequately suppressed by low-dose oc's than the majority in terms of follicular activity , although they do not ovulate .

In conclusion it can be said that , all of the currently available combined oral contraceptives suppress ovulation by disrupting the hypothalamo-pituitary axis . Hence , no user of these drugs will experience a true luteal phase in terms of corpus luteum formation and endogeneous progesterone secretion . The degree of follicular activity experienced may however be variable , both during the pill free week and the duration of pill administration.

2.5 SUMMARY

The female reproductive cycle is controlled by a complex and sensitive sequence of endocrinological events . The hypothalamus , pituitary and ovary communicate their respective physiological statuses one to another by means of the hormones GnRH , LH , FSH , Oestrogen and Progesterone . The potential roles of other hormones such as prolactin or inhibin are little understood in this context . This system can suffer disruption at any one of the three control levels , evidenced by menstrual and ovulatory disturbance . Deliberate disruption can also occur , having the beneficial contraceptive effect of reliably suppressing ovulation . However , the precise endocrine and physiological parameters of either type of disruption are poorly understood . As Short (1977) said - " Although much is known , much still remains to be discovered ; and much of what has already been discovered needs to be uncovered ."

CHAPTER THREE
THE RELATIONSHIP BETWEEN PREMENSTRUAL SYMPTOMS AND THE OVARIAN CYCLE

3.1 INTRODUCTION

In the previous chapters , the two components of this thesis have been discussed independently . In this section , an attempt will be made to draw them together and assess the interaction between them .

The causal nature of the correlation between premenstrual symptoms and the ovarian cycle has been an inherent assumption throughout PMS research. Aetiological theories take the temporal features of the menstrual cycle to be causally meaningful even if a role for the ovarian hormones *per se* is rejected . The problems of empirical research in both fields of human female endocrinology and psychology have resulted in very few attempts to elucidate the nature of the link between them.

The first step in most physiological studies would be to establish an animal model for the syndrome under investigation . As yet , however , no appropriate *in vitro* or animal system has even been hinted at in this field . The possibility that some apes i.e. free living Yellow Baboons (*Papio cynocephalus*) experience perimenstrual changes in behaviour has however been observed (Hausfater & Skoblick 1985) , and further investigations of this may be informative . For the most part however , research into PMS and the ovarian cycle is restricted to *in vivo* studies on humans , with all the attendant problems of interpretation and validation .

Three major approaches have been used to a greater or lesser extent in the investigation of the PMS / ovarian hormones relationship .

1) The observation of the ovarian cycles of PMS sufferers and the comparison of such to menstrual cycles in asymptomatic women.

2) The observation of hormonally unusual menstrual cycles and the assessment of such for PMS symptoms .

3) The observation of artificially disrupted menstrual cycles either to assess the prevalence of PMS or to assess the efficacy of the intervention in the alleviation or exacerbation of premenstrual symptoms .

Since PMS is now a recognised clinical condition , the major purpose of research is not only to find a cause but , perhaps more emphatically , to effect a cure . Hence the most popular avenue of research involves the administration of various hormonal preparations either with the object of abolishing endogeneous hormonal fluctuations, or of supplementing some supposed hormonal deficiency. As will be seen later , this may not be the

most fruitful approach to the aetiology of PMS from a theoretical point of view .

The recent literature pertaining to the relationship between PMS and the ovarian cycle will be discussed according to these three major approaches . The outline of the research pursued in this thesis project will then be outlined .

3.2 HORMONAL PROFILES OF WOMEN WITH PMS

The relationship between ovarian steroids and PMS can be examined in two ways by a consideration of the endocrinology of the PMS sufferer . Firstly - a detailed study can be made of the temporal relationship between premenstrual symptoms and hormonal events in an attempt to elucidate potential trigger mechanisms or consistent pattern correlations . Secondly - endocrinological comparisons can be made between women diagnosed as suffering from PMS and those who don't . Some endocrinological studies have employed both of these methodologies , however for the sake of clarity, they will be considered seperately .

3.2.1 THE TEMPORAL RELATIONSHIP BETWEEN PMS AND OVARIAN HORMONES

The crude relationship between PMS and the ovarian cycle has long been established , i.e. the symptoms tend to occur in the second half , or luteal phase , of the cycle . However the finer details of this relationship remain elusive . Few reported studies have assessed psychological and hormonal parameters at sufficiently frequent intervals to allow conclusions to be drawn . One of the earliest studies to attempt to relate "psychodynamic processes " with ovarian activity was that of Benedek and Rubenstein (1939) . Although the patients in this study were not strictly diagnosed as PMS sufferers , they were under treatment for " various neurotic disturbances " , some of them show classic PMS symptoms in the premenstruum ; e.g. craving for sweets (Case R.E.) , depression and insomnia (Case R.R.) , anger, disorientation and hostility (Case X) ; which are absent in the postmenstrual phase . These women were studied by daily psychoanalytic sessions and vaginal smears . Although a clear cyclic pattern is demonstrated , and the authors assert strong correlations

between psychological processes and hormonal state , it must be said that their estimates of hormonal milieu were insensitive by current standards .

More recent studies have used plasma or urinary measures of hormone secretion or excretion . Ablanalp,Donnelly,Rose & Livingston-Vaughan (1979) studied fourteen " psychologically healthy " women by means of daily questionnaires and thrice weekly blood sampling . No correlation was found between oestradiol or progesterone levels and mood states. However, none of these women were diagnosed as having PMS .

A study of daily measures of mood and ovarian hormones in women with PMS is reported by Backstrom,Sanders, Leask, Davidson,Warner & Bancroft (1983) . Maximum levels of depression and irritability were found to occur during the last five premenstrual days and to decrease rapidly during menses. The symptoms began to increase 2 or 3 days after the LH surge , and continued to increase up to menstruation , even after oestradiol and progesterone levels had fallen . Similar temporal relationships were shown for symptoms of swelling and breast tenderness . Positive moods followed the opposite pattern , peaking at the time of the preovulatory oesrtradiol peak . Hence , the premenstrual symptoms were seen to be closely related to the premenstrual phase but not directly to absolute oestrogen or progesterone levels (Bancroft & Backstrom 1985) .

Halbriech,Endicott,Goldstein & Nee (1986) studied the temporal relationship between plasma steroid levels and mood changes in 17 PMS sufferers . In this study , a time-lag of 4 - 7 days was found between changes in progesterone levels and changes in clinical features , suggesting a delayed or priming action of gonadal hormones on some brain mechanism . Variability was observed between subjects however , with some women starting to show clinical changes as progesterone levels begin to increase , before the peak , whilst others showed changes only after the progesterone peak . Most women had their most severe symptoms immediately before menses .

These studies reinforce the observations that premenstrual symptoms are related to that part of the cycle in which progesterone is present . However , they do not appear to be related to either progesterone or oestradiol levels on a day-to-day basis . The possibility of a time-lag between hormone levels and symptom manifestation has been suggested but requires further investigation.

3.2.2 ENDOCRINOLOGICAL COMPARISONS BETWEEN WOMEN WITH AND WITHOUT PMS

Several studies have now been undertaken in this area . All of them involve the identification of women with , or without , premenstrual symptoms, and regular monitoring of ovarian hormone levels . However , both of these procedures are open to methodological problems . Firstly - no standard definition of , or diagnostic procedure for , PMS yet exists . Hence , the inclusion criteria, both for the PMS group and the control group vary between studies . In some cases , high and low levels of symptomatology are identified on the basis of prospective assessments and compared endocrinologically (e.g. Backstrom et al 1983 ; Watts,Butt & Logan-Edwards 1985) . Other studies identify symptomatic and asymptomatic women in a similar manner , but with no measure of the degree of symptom experience (e.g. O'Brien,Selby & Symonds 1980) . Still others diagnose PMS on the basis of clinical interviews - involving essentially retrospective reporting (e.g. Andersch,Abrahamsson, Wendestam,Ohman & Hahn 1979) .Whilst it is probably true to say that some subjects would be identified as symptomatic or otherwise by any procedure , others may not . Hence comparability across studies is reduced . Another important issue here is the use of an appropriate control group . At present the mechanisms of PMS are not identified . If the syndrome is caused at all levels of severity by the same hormonal abnormality , then the use of a control group who experience low levels of symptoms would not be meaningful .

Secondly - recent evidence suggests that ovarian hormones show diurnal variations in secretion rate (Younglai, Smith,Cleghorn & Streiner 1975) and that progesterone particularly is secreted in a pulsatile fashion (Steele, Braund & Judd 1986) . This raises two issues . Firstly - as Reid (1985) has pointed out , diurnal variations in plasma hormone levels invalidate to a large extent studies utilizing an infrequent plasma sampling schedule , or failing to standardise collection times across subjects . Any differences which occur with standardized collection times may be due to a shift in the circadian rhythm of steroid secretion in PMS sufferers (or non - sufferers !) rather than a difference in the absolute levels of oestrogen or progesterone . Secondly - the physiological significance of progesterone pulsatility is not yet understood . It is conceivable that women with PMS may

exhibit a different pulse profile to women without PMS - in terms of pulse frequency , amplitude etc. These factors will be obscured if only single samples are considered , but may result in spurious differences between groups in terms of absolute hormone levels . Research into the actions of progesterone on tissues such as the uterus , suggests that adequate oestrogen priming is necessary before progesterone can be effective (e.g. Baird 1984) . This possibility has been neglected in PMS research . Few studies have assessed follicular hormone levels with any degree of regularity .

Hindsight indicates that the variability occuring between studies of PMS endocrinology may be explicable . Several studies have failed to demonstrate any consistent differences between symptomatic and asymptomatic women (e.g. Andersch et al 1979 ; Taylor 1979 ; Backstrom et al 1983) . Other studies have suggested differences between groups at specific points in the luteal phase . For instance , higher progesterone levels have been found in the immediate postovulatory phase in symptomatic women (O'Brien, Selby & Symonds (1980); Watts, Butt & Logan-Edwards 1985). However , Munday,Brush & Taylor (1981) demonstrated lower progesterone levels in the early to mid luteal phase in their series of PMS sufferers . Several studies have suggested that late luteal phase oestrogen levels may be elevated in PMS (Backstrom & Carstensen 1974 ; Backstrom , Wide,Sodergard & Carstensen 1976 ; Taylor 1979 ; Munday, Brush & Taylor 1981) . In some studies an increase in the oestrogen / progesterone ratio has been implicated (Backstrom et al 1976 ; Munday et al 1981) , whilst others have failed to substantiate this finding (Taylor 1979; Sanders 1981). Halbriech,Endicott, Goldstein & Nee (1986) have suggested that the rate of change of gonadal hormones is a key factor in the differentiation of women with or without PMS . Women with clinical PMS had differential rates of decrease of oestrogen and progesterone in the late luteal phase , whereas non-sufferers showed parallel curves . This data however only represents 6 sufferers and 3 non-sufferers and hence can only be treated as anecdotal .

Watts , Butt & Logan - Edwards (1985) in a careful study utilizing both endocrine assessments and ultrasonic visualization of developing follicles, found that a subgroup of PMS sufferers showed evidence of early ovulation (i.e. more than 14 days before menstruation) . These women also showed

an earlier progesterone rise than control women , possibly due to the earlier ovulation . This pattern occured in 18 of 35 women with PMS compared to only 2 out of 11 controls . The two groups were indistinguishable on the basis of overall cycle length . Ultrasound scanning of follicular growth suggested that follicles were smaller throughout the preovulatory phase in PMS patients and consequently , follicle diameters were significantly lower at the time of ovulation . Oestradiol concentrations were also lower in the PMS group correlating with follicle diameter . Hence , they suggest that PMS is associated with premature ovulation and an elongated luteal phase , but no apparent abnormality in steroid production during the luteal phase . Backstrom,Smith,Lothian & Baird (1985) studied the follicular phase in PMS and control patients after hysterectomy and corpus lute-ectomy . The rise in FSH following enucleation of the corpus luteum was delayed in the PMS group resulting in a significantly longer time to ovulation (21 days compared to 19 days) . Once FSH had begun to rise , the follicular phases were indistinguishable between the two groups in terms of oestradiol , although serum FSH levels were lower in the late follicular phase in PMS patients . No information is given about the level of symptomatology experienced by the women ion these cycles . The authors suggest that these results imply a more sensitive " feedback " in PMS patients i.e. the hypothalamus and pituitary are more sensitive to normal levels of oestradiol.

The literature in this field is confused due to the current paucity of knowledge about endocrinological normality and the nature of PMS . The normal menstrual cycle and the actions of ovarian hormones are still subjects of controversy . Hence , an attempt to associate mood changes with ovarian activity in this manner is inevitably inconclusive . No evidence has been found to link PMS with an overall luteal progesterone deficit , although finer measures of corpus luteum dysfunction have not been assessed . The temporal link with the latter part of the menstrual cycle suggests an involvement for some factor associated with corpus luteum function , possibly independently of either oestrogen or progesterone , or alternatively some follicular deficit which is not apparent endocrinologically in the luteal phase .

3.3 PMS AND THE ABNORMAL MENSTRUAL CYCLE

Abnormal menstrual cycles , in terms of anovulation or suboptimal luteal function , tend to occur at either end of the reproductive lifespan and after some hormonal disruption e.g. pregnancy and lactation , oral contraceptive use , physical and emotional stress etc . (see Section 2.3) . If PMS is associated with an endocrine abnormality , then a high prevalence of the problem might be expected to occur amongst women who are experiencing hormonally unusual cycles . As yet , little research has centred upon this aspect of PMS .

Studies of the menopausal transition and the post-partum phase have largely been concerned with psychiatric morbidity . In the first case , the relationships between diminishing ovarian activity and the " climacteric syndrome " , in the latter case the phenomenon of post-partum depression (e.g. Ballinger 1975 , 1976 ; Nott,Franklin,Armitage & Gelder 1976 ; Steiner 1979; Greene & Cooke 1980 etc.) . Some authors have suggested that a history of post partum depression may be associated with the later appearance of premenstrual symptoms (Nott et al 1976 ; Dalton 1984) , however there is little prospective evidence to support this assertion . Adolescence is also an under researched phase of development from this point of view . Although the hormonal profiles characteristic of puberty are gradually being described , no attempts have yet been made to correlate adolescent moodiness with ovarian cyclicity (Hays 1978). Another time of "raging hormones " in women is pregnancy . Few studies have been made of mood changes during pregnancy , a time of relative excess rather than deficiency . Kyger & Webb (1972) compared scores on various psychological tests from groups of women assessed during normal menses, at the time of the normal cycle progesterone peak , during oral contraceptive therapy or in the third trimester of pregnancy . The hypothesis being that these times of differing progesterone levels should reveal different psychological states. Of the 57 variables analyzed , only two varied significantly between the groups , suggesting increasing emotional vulnerability with increasing progesterone levels . However , the probability of these results occuring by chance in such a large test battery is high .

Several researchers have commented on the presence of premenstrual symptoms in anovulatory cycles (Adamopoulos,Loraine, Lunn,Coppen &

Daly 1972 ; Andersen,Larsen,Steenstrup,Svendstrup & Nielsen 1977) or the lack of symptomatic differences between ovulatory and anovulatory cycles in different women (Persky,O'Brien & Kahn 1976) . Backstrom et al (1983) , however failed to find any cyclical mood changes in five anovular cycles , although significant increases in breast tenderness and body swelling were noted premenstrually . However , these women werenot diagnosed as PMS sufferers . Magyar,Boyers,Marshall & Abraham (1979) suggest that regular menstrual cycles coupled with premenstrual molimina can be considered to be indicative of ovulation . However , all their measures of PMS were retrospective , their subjects were aged between 20 and 40 years , and therefore likely to be ovulating regularly , and they make no comment about the presence or absence of symptoms in the cycles studied . The findings then are probably due to the age group studied and the high prevalence of PMS when assessed by retrospective questionnaire. One subject in this series did experience anovulatory cycles , despite a past history of regular menses and PMS . No comment is made on whether or not these cycles were symptomatic . No evidence is yet available comparing ovulatory and anovulatory cycles within the same subject , although such data is likely to be informative .

The co-presence of PMS and luteal phase defects was the subject of a recent study by Ying,Soto-Albors, Randolph, Walters & Riddick (1987) . In a study of 83 infertile patients , they assessed luteal phase adequacy by endometrial biopsy and PMS by a retrospective questionnaire of symptoms and moods in the previous 24 hours . Both assessments were made on day 12 of the luteal phase . Their results suggest a lack of correlation between luteal phase abnormalities and somatic premenstrual symptoms . However , less severe psychological symptoms were observed in women with abnormal luteal phases . Hence they suggest that PMS is unlikely to be associated with suboptimal luteal function . The lack of prospective and frequent data in this study , however , reduces its conclusiveness .

As yet , little more than circumstantial evidence links PMS with abnormalities of the menstrual cycle . Although times of hormonal change are traditionally associated with a higher incidence of psychological problems , no data has been reported to link PMS with such life events . The effects of pregnancy , lactation , and the perimenopause on the PMS sufferer have not been documented .

3.4 PMS AND THE MANIPULATION OF THE HORMONAL ENVIRONMENT

The third major source of information about the relationship between PMS and the ovarian steroids derives from studies of the effects of hormone administration and / or menstrual cycle manipulation . These studies can be divided into four categories based on broad aetiological notions of PMS :-

1) Disruption of the menstrual cycle with conservation of the ovarian cycle . These studies assess the relative contribution of menses *per se* to cyclical changes in mood and physical symptoms .

2) Suppression of the ovarian cycle . In these studies endogeneous cyclical changes in all ovarian hormones are suppressed due to interference at the hypothalamic or pituitary levels .

3) Supplementation of hormones in the luteal phase . These studies assume a physiological deficit of luteal hormones i.e. progesterone , and attempt to remedy the deficiency by exogeneous administration .

4) Suppression of the ovarian cycle with selective hormonal supplementation . In these studies , the precise hormonal milieu is manipulated to produce PMS like symptoms .

These four approaches will be considered in turn .

3.4.1 DISRUPTION OF THE MENSTRUAL CYCLE

These studies assess the effect of hysterectomy , removal of the uterus , on the manifestation of PMS . Since the ovaries may be conserved , the ovarian cycle remains intact . However , the temporal marker of menstruation is removed as are any biochemical factors deriving from the uterus . The psychosocial and emotional effects of non-cancer hysterectomies have been extensively studied and reviewed elsewhere (Dennerstein & Ryan 1982; Kav-venaki & Zakham 1983; Wijma 1984) . However few studies have assessed the effects of hysterectomy on cyclical symptoms. In a prospective study of 7 hysterectomized patients who showed ovulatory cycles on the basis of thrice weekly plasma assessments, small fluctuations in psychological and physical symptomatology were found (Beumont,Richards & Gelder 1975) . These differences were not significant although premenstrual symptom peaks were seen . The authors give no information about the previous premenstrual history of their

hysterectomized women and conclude that the presence of premenstrual symptoms in normally menstruating women is due , at least in part , to the woman's awareness of her position in the menstrual cycle .

In a similar study of women with PMS before and after hysterectomy , Backstrom,Boyle & Baird (1981) demonstrated that cyclical mood changes persist in the late luteal phase , although the symptoms were slightly but significantly improved . Hence , they assert that PMS can occur in the absence both of menstruation and of the uterus . The improvement in symptoms may be due to the removal of troublesome menstrual bleeding , the reason for the operation , leading to a better overall state of health ; the removal of the ' zeitgeber ' , menstruation ; a placebo effect of the operation or the removal of some aetiological uterine factor . The women in this study were monotored in the immediate post-operative period . It would be interesting to study a group of women longitudinally as adaptation to the operation occured - the possibility that "phantom " menstruation i.e. " this is the time when my period used to occur " , can still have a zeitgeber effect is not considered . The authors of this paper argue that their data support the view of a hormonal aetiology of PMS . A more appropriate demonstration of this might be a comparison of PMS sufferers who undergo either :- hysterectomy with bilateral oophorectomy ; hysterectomy alone ; a non-gynaecological abdominal operation (e.g. gall bladder removal) or nothing at all in the same age groups . The relative effects of ovarian hormones , menstruation , the potential placebo effect of the operation and time itself might then be elucidated .

3.2 SUPPRESSION OF THE OVARIAN CYCLE

Studies of medical ovarian suppression can themselves be divided into two categories according to the type of drug used :-

a) Those drugs which temporarily abolish ovarian activity without the addition of steroids ; and

b) Those drugs which manipulate the ovarian cycle via the steroidal feedback pathways .

In the first category , two drugs have been used - Danazol and GnRH agonist. Danazol is an isoxazole derivative of 17- ethinyl testosterone , and is a powerful antigonadotrophic agent , probably acting at the hypothalamic level (Asch, Fernandez,Smith,Siler-Khodr & Pauerstein 1979) . The

GnRH agonist , administered by injection , subcutaneous implant or nasal spray , acts by down regulation of pituitary gonadotrophin secretion , thereby producing a " medical ovariectomy " . In the second category fall the oral contraceptives . These drugs act by maintaining the negative feedback inhibition of gonadotrophin release and blocking the positive feedback effects of high oestrogen levels (see Section 2.4) . However , exogeneously administered synthetic steroids are present throughout the cycle

3.4.2 a) Ovarian Suppression Without Exogeneous Steroids

Several studies have now been conducted to assess the therapeutic efficacy of danazol for PMS . Day (1979) found a good response in patients with severe PMS , particularly if the main symptom was breast tenderness . However a high incidence of side effects was observed , especially weight gain , nausea and abdominal distension . Similar good effects were found by McKay-Hart , Hawthorn & Gilmore (1985) in a double blind placebo controlled crossover trial of danazol in patients who had previously been unsuccessfully treated with other drugs . In this study only 3 women withdrew due to side effects . Watts,Butt & Logan Edwards (1987) have also found positive benefits of danazol for breast symptoms and for irritability , anxiety and lethargy by the third month of a double blind trial . Although this trial assessed the effects of different doses of the drug , the high dropout rate disallowed a dose response comparison . Hence it would seem that danazol can reduce some symptoms and in particular breast symptoms . The lack of endocrine assessment in these studies however makes interpretation of the results difficult . The level of ovarian suppression may be variable between women , resulting in differential symptom responses . No temporal relationships been symptoms and danazol suppressed endocrine states have yet been reported .

The use of GnRH analogues is a very recent advance in endocrinology research . The first published study of their use in PMS was by Muse,Cetel, Futterman & Yen (1984) , although they have found practical applications in other clinical conditions e.g. precocious puberty , hormone dependent tumours etc (Sandow 1983) . In the Muse et al study ,daily self administered subcutaneous injections of 50 μg of GnRH agonist were used. The trial was completed in a double blind crossover manner , using a placebo, over six months , although only 8 patients were studied . All

symptoms , both behavioural and physical were significantly improved compared to placebo , and this improvement was coincident with ovarian suppression in all cases . Studies with the LHRH nasal spray , buserilin , have shown less clear cut results (Bancroft,Boyle,Davidson,Gray & Fraser 1984 ; Bancroft,Boyle & Fraser 1986 ; Bancroft,Boyle,Warner & Fraser 1987). These studies assessed responses to the drug in a non-blind , exploratory , clinical fashion . The treatment consistently resulted in an effect on PMS , however this effect was not always a suppression of premenstrual symptoms . In all cases , an initial stimulatory phase of the drug is evident , producing aggravation of premenstrual symptoms if it is begun in the luteal phase , and precipitating symptoms in the normally asymptomatic follicular phase , in the absence of corpus luteum activity . In some cases , these symptoms became persistent , whilst in others they subsided and remained at low levels throughout treatment . The control of ovarian cyclicity was also variable. Although ovulation was consistently suppressed , follicular development was not . In some cases menstruation continued to occur during treatment , and these women also continued to show mild physical symptoms premenstrually although no changes in mood . In all cases mood symptoms lost their relationship to menstruation .These problems are important from the therapeutic point of view, possibly reflecting individual differences in absorption rates or sensitivity to the drugs . However , from the theoretical point of view , studies with the GnRH agonist demonstrate a link between mood states and the hypothalamo-pituitary- ovarian axis . Bancroft et al (1984) argue that these effects cannot be due simply to the removal of ovarian steroids , since symptoms were induced by the agonist in the absence of luteal activity , although the presence of superphysiological oestrogen levels . The possibility also arises that the physical and psychological aspects of PMS are dependent on different hormonal mechanisms .

Altogether , the use of danazol and GnRH agonists have suggested that PMS symptoms can be improved , induced or disrupted by the removal of ovarian steroids . The question of whether this effect is due to the absence of oestrogen and progesterone , the disruption of the HPO axis or some other , unrelated , action of the drugs themselves is uncertain . Unfortunately, these drugs are not without problems of administration or side effects . The possibility of variance in optimal dose regimes for ovarian

suppression between women also clouds the issue . Bancroft & Backstrom (1985) suggest that mood states in PMS are related to the " ovarian clock " rather than specific ovarian factors . Hence disruption of the clock would lead to disruption of the mood rhythm . This theory could account for the variability seen in these studies . Further studies are needed with both of these drugs to assess their precise effects on gonadotrophin and ovarian steroid levels and the temporal relationship with sensitive symptom measures . The possibility of diverse effects between symptoms has not been assessed .

3.4.2 b) Ovarian Suppression With Exogeneous Steroids

Ovarian suppression by administration of exogeneous steroids is commonly achieved in Western society by use of theoral contraceptive pill (oc) . These drugs have been extensively reformulated in recent years , leading to vast differences in the dosages of steroids used in early studies compared to recent research . Depression and loss of libido have often been cited as side effects of oc's , suggesting a relationship between steroid levels and mood . However , studies of oc effects are notoriously badly designed and open to a variety of alternative interpretations (see Glick & Bennet 1982) . Studies specifically assessing the effects of oc's on PMS are few and far between . They can , however be divided into two categories , those studies which assess the changes in PMS in women starting oc's , and those studies which compare symptoms in established pill users with non users .

The majority of PMS studies fall into the former category , and include PMS as one of the potential side effects of , or parameters which may change with , oc use . The means of assessment used in these studies is usually a retrospective questionnaire administered before , and at various points during , oc use . In this way the prevalence of premenstrual depression and irritability has been shown to decrease with oc use (Nilsson & Solvell 1967 ; Grant & Pryse-Davis 1968 ; Herzberg & Coppen 1970) . However none of these studies used a control group, neither were the effects of oc on the individual assessed . Cullberg (1972) in a double blind placebo controlled crossover trial of several different oestrogen: progestagen combinations showed a non-significant trend towards improved premenstrual irritability with increasing progestagen . He did , however , identify a subgroup of women whose PMS appeared to be

"hormone responsive " , who reacted positively to progestogen dominated medication and negatively to oestrogen dominated pills . The use of monthly retrospective questionnaires in this study , however reduces its sensitivity .

Two studies have assessed the effects of oc's in a prospective fashion (Silbergeld,Brast & Noble 1971 ; Morris & Udry 1972) showing no differences in day to day feelings of well being between pill cycles and placebo cycles . However , both of these studies were short term and neither of them diagnosed subjects as PMS sufferers .

A recent study comparing monophasic and triphasic new pill users (Bancroft, Sanders,Warner & Loudon 1987) found that those women who had PMS before starting the pill were more prone to negative mood changes on the triphasic pill . These changes started in the first half of the cycle when progestagen levels were lowest and continued until the pill free week , suggesting that PMS symptoms are more likely to occur coincidentally with low progestogen levels .

The alternative approach to PMS and oc's is a cross sectional one , comparing established oc users with a control group . Arguably in this way the placebo effects of oc use and the endocrine variability in response over the first few cycles of use are avoided . These studies tend to include large numbers of women receiving varied doses of steroids . Kutner & Brown (1972) used a one-off retrospective questionnaire to assess the prevalence of depression , premenstrual depression and premenstrual irritability amongst 5151 pill users , ex- users and never users . They found that a smaller proportion of pill-users reported premenstrual depression than controls , and that combined pill users had lower rates of premenstrual depression than sequential pill users . The higher the progestogen dose , the less severe the depression . This agrees with Cullberg's (1972) observations (see above) . The major problem with a study of this kind is the " survivor effect " - possibly those women who experienced premenstrual symptoms before starting an oc , were prone to side effects and discontinued it . Hence a disproportionately low prevalence rate amongst pill users . If this were the case , then past pill users might be expected to show a higher rate of premenstrual depression than never users . This hypothesis is substantiated in the Kutner & Brown (1972) study , although no distinction is made between ex-users who discontinued the pill

because of side effects and those who stopped for other reasons e.g. the desire for pregnancy or the ending of a sexual relationship .

Two studies have assessed pill users in a prospective longitudinal fashion. Forrest (1979) studied twelve women using low dose combined oc's (i.e. ≤ 30μg oestrogen) over thirty days . Daily visual analogue ratings were made of mood and anxiety . A steady increase in levels of depression was shown across the pill cycle which fell during the pill free week . This effect was also demonstrated in a cross sectional study by Abramson , Repezynski & Merrill (1976) with respect to self reports of sexual arousal in response to an erotic story. The second longitudinal study is that of Paige (1971) . She compared combined pill users , sequential pill users and controls at four points during the menstrual cycle , using the Gottschalk method of content analysis of speech samples . In this study the control group showed a typical U shaped pattern of negative affect , with premenstrual and menstrual peaks of depression . The combined group showed a much flatter pattern and the sequential group fell partway in between . Total negative affect scores did increase from day 4 to day 16 , although not significantly , in the combination pill users suggesting a similar trend to that seen by Forrest . This may suggest a cumulative effect of oc steroids on psychological states , with relief during the pill free week .

Although both of these studies give some clues about the effects of oc's on mood , neither of them diagnosed the presence or absence of PMS in their subjects either currently , or retrospectively . The available evidence would suggest that women using the combined pill especially , show a different pattern of symptoms from women who are not influenced by exogeneous steroids .

The studies of the effectsof oc's on PMS , or the presence of PMS during oc use , provide only fragmentary data . Two suggestions arise . Firstly - that women with PMS are more likely to become chronically depressed when they start to use an oc , and that this effect is itself more likely with decreasing levels of exogeneous progestogen . This might suggest that women with PMS are more sensitive to ovarian steroid levels , and particularly to low levels of progesterone . This adds weight to the hypothesis that PMS is due to, or coincident with , a physiological deficiency of progesterone (see Section 3.4.3) . The second suggestion is that the pattern of symptoms (i.e. negative affect) in pill users is different from that in

controls , with the possibility of a cumulative effect of oc constituents . No longitudinal assessments have yet been made , however , of women who have PMS before and during oc use , the patterns of symptoms experienced by those women on the pill who feel they have PMS , or the effects of the new lower dosed oc's . Studies of this type are likely to be informative .

3.5 CONCLUSIONS AND OUTLINE OF RESEARCH PROPOSALS

The literature reviewed in both this chapter and its predecessors , reveals many areas of inconsistency and inadequacy in both the basic aspects of research into PMS and the menstrual cycle , and in the quest to elucidate the link between them . That there is a link is still an assumption rather than a proven finding , however more and more evidence is suggesting that the ovarian cycle has some role to play at least in the temporal manifestation of the so called PMS .

Two major approaches to the area have been neglected . Firstly observational studies of temporal links between symptom patterns and hormonal events in normal menstrual cycles and hysterectomized ovarian cycles, and secondly - studies of links between symptom patterns and abnormal menstrual cycles i.e. cycles which are anovulatory or incorporate a luteal phase deficiency . The latter approach forms the theoretical basis for this thesis . The major question arising from this approach being :- Can PMS occur in endocrinologically abnormal cycles ? In order to investigate this question , six sub-questions were formulated allowing a practical approach to the problem .

1) Can PMS symptoms occur in the natural absence of ovulation and / or menstruation ?

2) Can PMS symptoms occur in naturally ovulatory and anovulatory cycles in the same woman ? - and if so , are they similar in type , intensity , timing of onset or duration ?

3) Are PMS symptoms similar or different in totally ovulatory versus totally naturally anovulatory women of the same age group ?

4) Can PMS symptoms occur in artificially anovulatory cycles ? - and if so are they similar in type , intensity , timing of onset or duration to matched ovulatory cycles ?

5) If PMS symptoms can occur in artificial menstrual cycles , are they related to levels of exogeneous hormones ?

6) Is symptom timing or severity related to the adequacy of corpus luteum activity ?

Regular monitoring of cycles in which anovulation or luteal phase inadequacy are likely to occur , may allow answers to these questions to be drawn . In these studies , the definition of PMS is not an issue . The selection of women who feel they have PMS is preferential since demonstrable mood changes are more likely to occur in these women . The studies described in this thesis do not endeavour to answer questions about the nature of PMS , its epidemiology or prevalence rates in certain situations , nor do they attempt to demonstrate endocrinological differences between women who have PMS and those who do not . The purpose of this thesis is twofold . Firstly - to investigate the possibility that PMS symptoms can occur in anovulatory or otherwise unusual cycles and secondly - to relate the occurence of such synptoms to specific hormone variables .

In practical terms , this purpose can be achieved in two ways . Firstly by the study of women who are likely to experience hormonally unusual cycles , and secondly by the comparison of women whose menstrual cycles have been rendered anovulatory with women having normal menstrual cycles. The materials and methods used to achieve these aims , the data resulting from the studies and a discussion of the results form the rest of this thesis .

CHAPTER FOUR
MATERIALS AND METHODS

4.1 INTRODUCTION

In this chapter , those materials and methods which were used routinely, or whose description in the text would interfere adversely with data presentation are described . The recruitment and selection of subjects for the two studies is described at the beginning of the appropriate chapters . Hence, the routine materials and methods fall into three categories . Firstly , the manner by which mood and symptom data was collected in order to assess premenstrual symptoms . Within this category also fall those instruments used to investigate symptoms reported retrospectively , to assess personality characteristics and to collect demographic data . The second section describes the assessment of ovarian function in those subjects for whom hormonal data was collected , together with the descriptions used for abnormality . The third section refers to the statistical analysis of this type of daily rating scale data generally and the particular methods used in this thesis.

4.2 THE ASSESSMENT OF PREMENSTRUAL SYMPTOMS

4.2.1 THE DAILY DIARY

Early studies of premenstrual symptoms , with occasional exceptions , used retrospective questionnaire or interview techniques to collect data on the type and intensity of symptoms experienced . However , within the past ten to fifteen years , concern has been expressed that ratings in such a context may be influenced by subjective attitudes and beliefs about the menstrual cycle and menstrually related mood changes . Evidence has been put forward in support of this observation to show that both men and women do have specific ideas about the way in which menstruation is experienced generally (e.g. Parlee 1973 , 1974) . Hence , the use of daily self rating scales has become an important feature of scientifically rigorous research in this area [1] . The number and type of symptoms assessed and the manner in

[1] Those studies which have attempted to directly relate retrospective and prospective ratings (e.g. McCance , Luff & Widdowson 1937 ; May 1976 ; Ablanalp , Donnelly & Rose 1979 ; Endicott & Halbriech 1982 etc .) have shown that daily ratings can either confirm or deny the premenstrual symptoms expressed in a retrospective questionnaire . This lack of uniformity between individuals is usually cited as evidence that some

which they are measured varies considerably between studies . The majority of researchers have used a daily version of the Moos Menstrual Distress Questionnaire (MDQ) (e.g. Parlee 1974; Wilcoxon , Schrader & Sherif 1976; Sampson & Jenner 1977 ; Rogers & Harding 1981 ; Van den Akker & Steptoe 1985 etc.) which measures symptoms on a six-point scale . Other studies have used idiosyncratic groups of symptoms in attempts to investigate particular aspects of mood change e.g. depression (Endicott & Halbriech 1982) . However , in all of these studies , numerical category scales are used, requiring the subject to describe her symptoms or feelings in terms of defined numbers . These scales have the advantage that the researcher always knows precisely what the subject meant , and they are relatively easy to score . However , such scales have been criticised generally in the field of measurement of feelings for being too restrictive . Aitken (1969) argues eloquently that exact feelings are often beyond the scope of words to describe:-

" Feelings are states of the self , and incorporate moods and sensations . Although a person may appreciate precisely his state on a selected dimension , words may fail to describe the exactness of the subjective experience. The paucity of suitable quantitative terms in common speech limits the amount of information which can be transferred . Continuous phenomena have to be graded in artificial categories . "

Aitken (1969)

This argument is particularly relevant in the case of daily ratings in which sometimes small and undefinable changes in subjective feelings are being assessed . A potential solution to this problem is the use of a " visual analogue scale " . These scales consist of a line of a defined length (usually 100 mm) with defined end-points . The lines can be either unipolar or bipolar. The subject can place a mark at any point along the line , allowing

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subjects may be responding according to cultural stereotypes and hence retrospective questionnaires are of dubious validity . However , one potentially important point is neglected - that is that variability in symptoms may occur between consecutive cycles in the same individual . If the retrospective questionnaire is completed before the prospective data are collected , then the two are referring to different time periods , and hence both could reflect true symptom experience without necessarily being concordant. As yet no good data is available to compare retrospective and prospective reports of the same cycle . However , such data might yield valuable information about the accuracy of retrospective data and the potential influence of attitudes and beliefs .

even slight alterations in mood to be expressed . Such scales have been shown to be valid and reliable in the regular measurement of mood states (e.g. Zealley & Aitken 1969 ; Luria 1975) , and have now been used in several studies of premenstrual symptoms (e.g. Sanders et al 1983 ; Rubinow , Roy-Byrne , Hoban , Gold & Post 1984) . The use of such scales is not however without problems . The first of these is interpretation . The conceptual possibility exists that " drift " may occur , particularly if the scales are used over an extended period of time (Warner : personal communication) . That is ; the subject may unconsciously recentre herself on the scale particularly after a period of changeable mood such as may occur premenstrually . Hence , a score near the beginning of a dataset may not necessarily be comparable to the same score near the end of a dataset . Unfortunately little can be done to control for this type of error , although the removal of any trend in the data may to some extent reduce it . The second problem arises from the scoring of such scales . This is usually done by measuring the distance of the mark made from the origin and expressing the result in millimetres , or centimetres to one decimal place , or as a proportion of the total length of the line , hence taking into account the sensitivity of the measure . If multiple scales are being completed each day over a prolonged length of time , this scoring technique rapidly becomes unwieldy and time consuming . Little can be done to account for this whilst maintaining the scale sensitivity .

Visual analogue scales were used throughout this thesis and take the form of a " daily diary " (Figure 4.1) . It consists of eleven named unipolar scales , which are reduced to eight during scoring by combining " cheerful & happy " with " depressed & unhappy " to give an overall mood score , and " energetic & active " with " fatigued & tired " to give an overall energy score . The part of the diary measuring moods has been assessed previously and all the scales have been found to demonstrate face and construct validity , and cross validity when compared to the Lorr-McNaire Mood Adjective Check List (Sanders 1981) . Blank lines were incorporated to allow flexibility , the subjects can score regularly any particular feelings or symptoms which are an important part of their premenstrual experience . In this thesis , however , only the eight major symptom scales were analysed . The scales of sexual interest and activity were made optional for all study participants , resulting in smaller N values on this measure in all cases .

Code No: ☐ ☐ ☐ Date: ☐ ☐ ☐ ☐ ☐ ☐

Menstrual Period
(leave blank if not bleeding) 0 _____ 10

MOODS

Cheerful and happy 0 _____ 10

Irritable 0 _____ 10

Energetic and active 0 _____ 10

Depressed and unhappy 0 _____ 10

Fatigued and tired 0 _____ 10

Tense and anxious 0 _____ 10

..... 0 _____ 10

PHYSICAL STATE

Breast tenderness 0 _____ 10

Body swelling 0 _____ 10

Period-type pain 0 _____ 10

..... 0 _____ 10

..... 0 _____ 10

Sexual interest 0 _____ 10

Sexual activity (leave blank if no activity) 0 _____ 10

Self ☐ Partner ☐ Both ☐

Note any significant events which occurred .....

.....

Note any physical changes or symptoms (other than those mentioned above) .....

.....

Note any drugs or medication .....

Dd8865858 20M 7/86 (18023)

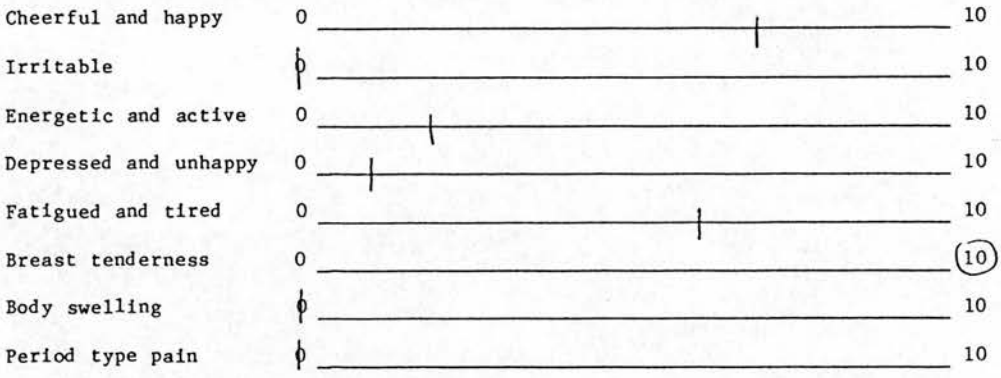
Figure 4.1 The Daily Diary

Daily Mood Diary Instruction Sheet

This 'diary' has been designed to compare your feelings from day to day. Since we are trying to build up an accurate picture of how your moods change, it is most important to mark each scale every day. If you have not experienced that mood or symptom at all that day, mark the scale at zero, please do not leave it blank.

A mark at zero means that you did not experience any of this emotion or symptom on this day. Further along the line shows more of the mood has been experienced until a mark at '10' means that you have experienced that mood or symptom as strongly as you can remember ever having experienced it.

So: for example:
If a diary was marked like this:-



we would say that the woman was very cheerful, not at all irritable, not very energetic, a little bit depressed, quite tired had very very tender breasts, no body swelling and no period pain.

Please make sure that if you have had no experience of a symptom at all, you put a mark through zero (or circle it), not just near it, or you will be given a score which may be wrong.

The menstrual period line should be used to indicate the heaviness of bleeding in the same way (eg, a score of 10 means the heaviest bleeding you can ever remember). Please mark any 'breakthrough bleeding' or spotting on this line too, and leave it blank when there is no bleeding at all.

I would be grateful also if you could make a note on the bottom of the diaries of any drugs etc you have been taking and any major events in your life - all of which can influence your mood quite independently of your menstrual cycle.

It is important that the diaries should be filled in at approximately the same time each day, eg, just before going to bed; and that each line should be marked every day.

Figure 4.2 The Daily Diary Instruction Sheet

Sexual activity and its instigation (indicated in the self , partner , both boxes) is also not assessed in this study .

The large amounts of data collected necessitated that some method of scoring be devised to increase the speed with which each individual diary could be assessed . A template was devised for this purpose , fitting precisely over the diary sheet , and having each line divided into ten equal sections . Marks were categorised according to the section in which thy fell . Arguably , this system defeats the purpose of the sensitivity of visual analogue scales , however the definitional problems are still avoided and even a ten point scale allows considerably more flexibility than a numerical six-point scale .

The diaries were printed on both sides of A5 sheets and were collected at regular intervals , either by post or by personal contact with the researcher . All of the diaries were identified by code numbers only . An instruction sheet was provided in each case , which is displayed in Figure 4.2 .

4.2.2 OTHER PSYCHOMETRIC TESTS USED IN THE ASSESSMENT OF SUBJECTS

The main purpose of the studies described in this thesis is the assessment of changes in mood over time . Hence , little importance was attached to the retrospective measurement of symptoms etc. .However , several instruments were used in a descriptive capacity . These were :- a modified version of the Moos MDQ ; the Menstrual Health Questionnaire (MHQ) designed for use in a national magazine survey (Bancroft & Warner 1987) , and earlier versions of it ; the Eysenck Personality Inventory (EPI) Form B ; and an informal questionnaire for the collection of personal and demographic details . The data obtained from these instruments were used in subject selection and in the description of particular subject groups .

i) The modified Moos MDQ

This questionnaire assesses the twenty most common items from the original 47 item MDQ , with the addition of " repeated illnesses " (Figure 4.3). They are completed retrospectively according to symptom frequency and severity . The scores were assigned by considering only those symptoms occuring every month (i.e. a score of 0 was assigned to those occuring with lesser frequency) . The one to five scale was then used to assess symptom severity . Symptom scores were collected within seven

PREMENSTRUAL QUESTIONNAIRE (adapted Moos 1968)

This is a list of things that some women notice a few days before their periods

Please tick if you have noticed any of these and say 1. how often and
2. how strongly

Please leave out any you have never felt.

	1. How often?			2. How strongly?				
	every month	every second month	less often	only just	mild	moderate	strong	severe
Overactivity								
Restlessness								
Nevousness								
Irritability								
Anxiety								
Physical tension								
Excitement								
Bursts of energy								
Feeling down								
Fatigue/tiredness								
Difficulty in concentrating								
More accidents								
Feeling of swelling								
Weight gain								
Painful breasts								
Headache								
General aches & pains								
Insomnia - difficulty in sleeping								
Appetite changes								
Palpitations								
Repeated illnesses (please describe)								

Figure 4.3 The Modified Moos MDQ

TABLE 4.1

SUBSCALES AND SCORE RANGES FOR THE MODIFIED MOOS MENSTRUAL DISTRESS QUESTIONNAIRE

CATEGORY	SUBSCALES	SCORE RANGE
PAIN	Headache Fatigue General Aches & Pains	0 - 15
CONCENTRATION	Insomnia Difficulty in concentrating More accidents	0 - 15
WATER RETENTION	Weight gain Painful breasts Feeling of swelling	0 - 15
NEGATIVE AFFECT	Anxiety Restlessness Irritability Tension Feeling down Nervousness	0 - 30
AROUSAL	Bursts of energy Excitement Overactivity	0 - 15
CONTROL	Palpitations	0 - 5
EATING HABITS	Change in Eating habits	0 - 5
REPEATED ILLNESS	Repeated Illnesses	0 - 5

categories , approximating to five of the original Moos classifications , with the addition of repeated illnesses and change in eating habits . The clusters , and range of scores are described in table 4.1 .

ii) The EPI

The Eysenck Personality Inventory , Form B , was used to assess personality characteristics on those occasions when such an instrument was suitable (i.e. the questionnaire was not used in postal studies) The suggestion has been made in previous studies that women with PMS are likely to have high neuroticism scores (see Section 1.5.7), hence it was felt that this possibility should be investigated wherever possible . The EPI was chosen for its brevity , since this was not a major part of the study . The resulting forms were scored using the published template . The appropriate normal range in this case is probably that of " housewives " in the EPI manual, i.e. on the measure of extraversion (E) , a mean of 13.92 with a standard deviation of 4.22 ; and on the measure of neuroticism (N) , a mean of 9.42 with a standard deviation of 5.19 . the normal mean for the Lie (L) scale is 1.38 (standard deviation 1.35) (Eysenck & Eysenck 1964)

iii) The Menstrual Health Questionnaire (MHQ)

This is a descriptive instrument designed for the retrospective assessment of menstrual and premenstrual symptoms , together with the collection of a certain amount of demographic data (Figure 4.4) . The MHQ was designed for use in a national survey of menstrual health published in "Woman " magazine in August 1985 . The results of this study and the design of the questionnaire are described elsewhere (Bancroft & Warner 1987) . An earlier version of the MHQ was completed by all the subjects described in Chapter Five . The survey version was used in the selection of subjects for the study described in Chapter Six . The data accruing from this questionnaire with regard to premenstrual symptoms have not been analysed in this context[1] .

The Menstrual Health Questionnaire Part II (MHQ II) was completed by all the participants in the Pill study (Chapter Six) . This questionnaire is

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[1] The premenstrual symptom data collected from those women who took part in the " Woman " survey has been analysed as part of the total pool of participants . However , individual results from this are not available .

Menstrual health questionnaire

WOMAN readers have been asked to help with a very important medical research study, by Dr John Bancroft, a leading expert in women's health problems. After years of experience Dr Bancroft believes that changes in health and feelings in relation to the woman's cycle are poorly understood. Dr Bancroft needs the largest number of women he can get to answer this questionnaire. WOMAN were happy to assist with this very vital research. Please persevere with the questionnaire and answer as honestly as you can. By completing it you will be helping doctors to help all women.

Circle the number next to your answer

■ A FEW QUESTIONS ABOUT YOU

1 Are you:
- *Single* 1
- *Married/living with partner* 2
- *Divorced* 3
- *Separated* 4
- *Widowed* 5

2 How regular are your periods now?
- *Regular (start within 2/3 days each month)* 1
- *Irregular (start within 4/10 days each month)* 2
- *Very irregular (start varies by more than 10 days each month)* 3

3 How long do your periods usually last?
- *write in* ..... *days*

4 Are your periods:
- *Light* 1
- *Medium* 2
- *Heavy* 3

5 What date did your last period start?
- *write in* .....

6 What is today's date? .....

■ CHILDREN

7 Do you have any children of your own?
- *No* 2
- *Yes, write in how many* .....

8 How old is your youngest child?
- *write in* ..... *years*

9 Did you get depressed after your last childbirth?
- *Yes—a short time in first week after childbirth* 1
- *Yes—for more than a week but not severe* 2
- *Yes—it was bad enough to see my doctor about it* 3
- *No* 4

■ HEALTH AND FEELINGS DURING THE CYCLE

10 In the next column is a list of feelings, symptoms and changes which you may or may not have experienced, Before, During and After your *last* period. If you are having a period at the moment or finished one less than five days ago, report on previous period. Please put a *NUMBER* in *each* box to indicate whether you have experienced that symptom and if so how severe it was.
The number will indicate how severe the symptom is at that time.
Put 0 in the box for NO SYMPTOM at that time.

Any symptom should be scored 1-5
1. *Very mild*
2. *Mild*
3. *Moderate*
4. *Severe*
5. *Very severe*

EXAMPLE OF HOW TO ANSWER
If you feel moderately nauseated and sick during the week before your period but find the nausea starts to improve during the period and you are free of it in the week following your period, you would answer as follows:—

	Week Before Period	During Period	Week After Period
Nausea and Sickness	[3]	[2]	[0]

PUT A NUMBER IN EACH BOX TO INDICATE HOW YOU HAVE BEEN FEELING	Week Before Period	During Period	Week After Period
Headaches	☐	☐	☐
Feel bloated in the abdomen	☐	☐	☐
Feel depressed	☐	☐	☐
Change in bowel habit	☐	☐	☐
Get angry for no good reason	☐	☐	☐
Period-type pains	☐	☐	☐
Easily upset	☐	☐	☐
Craving for sweet foods	☐	☐	☐
Poor concentration or memory	☐	☐	☐
Irritable	☐	☐	☐
Tender breasts	☐	☐	☐
Craving for salty foods	☐	☐	☐
Craving for other type of food	☐	☐	☐
Backache	☐	☐	☐
Difficulty in sleeping	☐	☐	☐
Feeling tense	☐	☐	☐
Clumsiness (dropping things)	☐	☐	☐
Mood swings	☐	☐	☐
Passing water frequently	☐	☐	☐
Feel bad about myself	☐	☐	☐
General aches and pains	☐	☐	☐
Violent feelings	☐	☐	☐
Infections (colds etc)	☐	☐	☐
Allergic reactions	☐	☐	☐
Hot flushes or cold sweats	☐	☐	☐
Nausea and/or sickness	☐	☐	☐
Spots, e.g. Acne	☐	☐	☐

Any other particular symptom or feeling —please describe on a separate sheet.

11 During the month around this last period, were the unpleasant changes you experienced:
- *as bad as usual* 1
- *better than usual* 2
- *worse than usual* 3
- *no unpleasant changes* 4

12 Which is the worst type of change you *usually* experience
.....
.....
.....

13 Normally, do your levels of the following change during the month?

CHANGES	YES	NO	NOT APPLICABLE
Energy	1	2	—
Feeling of well being	1	2	—
Sexual interest	1	2	—
Sexual enjoyment	1	2	x

14 Considering the month around your last period:

	Week Before Period	During Period	Week After Period	Other Time	Never High/ Low	Not Applicable
In which part of the month is your energy level at its highest?	1	2	3	4	0	x
When is it at its lowest?	1	2	3	4	0	x
When are your feelings of well being at their best?	1	2	3	4	0	x
When are they at their worst?	1	2	3	4	0	x
When are you most interested in having sex?	1	2	3	4	0	x
When are you least interested in having sex?	1	2	3	4	0	x
When do you most enjoy sex?	1	2	3	4	0	x
When do you least enjoy sex?	1	2	3	4	0	x

■ PREMENSTRUAL SYNDROME

15 Do you believe you suffer from pre-menstrual syndrome (PMS) now?
- *Yes* 1
- *Maybe* 2
- *No—go to 22* 3
- *Don't know* 4

■ IF YES/MAYBE

16 For how long do you think you have suffered from PMS?
.....*years*

17 What suggests to you that you have PMS?
- *GP told me* 1
- *Husband told me* 2
- *Friend/relative told me* 3
- *After reading about it* 4
- *The changes are so regular it must be* 5
- *I have been checking on myself* 6
- *Other—write in*.....
.....

18 What is the worst thing that has happened when you were suffering from PMS?
write in.....
.....
.....

19 What worries you the most about PMS?
write in.....
.....

20 Have you found any cure for PMS?
- *Yes* 1
- *No* 2
- *If YES what is it?*.....
.....

21 How understanding is your husband/partner about your PMS?
- *Very understanding* 4
- *Fairly understanding* 3
- *Not very understanding* 2
- *Not at all understanding* 1

22 How happy is the relationship between you and your partner at the moment?
- *Very happy* 4
- *Fairly happy* 3
- *Not very happy* 2
- *Not at all happy* 1

23 Are you personally undergoing any unusual stress at the moment?
- *Yes a great deal of stress* 1
- *Yes some stress* 2
- *No* 3

■ SOME IMPORTANT GENERAL QUESTIONS

24 How old were you when your first period started?
.....*years*

25 Which method of contraception are you using *at the moment?*
- *None—no sexual relationship* 1
- *None—pregnant* 2
- *None* 3
- *Oral contraceptive (The Pill)* 4
- *IUD or Coil* 5
- *Diaphragm or Cap* 6
- *Sheath* 7
- *Withdrawal* 8
- *Rhythm Method* 9
- *Male Sterilisation/vasectomy* 0
- *Female Sterilisation* x
- *Other* .....
.....

26 How long have you used this method of contraception?
.....*years*

27 If you are taking the contraceptive Pill what is it called?
.....

28 If you are not taking the Pill now but have taken it in the past, how long ago did you stop taking it?
- *Write in* _____*years ago*
- *Never taken the Pill* 2

29 What age are you?
.....*years*

30 Do you have a paid job?
- *Yes—full time* 1
- *Yes—part time* 2
- *No* 3

31 If YES what is your job?
.....

For twin sisters only. Others go to 33
32 Does your sister experience similar changes during the month as you do?
- *Yes exactly* 1
- *No* 2
- *Don't know* 3

PLEASE WRITE ON A SEPARATE SHEET IN MORE DETAIL

33 In which region do you live?
- *North England* 1
- *South England/inc. East Anglia* 2
- *Midlands/Wales* 3
- *Scotland* 4
- *N. Ireland* 5

■ WILL YOU HELP?
Would you be prepared to help research further by answering other questions about how you feel? If so, please write your name, address and telephone number (if you have one) and you will be contacted. Dr Bancroft is particularly interested to hear from twin sisters.

NAME:.....
ADDRESS:.....
.....
.....Tel No:.....

Figure 4.4 The Menstrual Health Questionnaire

essentially an extension to the MHQ and collects detailed data about pregnancy, childbirth and post-partum experiences , previous medical and gynaecological complaints , and contraceptive history as well as more demographic details and has only been used in a descriptive context .

iv) Demographic Questionnaire

An informal questionnaire / interview was used to collect personal details from those subjects seen individually . Essentially its contents were similar to those of the MHQ II , in terms of medical history etc. , however a little more emphasis was placed on current life events (see Appendix) . These data were also used in a purely qualitative way , although the reporting of multiple disruptive life events could potentially lead to the exclusion of that subject's data from the study . (In practice , those who were experiencing such events excluded themselves by dropping out) .

4.3 THE ASSESSMENT OF OVARIAN FUNCTION

Ovarian function can be assessed in a variety of ways ; by visualisation of changes occuring in the ovary , or by measurement of some dependent of adequate function e.g. changes in body temperature , cervical mucus or peripheral hormone levels . The most appropriate of these for repeated use and accuracy is the assessment of ovarian steroid levels in plasma or urine . The recent demonstrations that the ovarian cycle can be accurately assessed by means of the hormone - creatinine[1] ratio in small regular urine samples (Collins , Collins , Kilpatrick , Manning , Pike & Tyler 1979 ; Stancyk, Miyakawa & Goebelsmann 1980 ; Metcalf , Evans & Mackenzie

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[1] Creatinine is a nitrogeneous waste product , similar to urea , the end product of the metabolism of muscle creatine . It is excreted in fairly large and measurable quantities in urine , with the amount excreted remaining approximately constant per 24 hours . Endocrine results from small urine samples are usually corrected for the amount of creatinine present , hence taking account of the " concentration " of the sample , and producing a result closely approximating to that from a 24 hour urine collection . This method has previously been shown to give a more accurate representation of the ovarian cycle than the use of uncorrected oestrone and pregnanediol values (Cekan , Beksac , Wang , Shi , Masironi , Landgren & Diczfalusy 1986) .

1984 etc.) have further eased the problem of the regular monitoring of ovarian functon .

In this study , early morning urine (EMU) samples were collected daily in standard 30ml plastic Universal Containers . They were frozen as soon as possible after collection in domestic freezers or refrigerator freezing compartments . Samples were collected from subjects in batches , either weekly or monthly depending upon individual storage arrangements , thawed and 5ml aliquots obtained . These aliquots were stored at -4 degrees centigrade , before being assayed for ovarian steroids and creatinine at the end of the study period .

4.3.1 ASSAY TECHNIQUES

The urine samples were assayed for two ovarian steroid major metabolites, oestrone-3-glucuronide (E1G) and pregnanediol- 3-glucuronide (PdG) , and creatinine . The creatinine levels were measured using an autoanalyser technique by the staff of the NHS Reproductive Endocrinology Laboratories in Edinburgh . The steroids were measured by radioimmunoassay (RIA) and enzyme linked immunosorbent assay (ELISA) techniques .

RIA and ELISA are essentially derived from the same conceptual framework . They both exploit the reactions between antigens , or foreign bodies , and antibodies , proteins which help protect an organism from invasion by foreign bodies (see Loraine & Bell 1971 ; Rodgers 1974 etc.). If an antigen is introduced into a system , antibodies will be produced which are highly specific to the particular antigen and will bind closely to it - in order to reduce its effectiveness . (N.B. Antibodies can also bind to compounds which are similar to the original antigen - a process described as cross-reactivity) . The basis of an RIA or ELISA system are the antibodies raised to the particular substance to be measured , in this case oestrone and pregnanediol glucuronides . Usually these antibodies are raised in domestic animals such as rabbits , sheep or donkeys . They are then labelled with antigen which has been rendered measurable in some way , either by means of a radioactive ligand , in the case of RIA , or an enzymatic ligand which converts the substrate into a coloured product, the intensity of which can be measured , in the case of ELISA . When a mixture of antibody and labelled antigen is added to a solution containing a known or unknown

quantity of unlabelled antigen , the two will compete for antibody binding sites , with the resultant amounts of " bound " and " free " antigen being proportionate to the ratios of their concentrations . In order to measure the amount of labelled antigen attached to antibody , and hence the relative concentration of unlabelled antigen, the " bound " and " free " labelled antigen fractions must be seperated . This can be done , either by the addition of a neutral absorptive substance , e.g. charcoal , which will " mop up " all the " free " molecules and leave the " bound " ones in solution , or by the use of a second antibody technique . In this case , a second antibody is raised which is specific to the first . This is usually generated by injecting serum from the species in which the first antibody was raised into another species , e.g. if the first antibody was raised in rabbits , the second might be raised in donkeys - hence DARS , Donkey- anti-Rabbit-Serum . The second antibody , when added to the system attaches itself to the first antibody , making a bulky molecule which precipitates , leaving the " free " fraction undisturbed in solution . Hence , the amounts of " bound " and " free " labelled antigen can be measured using a suitable device , e.g. a radioactivity counter or optical density meter . The calculation of quantity of antigen in an unknown sample is performed by the incorporation into the system of a number of standards of known concentration , covering the range in which the samples are expected to lie . The results from these standards are plotted on a dose-response curve, allowing unknown doses to be calculated .

The RIA techniques used to assess both E1G and PdG followed methods which have been described previously (Collins *et al* 1979; Samarajeewa, Cooley & Kellie 1979 ; Stancyk,Miyakawa & Goebelsmann 1980 ; Branch , Collins & Collins 1982 etc.) . These assays are both based on the measurement of the " bound " fraction of a trittiated antigen , having seperated bound from free by use of dextran coated charcoal. radioactivity was assessed in a Rackbeta scintillation counter . The antisera and radioactive labels were as follows :- Oestrone-3-Glucuronide 6,7 - 3H - specific activity 38 Ci/nmol ; Anti-oestone-3- glucuronide-BSA-sera ; [6,7 - 3H]-Pregnane-diol-3-glucuronide , specific activity 42 Ci/mmol ; Anti-pregnanediol-3-glucuronide-BSA-sera . Both radioactive labels were supplied in 9:1 v/v ethanol: water , whilst the antisera were freeze dried . All labels and antisera were stored at 4 ^{o}C before dilution and use according to

the suppliers instructions . All labels , antisera and reference preparations were supplied by Dr. P Sammarajeewa at the Cortauld Institute of Biochemistry . The inter-assay and intra-assay coefficients of variation were 10.14 % and 5.65 % respectively for E1G and 10.86 % and 6.94% for PdG . These compare well with those reported by Stancyk , Miyakawa & Goebelsmann (1980) .

Partway through the study , an ELISA system became available for the measurement of pregnanediol glucuronide . Several technical aspects of ELISA are superior to the RIA system , e.g. the use of a second antibody rather than the often messy and occasionally inaccurate charcoal seperation, the elimination of the centrifugation step , shortened incubation times , and the use of non radioactive labels , hence eliminating the need for cumbersome , messy and slow scintillation counting . Comparison of samples assayed by both systems showed a high level of correlation between them , and hence this method was used for approximately half of the pregnanediol samples in the study . The first antibody was as described above , the second antibody - protein A purified Donkey-anti-Rabbit-serum (DARS) , supplied by the Scottish Antibody Production Unit (SAPU). The enzyme label used was PdG - Horseradish peroxidase , prepared from reagents supplied by Sigma , by Mr. Ian Swanston of the MRC Reproductive Biology Unit , who also developed the assay system . The precise methodology of the assay is described in the Appendix . Inter and intra assay coefficients of variation were 7.57 % and 5.92 % respectively .

In both types of system , an assay consisted of appropriate standards and quality controls , together with all the samples obtained from one subject . The only exceptions to this occured when the number of samples for one subject was too large for incorporation into one assay (i.e. > 100 samples) , in which case , two assays were performed .

4.3.2 THE DEFINITION OF OVULATION AND LUTEAL FUNCTION

The changes in levels of ovarian steroids throughout the human menstrual cycle have been well characterized in several assay systems (see Chapter Two) . However , as with many physiological systems , the problem of individual variability in terms of absolute levels of ovarian steroids , makes the definition of specific endocrine events or abnormalities a difficult task . Frequent sampling procedures assist definition since events can be

described in terms of changes in absolute levels within an individual . Abnormalities in terms of the general population are more difficult to define , and require reference to a standard or control group .

Three parameters of ovarian function required definition for the purpose of this study :- ovulation , short luteal phase and inadequate luteal phase , in terms of urinary E1G and PdG . The first of these was defined in accordance with the criteria set out by Sanders (1981) . That is , a cycle is considered to be ovulatory if a peak in urinary E1G levels is followed within two days by a sustained rise in PdG levels .

The terms inadequate luteal phase and short luteal phase were defined with reference to the literature and a series of eight normal cycles , collected and assayed by Mr. Harry Boyle and the staff of the NHS Reproductive Endocrinology Laboratories in Edinburgh[1] . Both of these definitions first require an assignment of the day of ovulation . in the study data , only E1G values would be available to assess this parameter . In the eight cycles studied , the urinary E1G peak occured 2 days before the urinary LH peak in four cases and one day before in the other four cases . A previous study has shown that the urinary E1G peak occurs either on or one day after the plasma LH peak (Cekan , Beksac , Wang , Shi , Masironi , Landgren & Diczfalusy 1986) . If it is assumed that the urinary LH peak occurs one day later than the plasma peak (Roger , Grenier , Houlbert , Castanier , Feinstein & Scholler 1980) , then the majority of women in this study showed their urinary E1G peak one day before their urinary LH peak. This evidence suggested that for the purposes of the current study , day 0 , the day of the LH peak and ovulation , should be defined as one day after the day of the E1G peak . Although this definition was potentially wrong in as many as 50 % of the cycles assessed , it was only likely to be wrong by one day in either direction.

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[1] Daily EMU samples were collected in the normal cycles and were assayed for LH , E1G and PdG . Although E1G was assessed by the RIA techniques described earlier , PdG was assessed by gas chromatography . This latter technique produces results which correlate closely with those produced by RIA for the same samples , however it should be borne in mind that the use of these control values may be a source of some error in the assessment of inadequate luteal phase . All results were expressed as creatinine ratios .

The length of the luteal phase was assigned by counting from one day after the defined day of the LH peak (i.e. day +1) up to and including , the day before the onset of menses . Reference to the literature (see Chapter Two) suggested that a length of ≤ 9 days would probably indicate a short luteal phase . This length appeared the most appropriate taking into account the potential error of one day in the assessment of the LH peak .

The levels of PdG in the eight normal cycles were used as a baseline for the assessment of inadequate luteal phase . All values were logarithmically transformed before calculations were conducted . One method of definition has been suggested by Coutts (1985) with reference to plasma progesterone levels . In this system , a normal range is set up for the cumulative progesterone values from day 2 to day 6 of the luteal phase (inclusive) , counting the day of the LH peak as day 0 . This score provides a " progesterone index " , a measure of the amount of progesterone present during the middle section of the luteal phase . Since the timing of day 0 would be assessed from the day of the E1G peak in the study subjects , this marker was also used to pinpoint luteal phase onset in the normal group . After log. transforming and summing the appropriate scores , the mean PdG index for the normal group was found to be 2.5 with a standard deviation of 0.77 . Significant deviations from normal are often considered to have occurred statistically , if a value falls more than two standard deviations away from the mean . This criterion was applied in this case . Hence the definition of an inadequate luteal phase became any luteal phase having a PdG index of less than 1.0 .

4.4 STATISTICAL ANALYSIS

4.4.1 THE ANALYSIS OF DAILY DIARY DATA IN PMS RESEARCH

The use of daily self rating scales in the study of premenstrual symptoms has now become widespread , forming at least a part of most of the recent studies . Little attention has been paid , however , to the appropriate statistical analysis of such data . One of the reasons for this may be the lack of consensus about the purpose of such analysis . Four major purposes for the analysis can be delineated :-

i) In order to diagnose the presence of PMS in particular subjects or particular menstrual cycles (usually on the basis of one cycle of data)

ii) In order to assess changes in moods and symptoms with time

iii) In order to relate changes in moods and symptoms to changes on some other physiological measure , e.g. ovarian hormone levels.

iv) In order to assess the efficacy of a particular treatment .

Most of the effort in the field has been directed towards the achievment of the first of these purposes , and by extension the last . This approach has necessitated a definition of PMS and a statistical method of satisfying the definition . (As outlined in Chapter One , this process may itself be of dubious validity in this particular field .) Dalton's (1977 , 1984) definition is the one most popularly followed , implicitly or explicitly , i.e.

" Premenstrual Symdrome is the reccurence of symptoms in the premenstruum with their absence in the postmenstruum "

Dalton (1977)

Hence - the statistical analysis of daily data attempts to demonstrate the presence of a " significant rise " in symptoms premenstrually or a significant difference between premenstrual and postmenstrual phases . In some cases this analysis is conducted by the observation of charts showing the presence or absence of specific symptoms , e.g. migraine or breast pain . The timing of these symptoms and their frequency of occurence are the major diagnostic pointers . A favourable response to a drug , for instance , is demonstrated if symptom episodes become less frequent or unrelated to menstruation . This approach is epitomised in Katharina Dalton's research . Although it is useful in a clinical setting , it is rather subjective and insensitive for use in most research studies , allowing no measure of change in symptom severity , exacerbation of chronic symptoms or degrees of change in continuosly present mood variables . However , this approach is often used for the " confirmation " of retrospective ratings (e.g. Halbriech , Endicott & Lesser 1985) .

An alternative approach has been the imposition of various cycle "phases" onto the data - producing a mean score for each phase . Comparisons can then be conducted between the defined phases to detect

significant differences . These phases are usually defined in relation to menstruation and / or hypothesized or known hormonal variables . The number of phases usually varies between three (e.g. Wilcoxon , Schrader & Sherif 1976) and seven (e.g. Englander-Golden , Schleitner , Whitmore & Corbley 1986) , although occasionally more are used . These phases are usually compared within and / or between groups by means of Analysis of Variance (ANOVA) . This type of approach makes several assumptions , - firstly , that any changes seen will be menstrually related ; secondly , - that hormonally defined phases are meaningful and thirdly that ANOVA will provide conceptually useful results in this context . As yet little evidence has been presented to suggest that these assumptions are either meaningful or not .

Maitland-Schilling (1981) showed considerable variability between subjects in the symptom patterns reported - patterns which were lost when the whole group data was meaned together . Hence she argues that the application of a mean difference model , with large numbers of subjects , to this type of research is of questionable validity if the relationship between affective states and the menstrual cycle is to be explored and described , rather than being confined into a preconceived pattern .

This criticism does not however negate the use of this approach in the study, or clinical treatment of , a particular individual . In this situation the factor of time becomes all important . The temporal relationship between consecutive daily ratings means that the scores obtained are not necessarily independent of each other . In fact the reverse may be true - mood scores on one day are highly likely to be positively correlated with mood scores on the next day .This factor , known as autocorrelation , together with the fact that data collected sequentially over time are highly likely to show a general trend, either upwards or downwards , makes the application of conventional statistics , such as the mean and standard deviation of dubious interpretable validity . Hence , the use of ANOVA in this context may be questionable . Quite apart from the stringent statistical viewpoint , the meaning behind a significant or non-significant ANOVA result is difficult to conceptualize in this case . The test basically compares group means , assuming that the dispersions are equal . If we consider the case of an individual having constant moderate levels of , for instance , irritability in the follicular phase , but fluctuating high and low levels of irritability in the premenstrual phase - a

comparison between the two on the basis of ANOVA or t-test etc. might yield little difference , whilst in fact the experience is very different .However , as Sollberger (1965) points out , a positive outcome is proof that at least something occurs in the series of values , but does not specify what kind of changes occur nor in what temporal sequence .

Some of the problems of ANOVA usage can be reduced by grouping data along the time domain (i.e. reducing the effects of autocorrelation) (Sollberger 1965) . The use of non-parametric versions of the test has also been advocated , especially if the data collected was of an ordinal rather than interval nature (Zimmerman & Parlee 1973) . The major problem here is the paucity of non-parametric tests which can cope with complex designs and repeated measures . The Friedman test is potentially applicable in this context (Winer 1971) , and this is the method suggested by Zimmerman & Parlee (1973) . This test involves the assignment of ranks to the data . Hence , if four phases were defined , they would be ranked in terms of their mean values from one to four . Therefore , in this case , the use of a non-parametric test has made no allowance for the potentially different levels of variability in diferent cycle phases . Another ignored possibility here is the occurence of premenstrual and periovulatory symptoms . Two or three bad days at both times could lead to a tied rank situation, and potentially no overall cycle effect. This approach is also not suitable for the assessment of an individual , or one particular menstrual cycle , factors which are important if individual diagnosis is the purpose of the analysis .

In all cases in which the daily ratings are grouped much of the original data is lost , allowing no measure of differential symptom timing or severity between cycles , or the possibility of different symptom patterns between subjects , or non menstrual symptom patterns . Hence , the conclusions which can be drawn from such a study are limited .

Two attempts have been made to cope with some of these problems ; to make use of all the data gained in terms of symptom onset and severity , to allow for the effects of time , to avoid the use of conventional statistics and to allow individual analysis . Both of these methods are aimed at the clinical diagnosis of PMS rather than the investigation of symptom patterns etc. from a theoretical point of view .

The first method is that described by Sampson & Jenner (1977) . In this technique , sine waves are fitted to daily rating data , by the method of least

mean squares . Various parameters of the fitted sine wave can then be described , e.g. its amplitude and its acrophase[1] ,and can be assigned confidence limits . Hence , the number of datasets for which a significant curve can be fitted gives an estimate of the number of people experiencing premenstrual changes . The size of the amplitude of each wave gives an index of individual symptom severity , and the acrophase allows the timing of maximal symptoms to be related to menses . This method is useful in the detection of both premenstrual changes and cycles occuring out of phase with the menstrual cycle , however it also has several drawbacks . Firstly - the technique of harmonic analysis calculates many potential curves for the data and then fits the best one in terms of the variance between the raw data and the fitted curve , i.e. :-

" the sine wave (chosen) is the one for which the sum of squares of the deviations of the sine wave from the crude data is minimal "
Sampson & Jenner (1977)

Although this curve may have a statistically descriptive meaning as opposed to white noise, this does not imply that it has a biological meaning (Sollberger 1965) - especially if only one (purported) cycle was used in its construction . Secondly - the method does not allow any measure of symptom onset or duration . Thirdly - no account is taken of other factors which might influence moods etc. for a sufficient length of time to produce a significant result (e.g. illness of a family member etc .) - however , in fairness , none of the other techniques take this factor into account either .

The second method used on daily data is that described by Magos & Studd (1986) . They point out that a branch of statistics exists specifically to analyse observations made sequentially in time , that is Time Series Analysis (TSA)[1] . One method used by some time series analysts is

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[1] The acrophase is defined as " the time of maximum value of the best fit curve compared to the onset of menses " . Although it is calculated in radians , it can be converted to days for each individual .

[1] It should be borne in mind that TSA as a branch of statistics was set up to address the needs primarily of economists and other financial analysts . Hence the major function of such analysis is the provision of a model enabling the accurate prediction of future events . The variables which are taken into account in building such a model , e.g. trend , seasonality etc. are crucially important in the analysis of the data for which the method was

"Triggs technique for measuring significant trends " . This is an adaptation of a method of trend analysis originally described by Brown (1963) for monitoring and forecasting long term changes in a mean . In essence , the technique exponentially smooths the data , using each of the preceding observations to predict the next .

The difference between the forecast and actual observation is then assessed to give an index of the degree of change in the forecast observations (the " forecast error ") , and the degree of random variation in the data (the " mean absolute deviation ") . The " tracking signal " (TS) is then defined as the ratio between these two measures . When the forecast error becomes larger , so does the tracking signal . The significance of this TS can then be assigned according to confidence limits . Hence , significantly different changes in symptom levels over a ' baseline ' can be seen , allowing for the normal level of fluctuation in the data . This method would appear to be logical and reasonable . It adds statistical rigorousness to simple ' eyeballing' of the data. However , it is not a method by which significant cyclicity can be assessed in long term data , nor which can distinguish between changes due to physiology and those due to coincident life events .

In summary , several attempts have been made to analyse statistically daily symptom data collected from individuals and / or groups . It cannot be said that the ideal method has yet been found to cope with the many reasons for which the data is being analysed . The majority of techniques formulate criteria for distinguishing between a " significant " premenstrual change, i.e. PMS , and a nonsignificant change , using statistical methods . Two problems arise from this . Firstly - the lack of certainty that a statistically significant change necessarily implies a biologically significant change . Secondly - the lack of an appropriate definition of PMS . Without the correct definition , the variety of techniques are simply converting linguistic confusion into statistical jargon , and are not increasing our knowledge or understanding of the phenomenon . In order to appropriately define PMS in statistical terms , methods are needed to investigate and describe long term daily data , delineating any cyclical changes seen and their association with

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designed . Although it has been used for biological and psychological data , little is yet known about its applicability .

physiological events . In the meantime , all of the methods outlined above are likely to provide comparable results which are clinically useful , but may not be methodologically or physiologically accurate or meaningful .

4.4.2 STATISTICAL TECHNIQUES USED IN THIS THESIS

The previous section gave some indication that little consensus exists about the appropriate statistical tools to use in the analysis of daily symptom ratings . A variety of methods have been used throughout this thesis to investigate particular hypotheses , and the details of these are described in the appropriate sections . Several methods are , however , either used recurrently and routinely , or would be clumsy to describe in the text , and hence will be discussed here . It should be borne in mind that this is not an exhaustive list of the methods used in data analysis .

i) Cycle Standardization

One of the inherent problems of menstrual cycle research , in terms of statistical analysis , is the normal variability in length of the ovarian cycle . This is particularly true in those parts of this research in which women were chosen from age groups or categories particularly for the likely abnormality of their hormonal cycles - a factor often associated with unusually long or short cycle lengths . Several of the comparisons undertaken require that cycle lengths should be identical between groups , producing the same number of " bits " of information per subject . Hence some method of extending or reducing cycles to some arbitrary length was required .

Two major approaches have been made to this problem in the literature . Either a 35 day cycle , for instance , is converted to an arbitrary length (usually 28 days) , whilst losing any relationship with ovarian events (e.g. McCance , Luff & Widdowson 1937) - or the cycle is centred around a particular point (usually ovulation) and the two limbs of it are converted to arbitrary lengths (Doty 1979 ; Abraham , Mira , McNeil , Vizzard , Fraser & Llewellyn-Jones 1985) . In the latter approach , the timing of ovulation and menstruation are fixed , with the intervening days being divided into seven points , being the average of the appropriate number of days - such that the cycle is described by 14 points . This method is admirable in that it maintains the association with the menstrual cycle , preventing distortions due to abnormally long

TABLE 4.2
EXAMPLES OF THE FRACTIONS USED FOR CYCLE STANDARDIZATION

a) 23 Days to 28 Days

DATA	CONVERSION
A	23A/28
B	5A/28 + 18B/28
C	10B/28 + 13C/28
D	15C/28 + 8D/28
E	20D/28 + 3E/28
F	23E/28
G	2E/28 + 21F/28
H	7F/28 + 16G/28
I	12G/28 + 11H/28
J	17H/28 + 6I/28
K	22 I /28 + 1J/28
L	23J/28
M	4J/28 + 19K/28
N	9K/28 + 14L/28
O	14L/28 + 9M/28
P	19M/28 + 4N/28
Q	23N/28
R	1N/28 + 22 O/28
S	6 O/28 + 17P/28
T	11P/28 + 12Q/28
U	16Q/28 + 7R/28
V	21R/28 + 2 S/28
W	23S/28
	3S/28 + 20T/28
	8T/28 + 15U/28
	13U/28 + 10V/28
	18V/28 + 5W/28
	23W/28

b) 33 Days to 28 Days

DATA	CONVERSION
A	A + 5B/28
B	23B/28 + 10C/28
C	18C/28 + 15D/28
D	13D/28 + 20E/28
E	8E/28 + 25F/28
F	3F/28 + G + 2H/28
G	26H/28 + 7 I /28
H	21 I /28 + 12J/28
I	16J/28 + 17K/28
J	11K/28 + 22L/28
K	6L/28 + 27M/28
L	1M/28 + N + 4 O /28
M	24 O /28 + 9P/28
N	19P/28 + 14Q/28
O	14Q/28 + 19R/28
P	9R/28 + 24S/28
Q	4S/28 + T + 1U/28
R	27U/28 + 6V/28
S	22V/28 + 11W/28
T	17W/28 + 16X/28
U	12X/28 + 21Y/28
V	7Y/28 + 26Z/28
W	2Z/28 + AA + 3BB/28
X	25BB/28 + 8CC/28
Y	20CC/28 + 13DD/28
Z	15DD/28 + 18EE/28
AA	10EE/28 + 23FF/28
BB	5FF/28 + GG
CC	
DD	
EE	
FF	
GG	

This table shows examples of the fractions used to convert cycles of various lengths to an arbitrary but comparable 28 days . The letters in the left hand columns represent the original data points , whilst the fractions in the right hand columns represent the conversion factor required to produce 28 data points .The two lengths chosen as examples are 23 and 33 days , however fractions were developed for all cycle lengths . The procedure used involves stretching short cycles and contracting long ones uniformly i.e. altering the scale of time . If a 23 day cycle is taken as an example , the 23 intervals are replaced by 28 intervals . The new scores are obtained from fractions of two adjacent points in the original 23 day cycle , as shown above

or short follicular phases . This quality can also have the effect of "highlighting " premenstrual changes and playing down follicular phase symptoms in long follicular phase cycles . However, the method is not usable in anovulatory cycles or in cycles without hormonal data .

In this thesis , the method described by McCance , Luff & Widdowson (1937) was used . By this method , a cycle is defined as the interval between the onset of one menstrual flow and the next . The cycles were then stretched and squeezed by altering the scale of time , such that 23 data points for instance were converted into 28 data points - with each of the final data points being 23 / 28 of the original (see Table 4.2 for an example) . The fractions appropriate to this calculation were applied by means of the Apple MacIntosh Plus " Excel " program . As mentioned above , this method is not ideal due to the loss of information about the menstrual cycle , however it proved adequate for the purpose of this analysis .

ii) Cycle Division

Several forms of cycle division are used throughout the analysis to satisfy particular requirements , for instance , in Chapter Six , four phase and five phase divisions are used . these are described in the text . In Chapter Five , however , cycles are divided according to hormonal criteria. This division is performed essentially according to guidelines laid down by Sanders (1981), with the inclusion of a three day " menstrual " phase , in an attempt to differentiate the effects of vaginal bleeding and the follicular phase . The phases are described in Table 4.3 . The design of the study necessitated the provision of criteria to apply in the case of anovulatory cycles . These were as follows :-

a) In the case of an anovulatory cycle with a midcycle E1G peak - the mid-luteal and late-luteal phases are assigned by dividing all remaining days into two equally , or with the mid-luteal phase being longer in the case of an odd number .

b) In the case of an anovulatory cycle with no E1G peak - the day of ovulation was arbitrarily assigned 14 days before the onset of menstruation , and the phases calculated as above .

c) In the case of first post-partum cycles , in which the beginning of the follicular phase is unclear , the first day of the cycle was assigned 28 days before the onset of menstrual bleeding .

TABLE 4.3

THE CRITERIA USED TO DEFINE CYCLE PHASES

(Adapted from Sanders 1981)

PHASE	HORMONAL CHANGES	CRITERIA FOR DEFINITION	DAYS IN STANDARD CYCLE
MENSTRUAL	Menstruation E & P low	The first three days of menstrual bleeding	1 - 3
EARLY FOLLICULAR	E Rising P Low	Early and Mid Follicular phases equally divide the time from day 4 to the late follicular phase with the Mid-Follicular phase being longer in the case of an odd number	4 - 6
MID FOLLICULAR			7 - 10
LATE FOLLICULAR	E Peak Ovulation P Rising	2 days before and 1 day after the E peak	11 - 14
EARLY LUTEAL	P Rising E Falling	4 days following the late follicular phase	15 - 18
MID LUTEAL	P Peak E Peak	From the end of the early luteal phase up to the day after the P peak	19 - 24
LATE LUTEAL	E Falling P Falling	From the end of the Mid-luteal phase to the day before menstruation	25 - 28

N.B. A standard cycle is 28 days in length with ovulation on day 14 and the progesterone peak on day 24 .

iii) Statistical Tests

The statistical methods and tests used included simple descriptive statistics , i.e. mean , standard deviation etc. calculated by hand or by use of Apple Macintosh Plus programs " Excel " and " Statworks " . Multifactorial Analyses of Variance , with repeated measures as appropriate were also performed on the Apple Macintosh Plus , by use of the Clear Lake Research " CLR ANOVA " program . In such analyses , simple effects were assessed using methods described by Winer (1971) , and a posteriori comparisons were conducted by means of the Tukey (hsd) test.

Chi-square tests , differencing and cross correlational procedures were conducted by use of " Minitab - Version 81.1 " accessed through Edinburgh University's Mainframe computer . All significance levels were assigned by reference to standard tables (Fisher & Yates 1963) .

CHAPTER FIVE
PREMENSTRUAL SYMPTOMS IN NATURALLY OCCURRING ABNORMAL MENSTRUAL CYCLES

5.1 INTRODUCTION

The postulation of a relationship between premenstrual symptoms and the ovarian cycle allows several testable hypotheses to be formulated . if PMS is seen as an " illness " or abnormal state of affairs , then it might be predicted that some physiological abnormality would be a causative factor . The assumption has been that this factor is to be found in the endocrinology of the menstrual cycle. However , the discussion in Chapter Three , suggests that attempts to identify and isolate this factor have met with only limited success .

In order to test the hypothesis that premernstrual symptoms are associated with some unidentified endocrine factor , two major approaches can be used . These could be described as the " inclusionist " approach and the "eliminationist" approach . The former is the method most often used in research to date . The " inclusionist " approach essentially compares endocrinologically women who experience PMS , or premenstrual symptoms, with those who do not, in an attempt to identify some factor or group of factors present in one group , but absent in the other . In this type of study , the minimum of interference to the normal cycle is necessary - the subjects are selected on symptomatic criteria rather than endocrine ones . Any cycles which are suspected to be abnormal are excluded .

The " eliminationist " approach takes a slightly different view . In this method various aspects of endocrine function are eliminated systematically , in order to identify which factors are associated with symptom occurence . This can be achieved pharmacologically , or by the observation of symptom patterns at times of naturally occuring endocrine abnormalities .

The first approach is largely observational in nature , and hence the risks of introducing extraneous factors by the means of factor elimination (e.g. the problem of side effects when ovulation is eliminated by oral contraceptive means) are reduced . However , in this context the approach is fraught with definitional complexities . In the absence of a standard definition or diagnosis of PMS , groups of sufferers and controls are difficult to identify , leading to a lack of comparability between studies and hence confusion in the interpretation of the evidence . The second approach allows for comparison both between groups who experience different endocrine milieu , and between differing menstrual cycles within the same individual . The use of endocrinology as the selection criteria , reduces some of the definitional

problems , and therefore enhances comparability . This approach also allows definite conclusions to be drawn about any particular factor , assisting the interpretation of " inclusionist " type studies .

Hence the two approaches to PMS research are complementary . However , as mentioned above , the " eliminationist " approach has arguably been under utilised . Hence , this was the method of choice for this study . The major factor to be eliminated is ovulation . Concomitant with the elimination of ovulation , however is the removal of luteal function . Therefore , it can be seen that some confounding of variables is present . This could be avoided in two ways . Firstly - it would be possible , pharmacologically , to suppress ovulation but replace luteal hormones exogeneously . Secondly - observations could be made of cycles of varying degrees of luteal phase normality , ranging from absent through deficient to normal . The first approach is discussed in relation to the oral contraceptive pill in Chapter Six . The second approach , however , forms the basis for this chapter .

5.2 STUDY DESIGN

5.2.1 SUBJECT RECRUITMENT

The aims of the study involved the recruitment of groups of women likely to be experiencing hormonally unusual or anovulatory menstrual cycles . The endocrinological literature suggested three phases during the female reproductive lifespan when such abnormalities might be common , i.e. puberty , perimenopause and the post-partum period (see Chapter 2) . Hence recruitment for the study was directed at these three groups . The use of an adolescent group proved not to be feasible in this context , hence the study concentrated on women immediately after childbirth, or lactation, and during the menopausal transition .

a) The Post-Partum Group

Since the purpose of the study was to investigate the relationship between mood changes and ovarian hormones , attempts were made to recruit women with some evidence of premenstrual symptoms before the current pregnancy . The assumption being made that such women would be more likely to experience such symptoms on resumption of cyclicity . Three sources were identified for such selection . The first of these was the Premenstrual Syndrome clinic at the Royal Infirmary of Edinburgh . Women who became pregnant during the course of their clinical assessment were

approached , with the co-operation of Dr. John Bancroft and research sisters Jenny Gray and Ann Cook . The second source of post-partum volunteers was a breast feeding and sexuality study being conducted at the Reproductive Biology Unit by Dr. Beth Alder . With her co-operation , women who scored highly on the modified Moos Menstrual Distress Questionnaire,administered retrospectively in the early stages of pregnancy , were approached and asked to participate in the current study . The third source of women was a national survey in "Woman " magazine in August 1985 , (see Chapter Six) . Women responding to the survey , who were pregnant or lactating at the time , felt that they had PMS before pregnancy , and lived within a reasonable radius of Edinburgh were approached and asked to participate in the study .

b) The Perimenopausal Group

Recruitment in this age group was undertaken with the co-operation and assistance of Dr. Maureen Roberts and the staff of the Edinburgh Breast Screening Clinic (EBSC) . Women within the perimenopausal age range from selected city general practices are referred to the EBSC for screening . The majority of these women are not experiencing any known pathological condition . After gaining the appropriate ethical clearance for the study , a poster was displayed in the clinic waiting room for three months , from April to June 1985 (Figure 5.1) . Respondents left their names and telephone numbers with the clinic receptionists , from whom they were collected on a weekly basis . The median reported age of menopause (i.e. the last menstrual period) in most Western studies is 50 years . Hence women were only asked to respond if they were between the ages of 45 and 54 years , still menstruating and not using steroidal methods of contraception .The poster also requested women who felt that they had recently experienced premenstrual symptoms .

c) The Clinic Group

A third small group of women were recruited from the PMS clinic , falling into neither of the above categories, but from whose case histories it seemed possible that abnormal menstrual cycles might occur with a greater than usual frequency . These women were also self diagnosed PMS sufferers .

DO YOU SUFFER FROM
PREMENSTRUAL TENSION ? (PMT)

Many women notice changes in their physical and emotional well-being in the few days before their period . For some women , these changes can be very disabling . This is usually known as Premenstrual Tension (PMT) .

The cause of PMT is not yet known , nor is there a cure at present . Dr. John Bancroft and Mrs. Anne Walker in the Department of Reproductive Biology are carrying out research to find the cause of PMT and need some help.

YOU MAY BE ABLE TO HELP

If you are 45 - 54 years old , still menstruating , not using the oral contraceptive pill , have suffered from PMT recently and would volunteer to help with the study , we would be very grateful . If you can help , please put your name, address and telephone number on the bottom of this paper and hand it in at the desk . Mrs. Walker will then contact you to give you further details .

Thank you very much indeed .

Dr. M. Maureen Roberts .

Figure 5.1 The Recruitment Poster Used in The Breast Screening Clinic

5.2.2 PROCEDURE

a) The Post-Partum Group

All of the women were contacted as early as possible during their pregnancy . At this first contact , during a PMS clinic attendance or by letter , they were given outline information about the study and asked if they would be willing to participate after the baby was born . If a positive response occurred , the women were asked the expected date of delivery and their preferred method of feeding for the baby . The next contact occurred as closely as possible to the time of delivery . At this point , all the women were visited at home , or occasionally in the post natal ward . The requirements of the study were discussed again , with ample opportunity being given for the women to change their minds if they no longer desired or felt able to participate . The course of the study from this point was decided by the method of infant feeding used . If the mothers were bottle feeding , the collection of daily early morning urine samples and daily mood diaries commenced immediately and continued until the third menstruation after childbirth , unless other factors intervened e.g. use of an oral contraceptive or removal from the area . If the mothers were breast feeding , regular contact (usually monthly , but occasionally more often) was maintained to determine the time at which night feeds were eliminated and/or breast feeding was reduced to a frequency of 2 or 3 times a day . At this point , ranging from three to nine months after childbirth , daily collections began and continued until the third menstrual period after childbirth . Monthly visits continued throughout the study period to maintain interest and co-ordinate urine and diary collections . Urine samples were usually stored in a domestic freezer and collected monthly . In cases where this was not possible , they were stored in the freezing compartment of a domestic refrigerator and collected weekly . At the final visit , a detailed interview covering medical , gynaecological and psychiatric history ,demographic data and recent life events was conducted . The modified Moos MDQ and the Eysenck Personality Inventory (EPI) Form B were also administered at this point.

b) The Perimenopausal Group

All of the respondents to the EBSC poster were contacted by telephone or letter within ten days of their clinic visit . The response slips were previously examined by clinic staff , with the removal of any woman for whom a diagnosis of a malignant condition was suspected . Little information was given about the study at this first contact , but arrangements were made for a

home visit . The option of meeting on " neutral ground " at the Simpson Memorial Maternity Pavilion was always offered . During the first visit , more information was given about the study and a Menstrual Health Questionnaire administered . The women were asked to consider their participation carefully and were contacted about a week later to give their decision . Those who did volunteer began daily urine and diary collections as soon as possible , continuing for three complete menstrual cycles , or for as long as they were willing to continue . In several cases the start date was delayed to avoid holidays etc. when urine collections might be difficult . As in the post-partum group , visits were maintained on a monthly basis throughout the study , with the same interview and questionnaire schedule being conducted at the final visit . No clinical assessment of the psychiatric or menopausal status of these women was made for this study .

c) The Clinic Group

In this group the study regime coincided with the standard two-cycle baseline symptom assessment normally conducted at the PMS clinic , with a third cycle being considered wherever possible . Throughout this assessment, diaries were completed daily and urine samples collected thrice weekly . This latter precluded the use of this data in some of the analytic techniques described later , but reduced to a minimum any interference with the subjects' treatment regime . As before , all of the participants were seen monthly , usually during their clinic attendance .

5.3 RESULTS

5.3.1 RESPONSE RATES , DEMOGRAPHIC AND ENDOCRINOLOGIC DATA

i) Response rates

a) The Post-Partum group

A total of seven women attending the PMS clinic became pregnant and / or delivered between October 1984 and December 1985 . These women were all approached and agreed to participate in the post-partum study . Only two of these subsequently produced sufficient data for inclusion . The reasons for this included lack of time to pursue the study - this reason usually occuring if the new baby was the second or third in the family , moving away from the area , illness of the baby , use of a progestagen only oral contraceptive and inadvertent loss of diary sheets .

Three women were recruited from Dr. Alder's Breast feeding study , all of whom completed the appropriate urine and diary assessments , although one was slightly curtailed due to emigration .

TABLE 5.1

REASONS GIVEN FOR NON PARTICIPATION IN STUDY

1) POST - PARTUM GROUP

Number recruited		13
Reason For Non Participation	Lack of time	1
	Baby ill	1
	Use of P-O-P	1
	Diaries lost	1
	Removal from area	1
Number providing usable data		8

2) PERIMENOPAUSAL GROUP

Number responding to poster		38
Reason For Non Participation	Uncontactable	1
	Not interested	3
	Lack of time	10
	Bereavment	2
	Family problems	2
	Unwilling to collect urine	2
	Not a PMS sufferer	1
Number providing usable data		17

Three women were recruited from the " Woman " survey , living within reasonable distance of Edinburgh . All three of these completed the study . Hence a total N of 8 was achieved in this group .

b) The Perimenopausal Group

A total of 38 women responded to the Breast Screening Clinic poster . One of these proved uncontactable , despite repeated efforts , and three others declined to participate on the basis of the first telephone contact . Hence , a total of 34 initial home visits were carried out . As a result of this , twenty-three women agreed to continue with the study . The most common reason for refusal being shortage of time , for instance being employed in a job which involved frequent travel away from home , making regular urine collections difficult . Of the 23 who agreed to continue , 17 completed the study . The others dropped out for unforseen reasons e.g. a sudden bereavment involving a period of time away from home , or family problems with subsequent disruption of mood patterns .

c) The Clinic Group

The selection of baseline data from clinic attenders makes the discussion " response rates " meaningless in this context . Ten women were considered from the clinic population to have a history suggesting the possibility of a proportion of abnormal menstrual cycles , for instance , a recent change in cycle regularity , the description of symptoms in alternate months , unilateral oophorectomy , or symptoms suggestive of early menopause . Five of these completed two or more cycles of baseline untreated data . The rest either commenced treatment before the completion of two cycles or did not produce complete data and were therefore excluded .

ii) Demographic Data

The personal and gynaecological data gathered from these women is represented in tables 5.2 to 5.4 . The majority are in Social Classes I and II and are equally divided into part-time , full-time or unpaid occupations . As might be expected , the post-partum group were more likely to be occupied at home or in a part-time capacity .

The perimenopausal group were more likely to experience irregular cycles and heavy periods , although the prevalence of the latter was small .The majority of the perimenopausal group were sterilized , with the remainder tending towards barrier methods of contraception . These latter

TABLE 5.2

DEMOGRAPHIC & GYNAECOLOGICAL DATA FOR ALL SUBJECTS

		Perimenopausal	Post-Partum	Clinic	Overall
N		17	8	5	30
Mean Age (sd)		47.6 (2.7)	30.0 (3.2)	32.2 (2.0)	41.5 (8.5)
Occupation	Full time	8	0	2	10
	Part time	7	3	0	10
	Unpaid	2	5	3	10
Social Class (Self)	I & II	11	4	2	17
	III	6	4	2	12
	IV & V	0	0	0	0
	Unclass	0	0	1	1
Social Class (Partner)	I & II	12	5	1	18
	III	3	3	3	9
	IV & V	0	0	0	0
	Unclass	2	0	1	3
Age at Menarche	Mean	13 yrs	14 yrs	13.4 yrs	13.3 yrs
	Range	10 - 16	11 - 16	10 - 16	10 - 16
Current Cycle Regularity	Reg	11	8	4	23
	Irreg	4	0	1	5
	V. Irreg	1	0	0	1
	N / A	1	0	0	1
Current Menstrual Blood Loss	Light	0	0	0	0
	Mod .	11	7	5	23
	Heavy	3	0	0	3
	Varied	2	1	0	3
	N / A	1	0	0	1
Current Dysmenorrhea	Yes	6	4	1	11
	No	10	4	4	18
	N / A	1	0	0	1
EPI Scores	E	15.7 (2.9)	15.2 (3.3)	-	15.6 (3.0)
	N	12.1 (4.9)	11.6 (6.3)	-	11.9 (5.4)
	L	1.3 (0.9)	1.6 (0.8)	-	1.4 (0.9)

KEY sd - standard deviation ; Unclass - unclassifiable ; Reg - regular ; Irreg - irregular
V. Irreg - very irregular ; N / A - not applicable ; Mod - moderate ; E - extraversion scale
N - Neuroticism scale ; L - Lie scale

TABLE 5.3
CONTRACEPTIVE HISTORY OF ALL SUBJECTS

		Perimenopausal	Post-Partum	Clinic	Overall
Method of Contraception	None	1	2	0	3
	Rhythm	1	1	1	3
	Barrier	5	4	3	12
	Ster	10	1	1	12
Number of Children (Pregnancies)	0	1 (1)	0 (0)	1 (0)	2 (1)
	1	2 (1)	5 (5)	1 (2)	8 (8)
	2	11 (9)	2 (2)	3 (1)	16 (12)
	3	1 (4)	1 (3)	0 (1)	2 (8)
	≥ 4	2 (2)	0 (0)	0 (1)	2 (3)
Number of Children Breastfed	N / A	1	0	1	2
	0	6	1	0	7
	1	2	4	1	7
	2	6	2	3	11
	3	0	1	0	1
	≥ 4	2	0	0	2
Post Partum Depression	N / A	1	0	1	2
	No	11	6	2	19
	Yes	5	2	2	9
Ever used Oral Contraceptive	Yes	13	6	5	24
	No	4	2	0	6
Effect of Oral Contraceptive on PMS	N / A	4	2	0	6
	CR/DK	9	2	2	13
	Worse	0	1	1	2
	None	2	1	2	5
	Better	2	2	0	4

TABLE 5.4

MEAN (STANDARD DEVIATION) MOOS MDQ SCORES OVERALL AND WITHIN THE PERIMENOPAUSAL AND POST-PARTUM GROUPS .

	Perimenopausal	Post-Partum	Overall
Pain	5.4 (3.2)	6.6 (4.1)	5.8 (3.6)
Concentration	2.5 (2.9)	2.8 (3.7)	2.6 (3.2)
Water Retention	5.7 (3.3)	2.4 (1.4)	4.6 (3.2)
Negative Affect	10.2 (5.7)	11.2 (5.8)	10.5 (5.7)
Arousal	2.8 (3.1)	1.2 (2.4)	2.3 (3.0)
Control	0.2 (0.6)	0 (0)	0.13 (0.5)
Change in eating habits	1.2 (1.5)	1.2 (1.6)	1.2 (1.6)
Repeated Illness	0 (0)	0 (0)	0 (0)
TOTAL	28.0 (15.1)	25.6 (13.9)	27.2 (14.8)

(Score ranges etc. are described in Chapter 4)

methods of contraception were also popular in the younger age groups . Most of the women were parous , with two children being the most common number . The majority had breast fed one or more of their children , with this proportion being higher in the younger age group, probably reflecting general changes in policy towards infant feeding . Approximately 30 % had experienced an episode of depression during the post partum phase , with this proportion being higher in the clinic group . Almost all of the women had used an oral contraceptive at one time or another . The effects of the pill on premenstrual symptoms were mixed with both positive and negative effects being reported .The majority however were unable to recall the the effects of the pill on PMS . This was particularly true in the perimenopausal group where pill taking ended an average of ten years beforehand .

EPI scores suggest a group of slightly extraverted , slightly neurotic women , although all scores fell within the normal range .

None of the women reported any serious medical , gynaecological or psychiatric problems, sufficient to lead to hospitalization within the last five years.

iii) Endocrinological Data

All of the urine samples collected were assayed using the routine RIA and ELISA techniques described in Chapter Four , the final results being expressed as hormone per creatinine ratios . Twenty five of the the thirty women collected daily urine samples , whilst the other five , all PMS Clinic attenders , complied with a thrice weekly collection regime in accordance with the clinical baseline assessment . Each cycle was then considered seperately and described as normal , anovulatory , short luteal phase (SLP) or inadequate luteal phase (ILP) according to the criteria described in Chapter Four .

The hormonal profiles produced are described in table 5.5 . Three of the women failed to produce any complete cycles despite keeping records for upwards of three months .Two of them menstruated only once during the period of the study , the third was hysterectomized and also proved to be anovulatory .

The remaining 27 women produced eighty complete cycles . Seven of these were pill cycles , twenty had deficient or absent luteal phases , and in one conception occurred . Two women failed to have a normal cycle during the course of the study , and their data are excluded from the analysis described in section 5.3.2 , but included in section 5.3.3 .

Cycle lengths varied from 16 to 49 days (Figure 5.2) with the majority falling within the " normal " 21 - 35 day range . Those cycles occuring before the first menstruation in the post-partum group have been assigned an arbitrary 28 day length and are not included in this distribution . A study time of less than 28 days before the first post-partum menstruation is described as an incomplete cycle in the context of this study , and is not included in section 5.3.2 .

5.3.2 ANALYSIS OF DATA BY MENSTRUAL CYCLE PHASE

Two forms of analysis are applied to the data collected to investigate the relationship between mood changes and the ovarian cycle . In this section , individual cycles are classified endocrinologically according to standard gynaecological criteria , as described in chapter four and section 5.3.1 .The mood and symptom data are then collected , within each individual cycle , into arbitrary cycle phases , and compared between " normal " and " abnormal " .

TABLE 5.5

ENDOCRINOLOGICAL DATA FOR ALL SUBJECTS

Subject number	Subject group	Number of days in study	No. of complete cycles	Cycle Category					
				1	2	3	4	5	6
002	PP	198	5	N	SLP	Pill	Pill	Pill	-
003	PP	130	4	SLP	N	N	N	-	-
012	PP	95	3	N	N	N	-	-	-
013	PP	135	4	N	ILP	Pill	Pill	-	-
043	PP	104	2	N	N	-	-	-	-
046	PP	115	4	ILP	Pill	Pill	ILP	-	-
047	PP	172	5	Incomp	N	N	SLP+ILP	SLP	Con.
050	PP	89	2	Incomp	N	N	-	-	-
015*	PM	81	0	Incomp	Incomp	-	-	-	-
016	PM	90	3	N	N	N	-	-	-
018	PM	52	2	N	N	-	-	-	-
020*	PM	130	0	Incomp	-	-	-	-	-
021	PM	96	3	N	A	A	-	-	-
022	PM	94	3	N	N	SLP	-	-	-
023	PM	66	2	N	N	-	-	-	-
024	PM	112	4	ILP	SLP	SLP	N	-	-
025	PM	90	3	ILP	N	N	-	-	-
027	PM	84	3	N	N	N	-	-	-
028**	PM	99	0	-	-	-	-	-	-
035	PM	98	3	N	N	N	-	-	-
038	PM	109	2	N	N	-	-	-	-
039	PM	84	3	N	N	N	-	-	-
042	PM	77	2	N	N	-	-	-	-
044	PM	97	3	N	N	N	-	-	-
045	PM	94	3	N	N	N	-	-	-
014	C	90	2	N	N	-	-	-	-
026	C	80	3	N	N	N	-	-	-
051	C	56	2	N	A	-	-	-	-
052	C	53	2	A	N	-	-	-	-
053	C	76	3	ILP	ILP	SLP+ILP	-	-	-

KEY PP - Post-Partum ; PM - Perimenopausal ; C - Clinic .
N - Normal ; SLP - Short luteal phase ; ILP - Inadequate luteal phase ; A - Anovulatory
Con - Conception ; Incomp - Incomplete

* - Only one menses during study ; ** - Hysterectomized

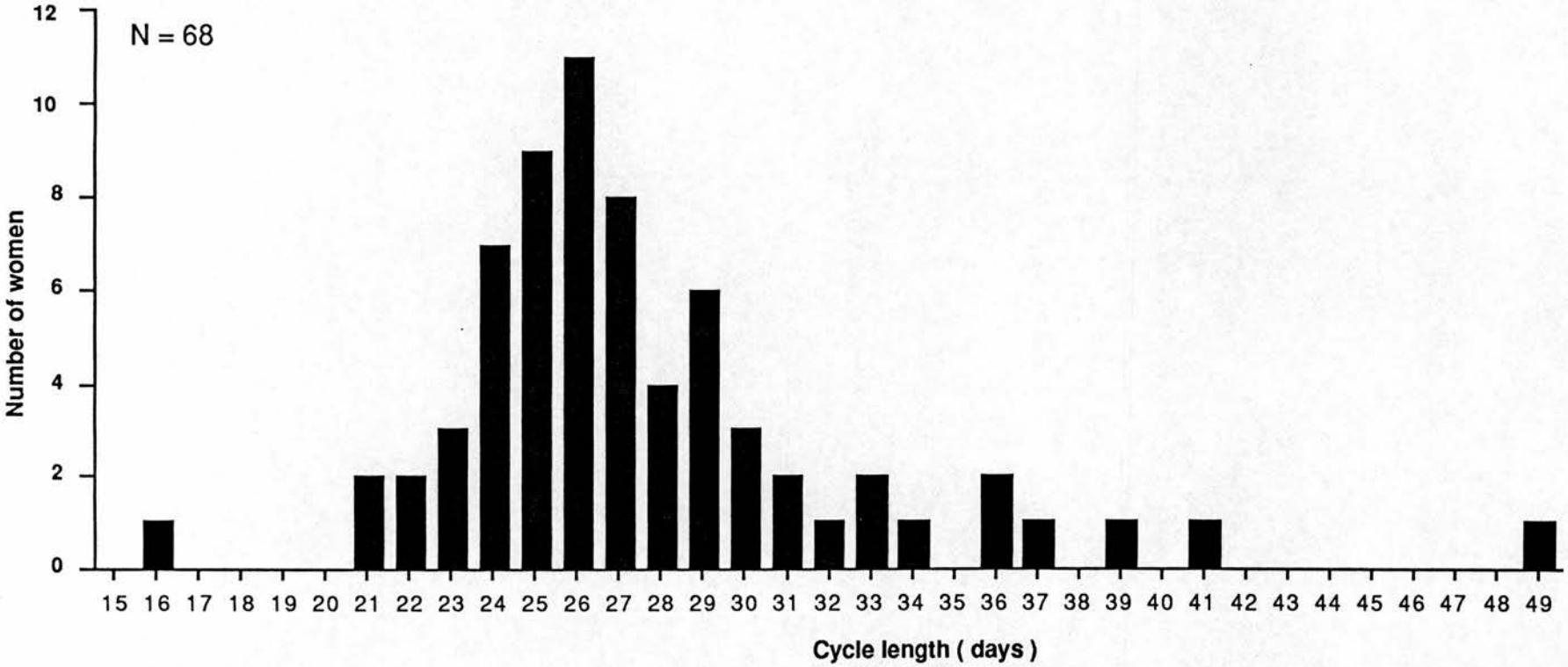


Figure 5.2 Distribution of cycle lengths throughout study

(N.B. All pill , conception , incomplete and first post-partum cycles are excluded)

cycles . Two forms of cycle division are used in this section . The first breaks the symptom data into segments representing changes in ovarian hormone levels. These phases are identical to those used by Sanders (1981) , with the addition of a three day " menstrual phase " at the beginning of the cycle . Hence seven cycle phases are defined :- menstruation (M) , early follicular (EF) , mid-follicular (MF) , late-follicular (LF) , early luteal (EL) , mid-luteal (ML) and late luteal (LL) . These phases are defined in more detail in Chapter Four . The day of the urinary oestrone peak is one of the crucial temporal markers in this cycle division , and was fortunately present in all of the anovulatory cycles studied . This allowed the differentiation of the follicular phase from the " luteal " phase in all cases . Since no pregnanediol peak was present in anovulatory cycles , the mid and late luteal phases were assigned by dividing the appropriate days into two sections , with the mid-luteal phase being longer in the case of an uneven number . Some difficulty arose in the case of those post-partum women for whom data was available for the time period before the first menses after childbirth . Although an oestrone peak (and usually ovulation) occuring before menses allowed the delineation of the late follicular and luteal phases , the early part of the " cycle " was more difficult to assess . In these cases it was decided to count back an arbitrary 28 days from the first day of menstruation , defining the day reached as day one of the cycle . If a period of less than 28 days was available before menstruation , the cycle was described as incomplete and discarded for analytic purposes . This methodology may be a source of error in the discussion of follicular phase symptomatology , however in the absence of defined hormonal markers for the follicular phase , it was felt that a reasonable approximation to reality would be achieved in this way .

The second method of cycle division was incorporated for two reasons . Firstly, some concern was expressed that abnormal cycles may be more likely to fall outside the normal range in terms of cycle length than do " normal " cycles . Hence the use of the cycle division outlined above may produce distortions , especially in the comparison of a seven day luteal phase divided into three portions with a fourteen day luteal phase divided into three portions for instance . Therefore it was felt that a method incorporating temporally comparable portions within different groups should be employed . The second reason came from the demands of the Analysis of Variance package used . To assess changes within a particular individual , a multifactorial repeated measures design is required . The package used ,

whilst being able to cope with such designs , is unable to cope with unequal cell sizes within them . Hence , each cycle must be divided into equal portions . Variability in cycle length within a particular individual again made this a problem . An arbitrary 28 day cycle length was assigned , with all cycles being adjusted to this by the methods outlined in Chapter Four . The subsequent data were divided into seven four day blocks . This method is by no means perfect on cycles of such variable length and losing as it does any relationship to the hormonal cycle . However , it does provide the means for a comparison , however crude .

Two comparisons were conducted using the " hormonally defined " and "standardized cycle " phases described above . These can be described as "Group " comparisons and " Individual " comparisons.The Group comparisons involved the assignment of individual cycles to categories according to their particular hormonal pattern ; i.e. normal , anovulatory , short luteal phase or inadequate luteal phase . (The category of short + inadequate luteal phase was not used in this analysis due to the small number of cycles falling into it , such cycles were not used in the group analysis) . It was felt that a straight comparison between all of the normal cycles and each of the abnormal categories would be inappropriate in this case for two reasons . Firstly , because of the small numbers of abnormal cycles , and secondly , because of the possibly confounding factor of symptom variability between normal cycles within an individual . Hence an analysis of variance design was developed utilising groups of paired cycles . Cycles were formed into normal-normal and /or normal-abnormal pairs within each subject , leading to the exclusion from the analysis of those subjects who only experienced abnormal cycles during the course of the study . A 2x2x7 ANOVA was developed (Figure 5.3) , with repeated measures on the latter two factors , and no subject being included in both groups . This analysis was performed for each of the eight symptoms within the three abnormality categories utilising both types of cycle division , and was followed up with 2x7 ANOVA's with repeated measures on both factors , within each of the two groups to assess simple effects .

The second analysis is described as the " Individual " comparison . This was conducted as a result of concern that grouping of cycles , especially with such small numbers within each abnormality , might mask individual

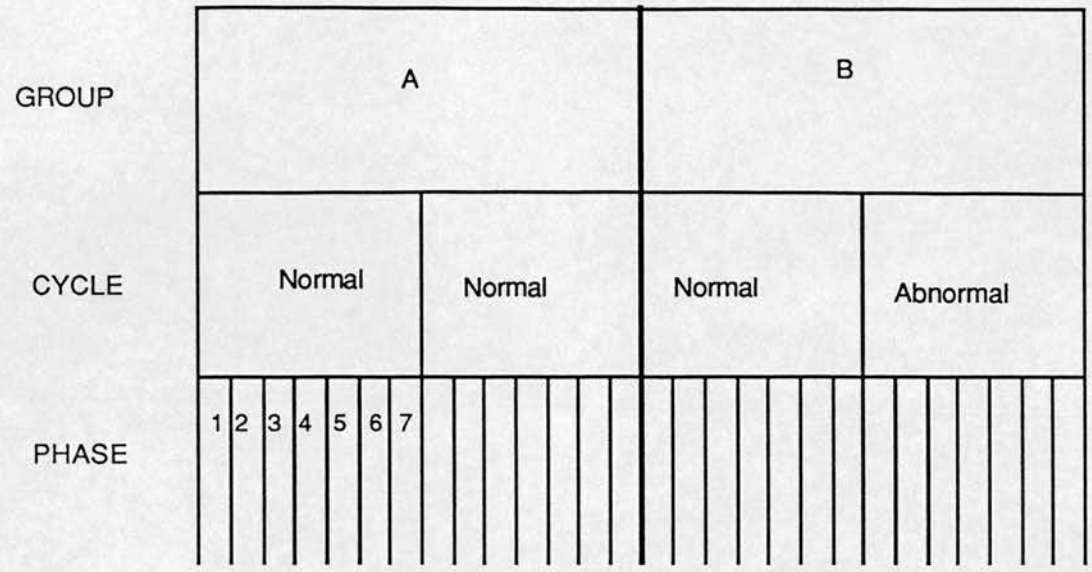


Figure 5.3 Analysis of variance design (2x2x7) for group comparison . (see text for details)

differences in the response to the hormonal milieu . Hence Xx7 ANOVA's with repeated measures on both factors were conducted for each individual , with

X being the number of cycles experienced by her during the course of the study . In this case , only standardized cycle phases were used , and only those women having combinations of normal and abnormal cycles were assessed . Only two subjects showed cycles with different abnormalities during the study (see Table 5.5) , hence the results will be presented according to the three major abnormalities under consideration , with the different analyses as subgroups .

i) Ovulatory vs Anovulatory Cycles

a) Group Comparison

Three women showed normal - anovulatory cycle pairs with 19 providing the normal - normal cycle comparison . The mean scores within each group across the hormonally defined and standardized cycle phases for each symptom form figures 5.4 to 5.6 inclusive , with the ANOVA results being displayed in table 5.6 . Standardized cycle results are presented in the Appendix . Only six variables could be compared statistically in this case due

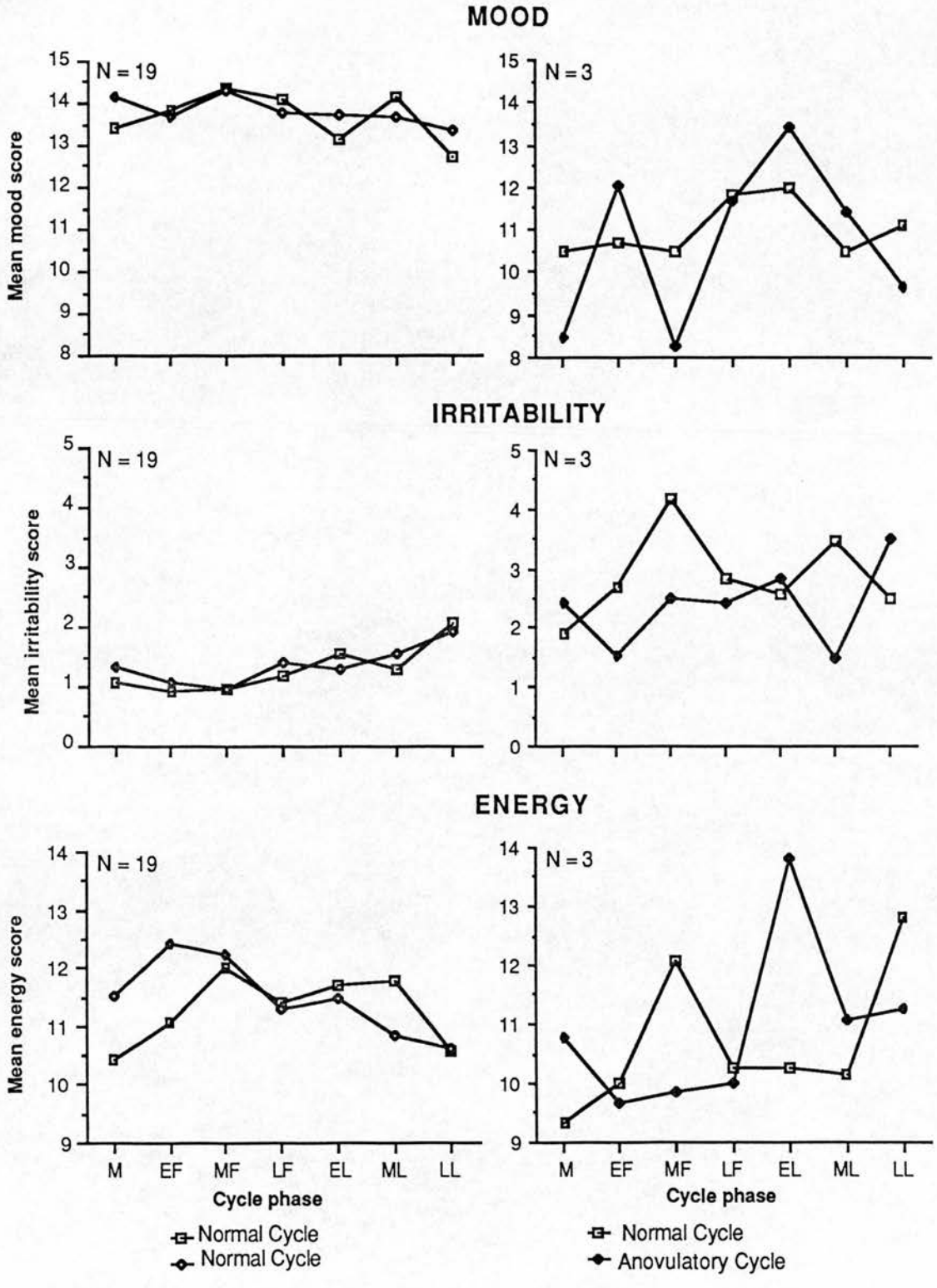


Figure 5.4 Comparison of mood , irritability and energy scores across 7 hormonally defined cycle phases in normal / normal cycle pairs and normal / anovulatory cycle pairs .

Key :- M = menses ; EF = early follicular , MF = mid-follicular , LF = late follicular , EL = early luteal ML = mid-luteal , LL = late luteal

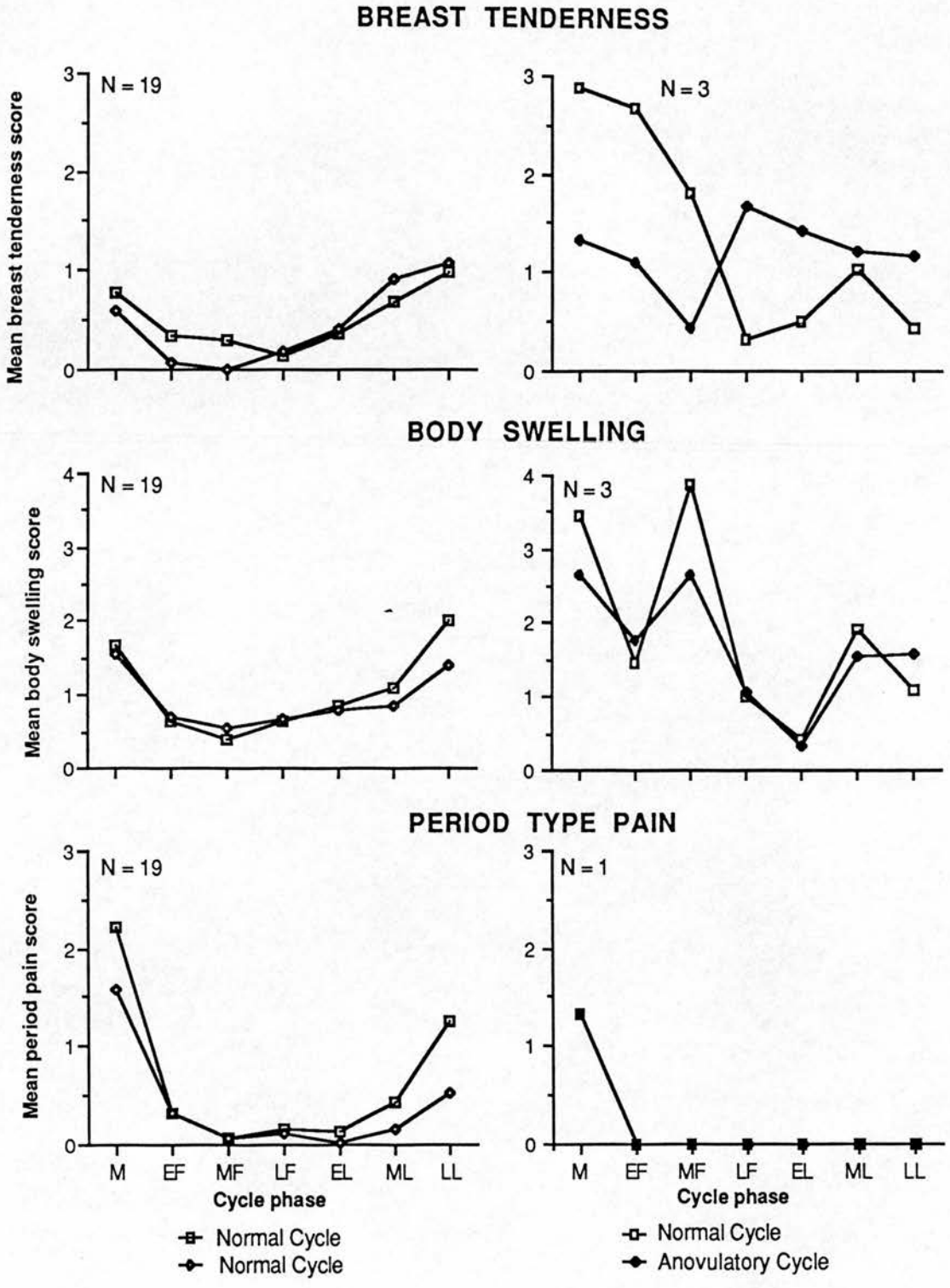


Figure 5.5 Comparison of breast tenderness , body swelling and period pain scores across 7 hormonally defined cycle phases in normal / normal cycle pairs and normal / anovulatory cycle pairs

Key :- M = menses ; EF = early follicular ; MF = mid follicular ; LF = late follicular
EL = early luteal ; ML = mid luteal ; LL = late luteal .

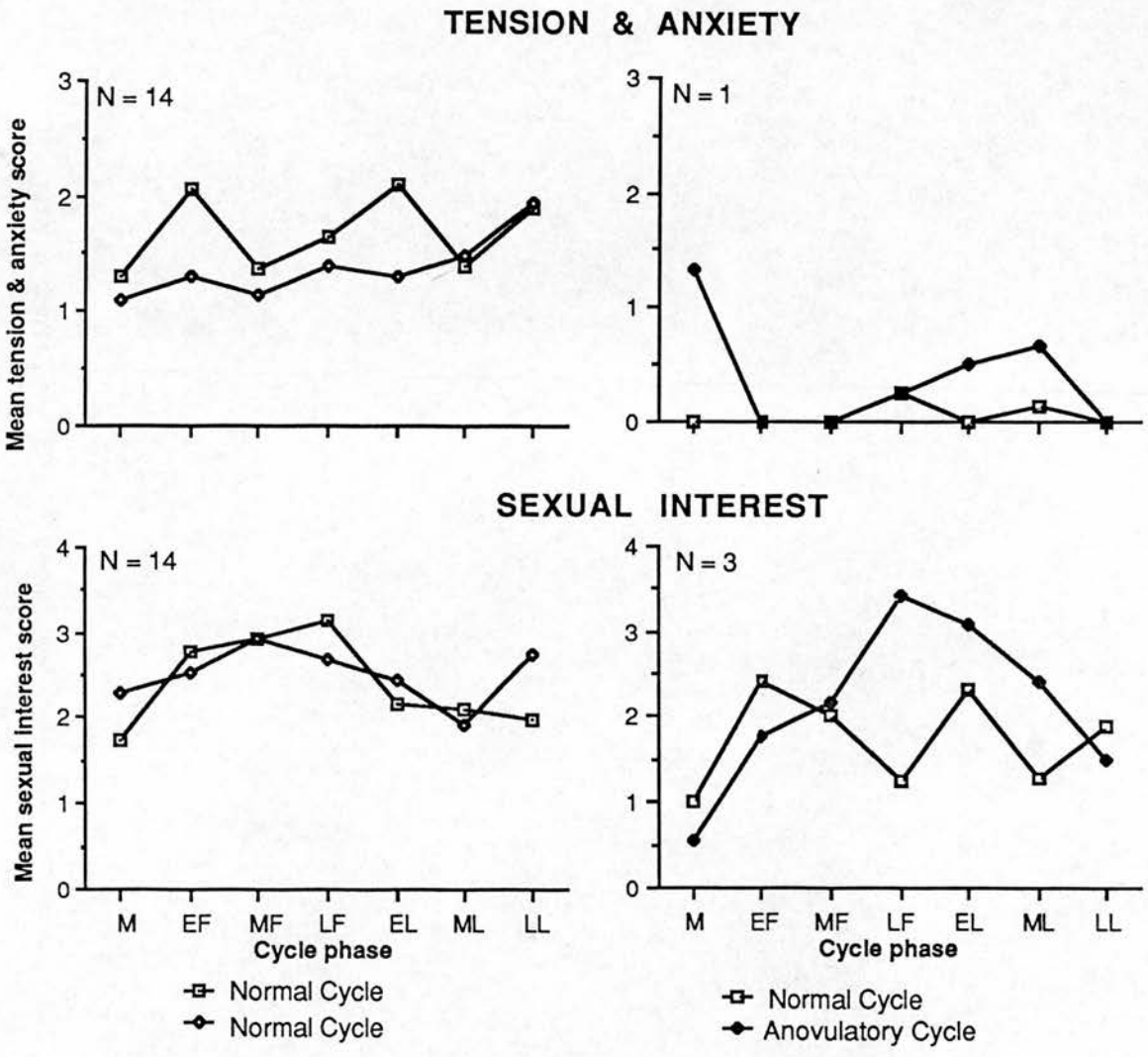


Figure 5.6 Comparison of tension & anxiety and sexual interest scores across 7 hormonally defined cycle phases in normal / normal cycle pairs and normal / anovulatory cycle pairs .

Key :- M = menses ; EF = early follicular ; MF = mid follicular ; LF = late follicular ; EL = early luteal ; ML = mid luteal ; LL = late luteal .

TABLE 5.6
THREE-WAY AND TWO-WAY ANOVA RESULTS (F-VALUES) FOR NORMAL AND ANOVULATORY CYCLES DIVIDED BY MENSTRUAL CYCLE PHASE

i) Three-way ANOVA

	G	C	G x C	P	G x P	C x P	G x C x P
Mood	2.83	0.04	0.26	1.25	1.85^{T}	0.78	1.21
Irritable	2.27	0.64	0.92	1.24	0.79	1.63	2.12*
Energy	0.11	0.24	0.001	1.05	1.47	1.32	1.65
Tense & anxious	Insufficient Data						
Breast tenderness	3.23^{T}	0.32	0.11	1.75	2.25*	3.10**	1.85^{T}
Body swelling	0.79	0.43	0.05	4.36**	3.88**	0.49	1.00
Period pain	Insufficient Data						
Sexual interest	0.26	0.32	0.13	2.32*	0.81	0.44	1.15
DF	1	1	1	6	6	6	6

ii) Two-way ANOVA between normal cycles

	C	P	C x P	P@C1	P@C2
Mood	0.92	1.17	0.32	0.78	0.69
Irritable	0.05	3.18**	0.41	2.44*	1.63
Energy	0.38	2.23*	1.77	1.54	2.76**
Tense & anxious					
Breast tenderness	0.11	5.28**	0.83	2.98**	4.37**
Body swelling	0.34	5.68**	1.04	4.82**	3.62**
Period pain					
Sexual interest	0.05	3.22**	0.71	2.35*	0.97
DF	1	6	6	6,108 (78)	

iii) Two-way ANOVA between normal and anovulatory cycles

	C	P	C x P	P@C1	P@C2
Mood	0.43	1.10	0.60	0.25	1.25
Irritable	0.94	0.35	2.16	0.89	0.63
Energy	0.18	0.73	0.66	0.55	0.86
Tense & anxious	Insufficient data				
Breast tenderness	0.11	0.89	0.54	1.00	0.16
Body swelling	0.38	2.70^{T}	0.28	2.84*	0.81
Period pain	Insufficient data				
Sexual interest	241.13**	0.58	1.06	0.54	0.80
DF	1	6	6	6,12 (12)	

Key :- DF - degrees of freedom ; G - Group ; C - Cycle ; P - Phase .; T - trend ($p < 0.10$)
* - $p < 0.05$; ** - $p < 0.01$ (Figures in brackets indicate DFe for sexual interest)

to the absence of sufficient data on measures of tension & anxiety and period type pain.

The graphs show a reasonably clear , if mild , premenstrual pattern in both control cycles on measures of irritability , breast tenderness and body swelling , with only slight differences in severity between the two cycles . Mood shows little change across the cycle , although a slight trend towards lower mood in the luteal phase is apparent . In the case of energy , tension & anxiety and sexual interest , some discrepancy exists between normal cycles in terms of symptom patterns . In both cycles , energy scores show a marked dip in the late follicular phase , coincident with ovulation . In the first cycle , these levels recover to produce a biphasic energy cycle , falling only in the late luteal phase .In the second cycle , the levels recover only slightly during the early luteal phase and show a more gradual decline to identical late luteal levels. Tension & anxiety scores similarly differ between the two normal cycles - in one cycle gradually increasing levels of tension are seen , whilst in the other the behaviour appears more erratic with peak scores in the EF and EL phases . Sexual interest also shows a slight difference in symptom timing between normal cycles - in one cycle , interest rises from a trough during menses to a peak in the LF phase, then falls sharply , remaining reasonably static throughout the luteal phase . In the other cycle , interest peaks slightly earlier in the MF phase , declining gradually to the ML phase and showing a marked resurgence in the LL phase . Hence it would appear that some difference in symptom pattern and severity at various points in the cycle can occur between normal cycles .

The normal - anovulatory cycle pairs show a greater degree of diversity in symptom patterns . Only two can be said to be similar between the two cycles, these are period pain , with an N of 1 and present only during menstruation , and body swelling . Although the symptom pattern here is consistent across the cycles , it is different from the controls in several respects . Firstly , the levels of body swelling are higher throughout the cycle . Secondly , a peak of symptoms occurs in the MF phase in both cases , declining to a minimum in the EL phase before a premenstrual rise . This peak of symptoms in the MF phase also occurs in the normal cycles on measures of irritability and energy and in the anovulatory cycles in the case of mood , and to a lesser extent , irritability .

Most of the symptoms measured , with the exceptions of mood and energy are fairly consistent between the two cycles during the follicular phase . The

symptom of breast tenderness shows the most dramatic difference in the luteal phase . In the normal cycles , levels are lowest in the LF phase rising gradually to a ML phase peak . Lowest levels in the anovulatory cycle occur earlier , in the MF phase , suddenly rising to a LF peak , with only slight decline during the luteal phase . Sexual interest shows a more clearly cyclical pattern in the anovulatory compared to the normal cycles , rising to a LF peak and gradual decline . Generally lower levels of sexual interest are displayed throughout the luteal phase in normal cycles .

The results of 2x2x7 ANOVA's suggest a trend towards a group difference only in the case of breast tenderness , supported by a GxCxP interaction on this parameter . A significant GxCxP interaction also occured on the measure of irritability . Examination of 2x7 ANOVA's show no cycle differences in the normal-normal cycle pairs . However , when phase effects are assessed within each cycle , differences were seen , with irritability , energy and sexual interest having significant phase effects in one cycle but not the other . Few phase effects were observed in the normal - anovulatory pairs , possibly due to the small size of the sample and the large degree of individual variation . Sexual interest did however reveal a cycle difference , suggesting that overall levels of sexual interest are higher in anovulatory cycles . In the case of body swelling , a marginally significant phase effect was observed in the normal cycle which was absent in the anovulatory cycle . This probably reflects a difference in absolute symptom levels between the cycles , since no difference in symptom profile is observed graphically .

The results obtained after standardized cycle division were essentially similar in the control group , with the exception of tension & anxiety . In this case a midcycle improvement in tension was replaced by a deterioration . In the ovulatory - anovulatory group the patterns were also similar to those found in the hormonal analysis . The major discrepancy in this case being on the measure of mood , in which both normal and anovulatory cycles displayed low mood during the follicular phase .

Analysis of variance results were also comparable , although the significant GxCxP interaction on the measure of irritability was lost , as were the significant anovulatory cycle phase effects on the measure of body swelling .

b) Individual Comparison

The data for the three women falling into this category are represented graphically in figures 5.7 , 5.8 and 5.9 , with the ANOVA results in table 5.7 .

Subject 051

In the case of mood and energy in this subject , a cyclical pattern seemed to emerge, supported by significant ANOVA phase effects .However ,in neither cycle could these measures be said to fit a classical premenstrual pattern . Rather , lowest levels of mood and energy are found at the beginning of the cycle . A significant cycle difference also occurs in the case of energy , indicating a lower mean energy level in the anovulatory cycle .Cycle x phase interactions are non-significant . Body swelling similarly does not show the classic premenstrual pattern in either cycle , with highest levels occuring coincidentally with low mood and energy . Overall levels of swelling are lower in the anovulatory cycle , sufficient to produce a significant C x P interaction .

In contrast to this , measures of irritability , breast tenderness and sexual interest show a more conventional pattern in one or both cycles . Sexual interest is highest in phase 3 of both cycles , although the levels are still low and insufficient to produce a phase effect . " Luteal " levels of sexual interest are slightly higher in the anovulatory cycle . Measures of irritability and breast tenderness show a similar pattern . In the normal cycle they gradually decline from a menstrual peak to a premenstrual trough . In the anovulatory cycle , breast tenderness gradually increases to a peak in phase 5 then falls . Irritability is also high during the first half of the normal cycle , levelling off at midcycle and falling off sharply towards the end . The anovulatory cycle also shows relatively high levels of irritability in the follicular phase , falling to a trough in phase 5 and rising again premenstrually . These pattern differences are supported by significant C x P interactions in the latter two cases and significant cycle effects , since the overall levels are higher in the normal cycle.

In summary :- three symptoms , mood , energy and sexual interest show little difference between the two types of cycle . However , although all three would appear to be cyclical , only the latter shows a typical premenstrual pattern , and this may be a postmenstrual increase rather than a premenstrual decline . Body swelling shows a difference between cycles in terms of absolute levels but essentially a similar pattern , being higher in the

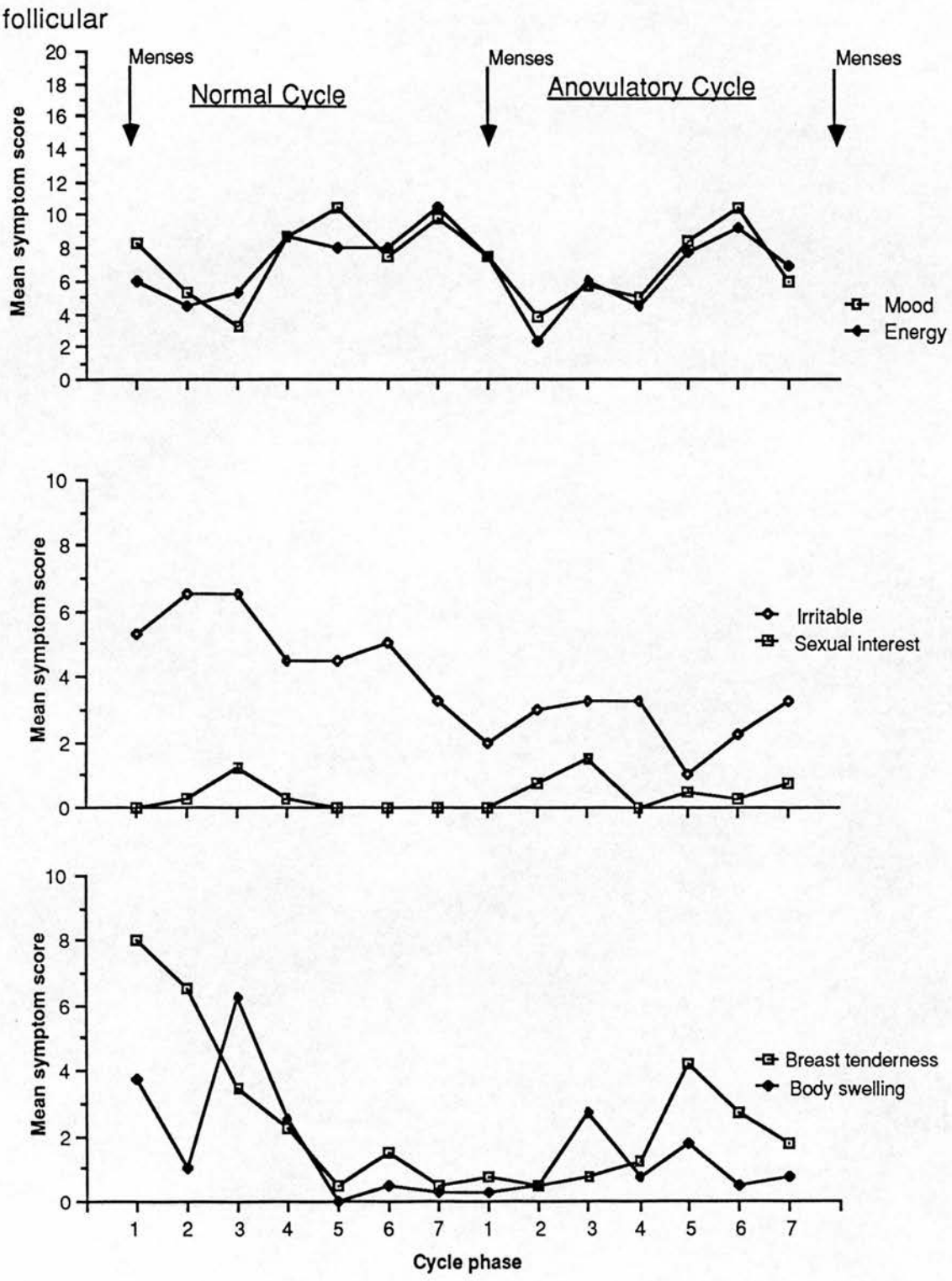


Figure 5.7 Changes in symptom levels with time across 7 standardized cycle phases in one woman (051)

TABLE 5.7

INDIVIDUAL ANOVA RESULTS FOR SUBJECTS 021, 051 AND 052

SUBJECT 021

	C	P	CxP	P@C1	P@C2	P@C3	C1vC2	C1vC3	C2vC3
Mood	445.3**	4.44**	1.97	6.27**	2.25	3.27**	**	**	**
Irritable	1.34	5.06**	4.02**	4.76**	2.03	8.43**	ns	ns	ns
Energy	54.49**	6.83**	5.20**	4.66**	3.90**	10.11**	**	ns	**
Tense & anxious	34.96**	1.51	1.19	1.07	1.27	1.79	**	ns	**
Breast tenderness	51.24**	4.42**	4.29**	2.05	4.47**	1.21	**	ns	**
Body swelling	7.94*	3.97**	1.56	2.09	2.45 T	0.85	ns	ns	*
Period pain	1.12	1.44	1.12	2.20 T	1.00	1.21	ns	ns	ns
Sexual interest	9.79**	6.17**	3.13**	10.10**	2.68*	2.79*	*	ns	ns
DF	2	6	12	6,18					

SUBJECT 051

	C	P	CxP	P@C1	P@C2
Mood	2.48	9.01**	2.52 T	4.93**	4.98**
Irritable	33.45**	2.31 T	2.61 T	2.04	3.43**
Energy	13.84*	10.49**	2.12	2.70*	16.76**
Breast tenderness	18.43*	3.79**	11.53**	8.44**	6.29**
Body swelling	10.74*	8.18**	3.15*	5.79**	3.56*
Sexual interest	2.13	2.19 T	0.23	0.83	1.46
DF	1	6	6	6,18	

SUBJECT 052

	C	P	CxP	P@C1	P@C2
Mood	0.49	2.14 T	1.50	2.58 T	0.40
Irritable	0.02	4.85**	2.10	2.40 T	6.04**
Energy	11.79*	1.99	18.24**	5.48**	7.73**
Breast tenderness	5.59 T	38.49**	27.47**	79.41**	7.46**
Body swelling	0.65	11.46**	4.37**	9.52**	6.89**
Sexual interest	8.78 T	4.96**	8.25**	9.73**	1.74
DF	1	6	6	6,18	

Key :- ns - not significant ; * $p < 0.05$; ** $p < 0.01$.

C - Cycle ; P - Phase; DF- Degrees of freedom .

phase . Irritability and breast tenderness differ in both timing and severity between the cycles , both showing a more typical premenstrual pattern in the anovulatory cycle , although at lower levels of severity than were seen in the normal cycle .

Subject 052

In this subject , a slightly more typical pattern is seen , although the picture is

far from clear . In the case of mood , a cyclical pattern is seen in the anovulatory cycle , with high levels at midcycle and low levels at the beginning and end of the cycle . However , in the normal cycle this is lost , with mood showing a gradual decline from phase1 to phase 7 . A similar energy pattern is observed in the anovulatory cycle , however energy is clearly cyclical in the normal cycle too , being at its peak in phase 3 and trough in phase 6. The 'shape ' of the symptom is quite different between the two cycles , leading to a significant interaction .

Irritability appears to show a biphasic pattern which does not differ greatly between the two cycles . This symptom is increased at midcycle (phase 3) falling to a nadir in phase 5 or 6 and rising again premenstrually . Body swelling also shows a cyclical pattern which is similar in both cycles . This symptom increases gradually from its lowest point in phase 5 to a peak during menstruation , then falling again . Hence body swelling appears to be centred around menstruation.This is also the case with breast tenderness . In the normal cycle levels are relatively high during menstruation and the early part of the cycle , falling to a trough in phase 5 and rising premenstrually .In the anovulatory cycle , although breast tenderness is present early in the cycle , " luteal " levels are absent . Sexual interest levels are also improved , i.e. higher , during the anovulatory cycle , although they still show a premenstrual decline similar to that in the normal cycle .

In summary , it would appear that all the symptoms measured occurred in both cycles in this subject , except for breast tenderness , which was absent from the second half of the anovulatory cycle .

Subject 021

In this subject , two anovulatory and one normal cycle were observed . Hence , a difference in symptomatology might be manifest by the classification of the normal cycle as " odd man out " . This does not appear

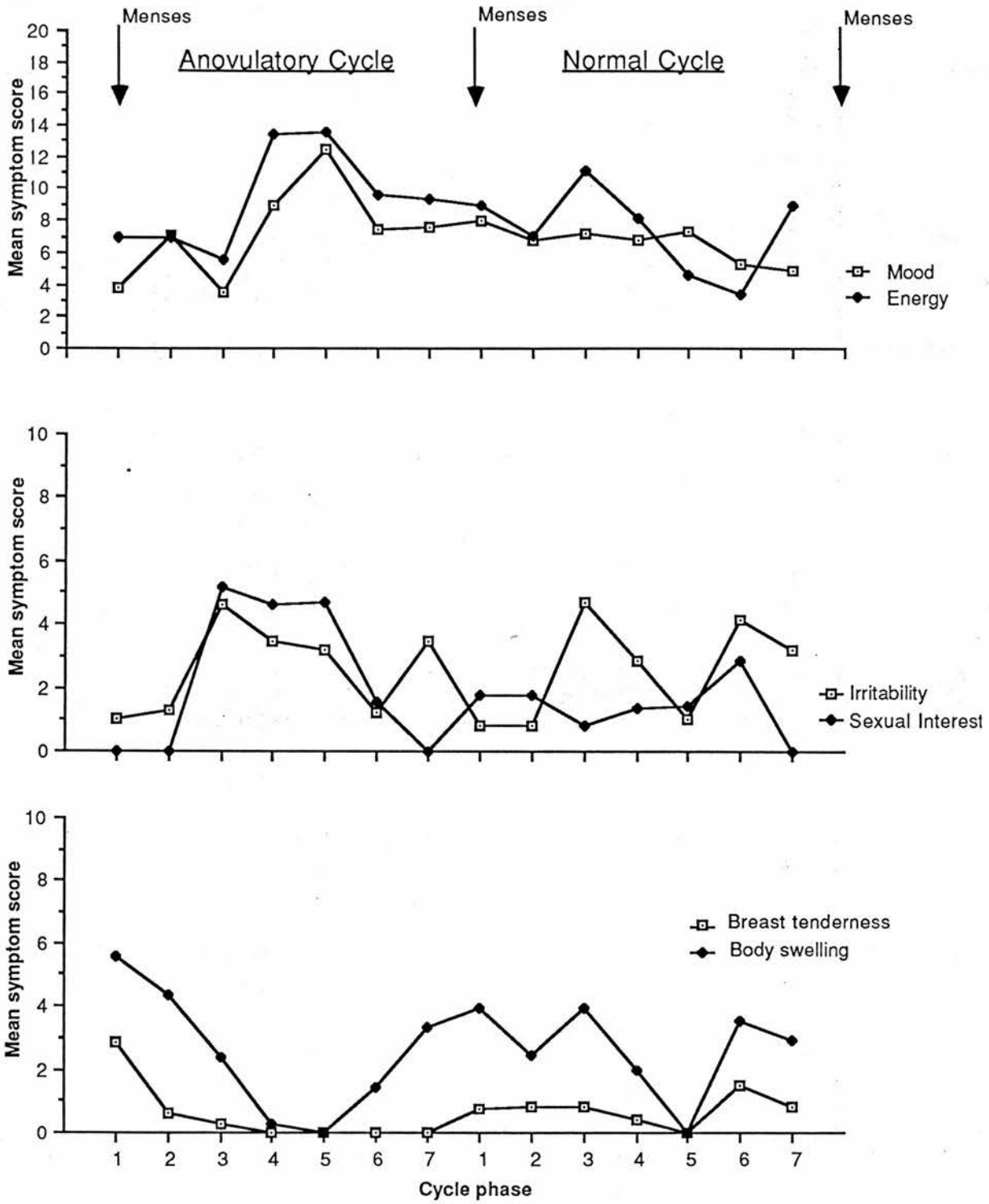


Figure 5.8 Changes in symptom levels over time across 7 standardized cycle phases and two consecutive cycles in one woman (052)

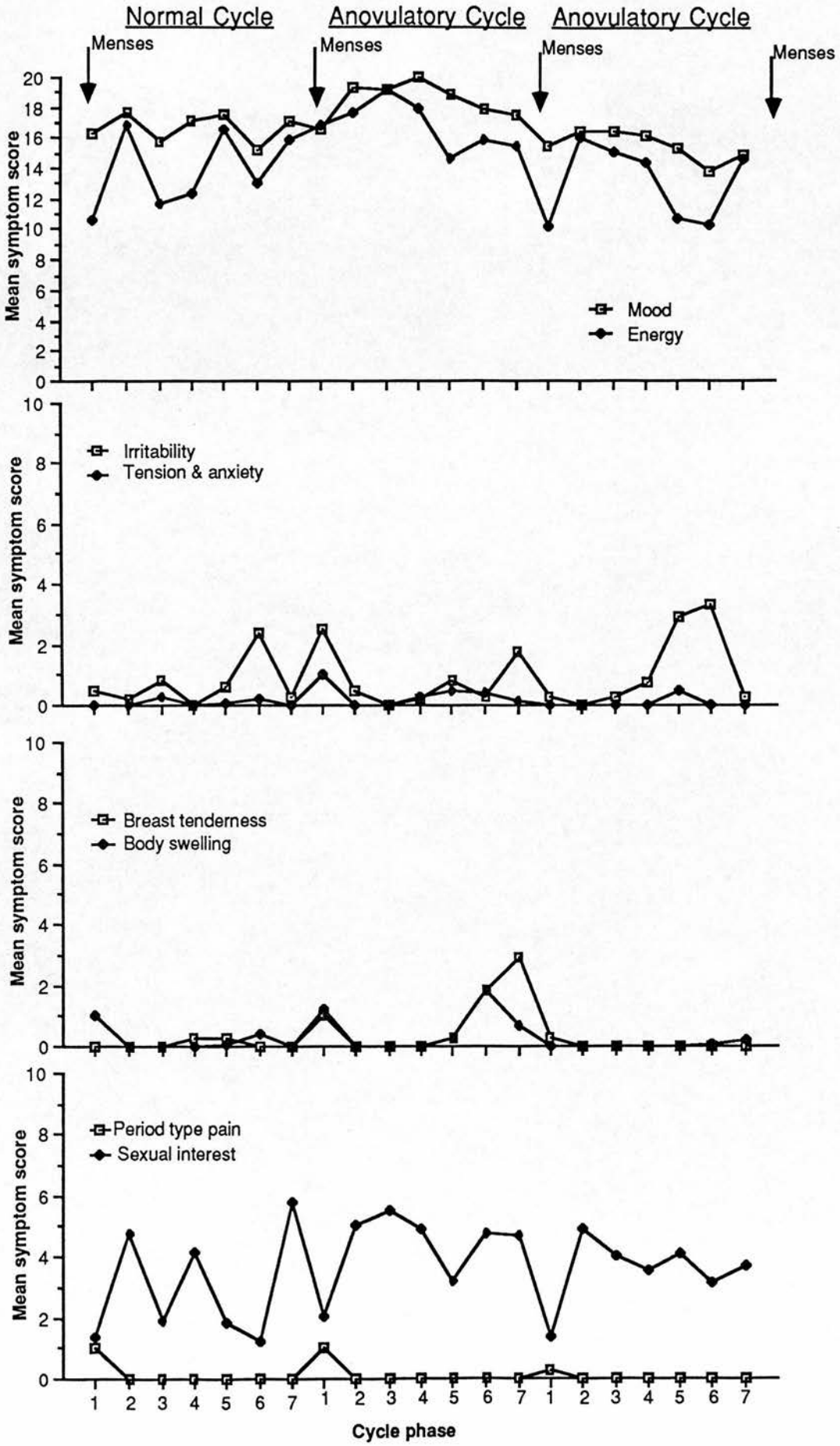


Figure 5.9 Changes in symptom levels with time across 7 standardized cycle phases in one woman (021)

to be the case . The symptom of mood , for instance , would appear to show a more pronounced menstrually related decline in cycle two than in either cycle one or three .

The physical symptoms of breast tenderness and body swelling appear to occur premenstrually during the first anovulatory cycle rather than menstrually following the ovulatory cycle , suggesting a possible alteration in symptom timing . However , this observation is not substantiated in the second anovulatory cycle . Period pain also seems to be less pronounced following an anovulatory cycle , but this difference was insufficient to cause a cycle effect .

Examination of the ANOVA results reveals cycle and cycle x phase effects on measures of energy , breast tenderness and sexual interest . Once more , no evidence appears to suggest that the first cycle is in any way different from the other two in terms of phase effects or average symptom levels . In terms of the latter , cycle two is significantly different from both of the others on measures of mood , energy , tension , breast tenderness , body swelling and sexual interest . The phase effects also suggest that in those cases for which the three cycles do not produce similar effects , cycle two is the odd one rather than cycle one .

In summary :- although mild cyclical changes would appear to be present on most of the symptoms measured for this subject whose timing and severity vary between cycles , this variability does not seem to be systematically related to the presence or absence of ovulation .

c) Summary

No consistent trend appeared in the Group comparison to suggest that anovulatory cycles are necessarily symptomatically different from normal cycles in this group of women . Two provisoes should be borne in mind - firstly , there would appear to be a certain degree of variability between normal cycles , especially on measures of energy , tension and sexual interest , suggesting a potential role for factors other than ovarian hormones . Secondly - the normal cycles in the normal - anovulatory group bore little resemblance to the controls . This may be a reflection of the discrepant sample sizes or may suggest that cyclical patterns are somehow different in women who are regularly experiencing anovulatory cycles from those who experience a consistently ovulatory pattern .

The examination of individuals within the normal - anovulatory group emphasizes the difference between the patterns shown by these subjects

and the typical premenstrual pattern . Premenstrual symptoms did occur in the anovulatory cycles , but these were not always concordant with those experienced by the same woman in a normal cycle . Breast tenderness is the only symptom to show a consistent reduction , in two out of the three women . The observation of symptomatic variability between two anovulatory cycles in the same subject suggests that interpretation of this type of data should be treated with caution .

ii) Normal vs Short Luteal Phase Cycles

a) Group Comparison

Sixteen normal - normal cycle pairs formed the control for this comparison with five normal - short luteal phase subjects . The mean scores within each group form figures 5. 10 to 5.13 inclusive , with ANOVA results in table 5.8 . As before , results from the standardized cycle phase analysis are presented in the Appendix.

The control group exhibited essentially the same patterns as described above (Section 5.3.2 i (a)) , with between cycle differences in symptom profiles evidenced for measures of energy and to a lesser extent sexual interest . Larger cycle differences were seen between the normal and SLP cycles . It should be emphasized here that the normal profile obtained from those women experiencing SLP cycles rarely coincided with that observed in the control group. Only measures of breast tenderness and period pain showed any degree of similarity .

Mood scores showed a marked luteal phase decline in both normal and SLP cycles . However , the fall commenced at an earlier stage in the SLP cycles - towards the end of the follicular phase . In the normal cycles , mood levels remained buoyant until the mid-luteal phase . A slightly biphasic pattern was observed in normal cycles with respect to irritability , with high levels occurring in both mid-to-late luteal and follicular phases . Hence the suggestion of a short period of symptoms at mid-cycle appears . However , in the SLP cycles , irritability levels remain constant throughout , with no evidence of cyclicity . Energy levels similarly show a slightly less marked premenstrual pattern in the SLP cycle , with levels falling in the late follicular phase to a trough in the early luteal phase but rising again before menstruation .This is in contrast to the normal cycles where levels start to fall in the MF phase and continue to fall until menstruation .

A flatter symptom profile in SLP cycles is also observed with respect to body swelling , however these levels are higher ar all phases (except

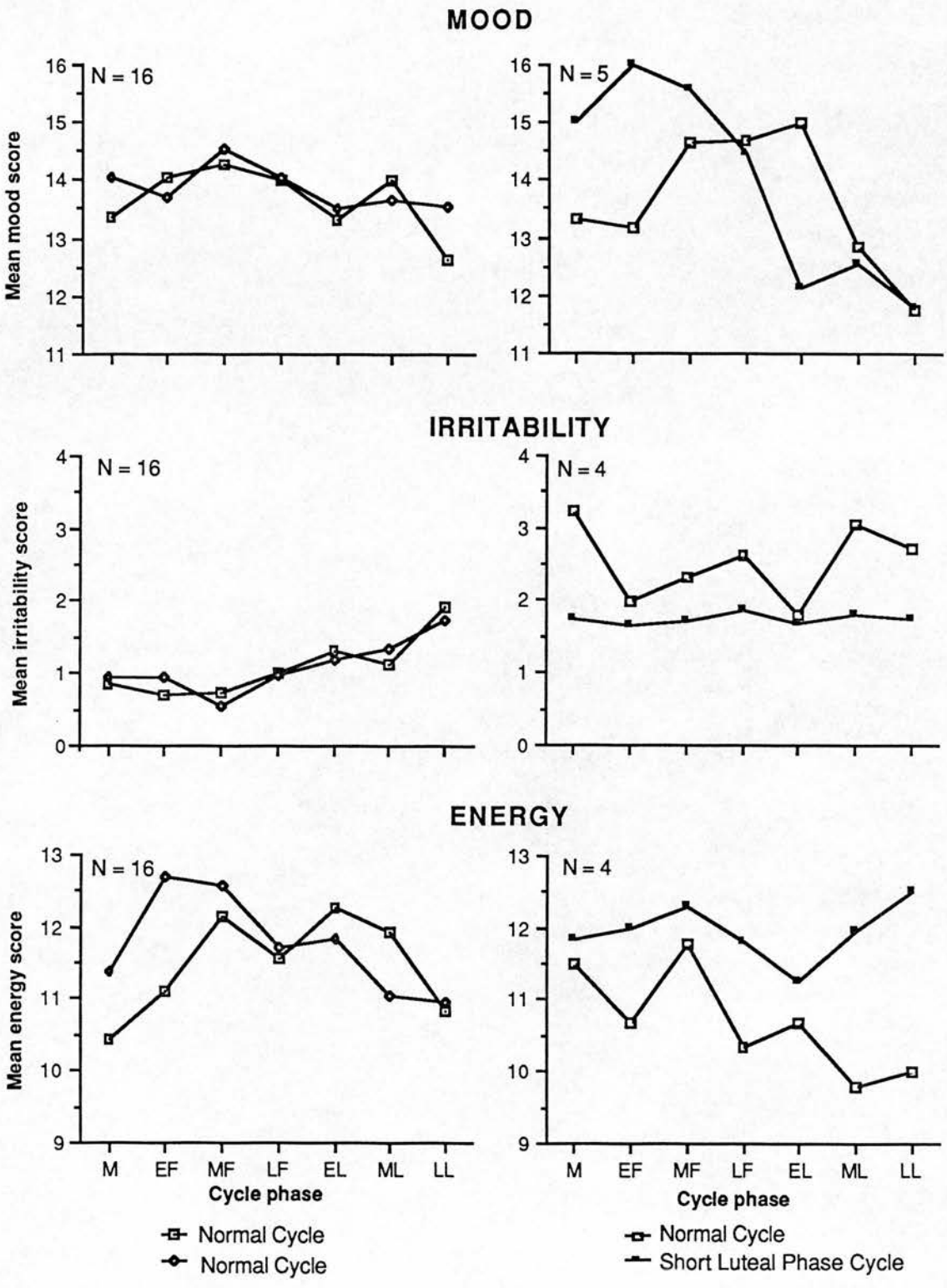


Figure 5.10 Comparison of mood , irritability and energy scores across 7 hormonally defined cycle phases in normal / normal cycle pairs and normal / short luteal phase cycle pairs .

Key :- M = menses ; EF = early follicular ; MF = mid follicular ; LF = late follicular ; EL = early luteal ; ML = mid luteal ; LL = late luteal .

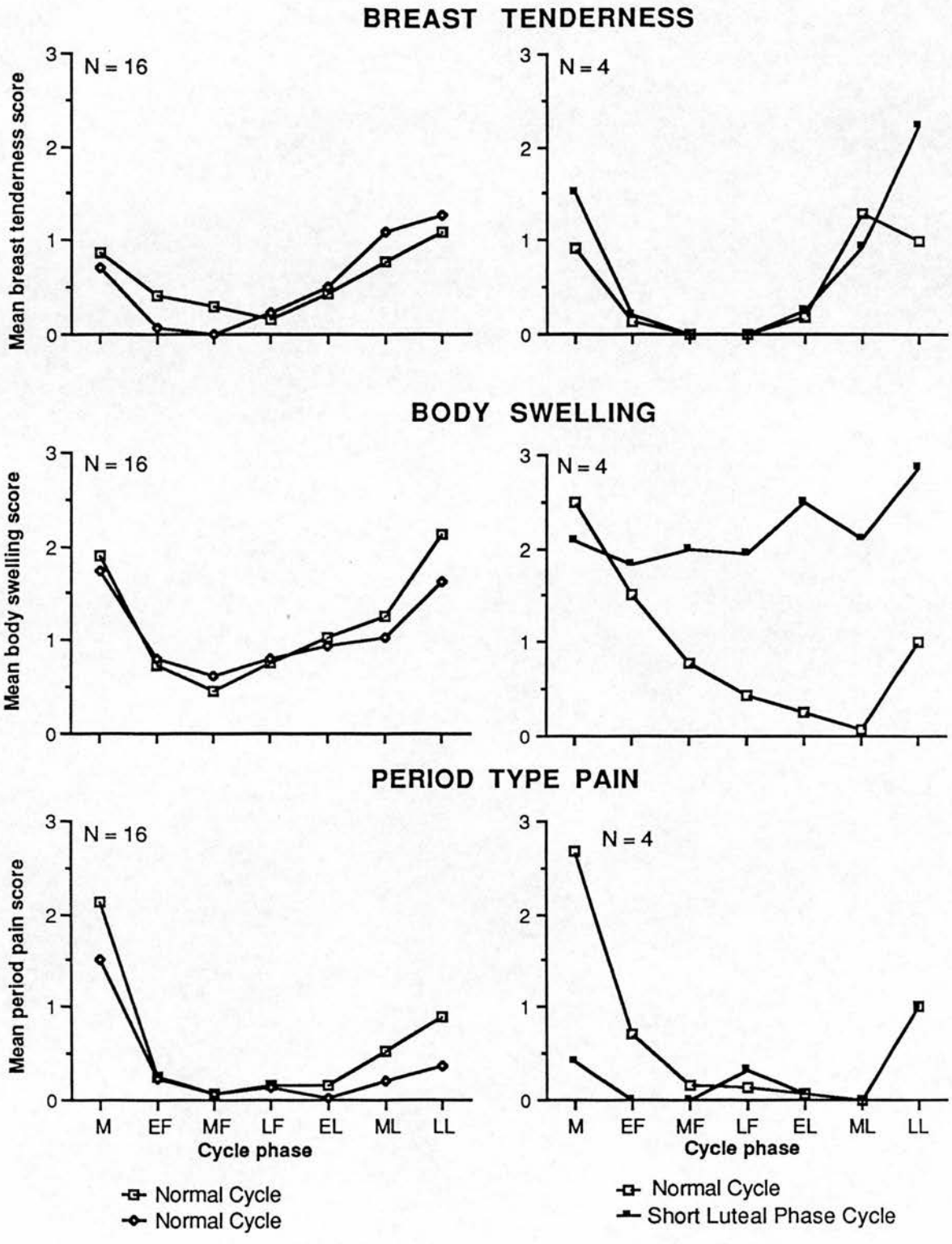


Figure 5.11 Comparison of breast tenderness , body swelling and period pain scores across 7 hormonally defined cycle phases in normal / normal cycle pairs and normal / short luteal phase cycle pairs .

Key :- M = menses ; EF = early follicular ; MF = mid follicular ; LF = late follicular ; EL = early luteal ; ML = mid luteal ; LL = late luteal .

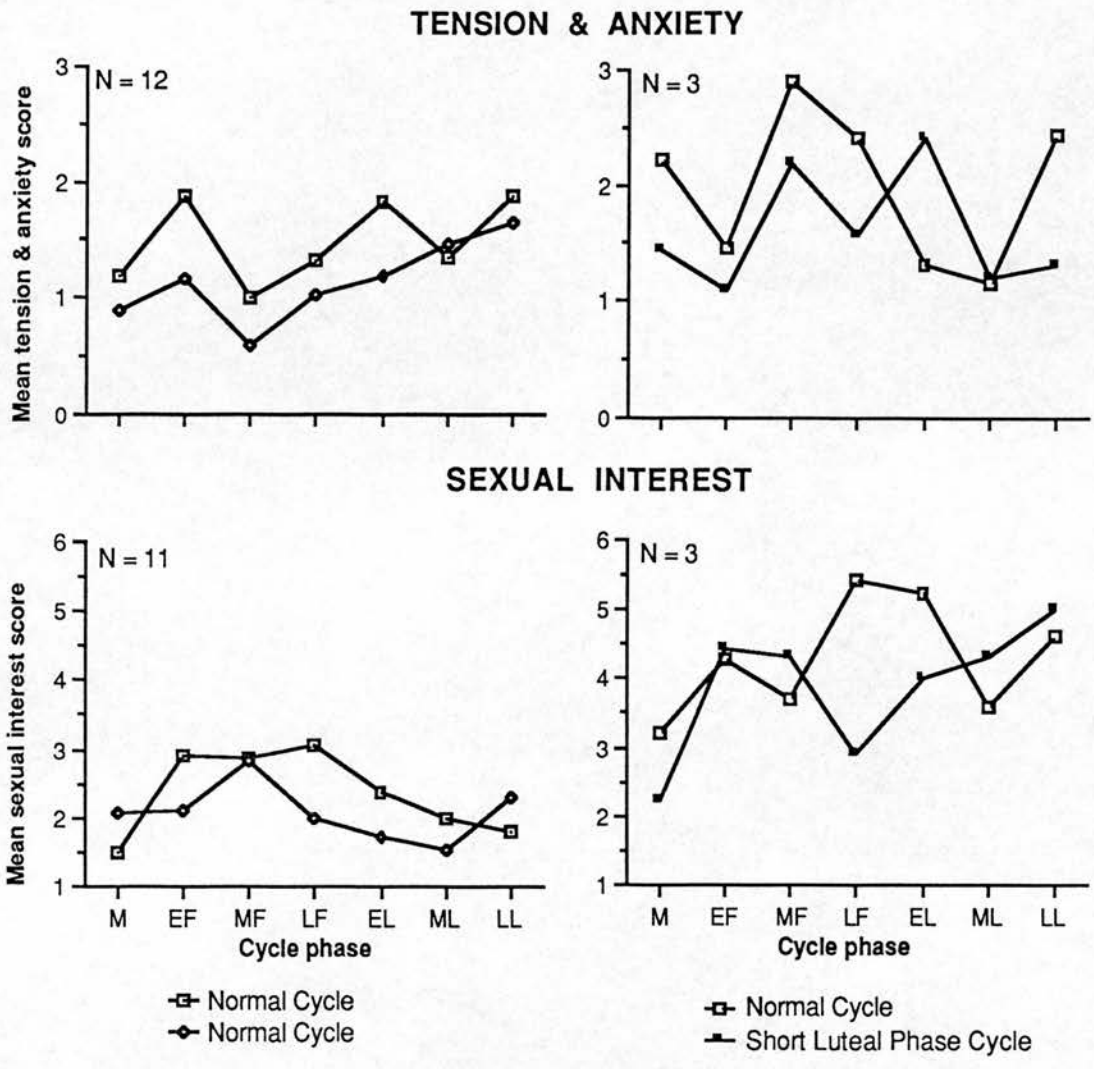


Figure 5.12 Comparison of tension & anxiety and sexual interest scores across 7 hormonally defined cycle phases in normal / normal cycle pairs and normal / short luteal phase cycle pairs .

Key :- M = menses ; EF = early follicular ; MF = mid follicular ; LF = late follicular ; EL = early luteal ; ML = mid luteal ; LL = late luteal .

TABLE 5.8

THREE-WAY AND TWO-WAY ANOVA RESULTS FROM NORMAL AND SLP CYCLES DIVIDED BY MENSTRUAL CYCLE PHASE

i) Three-way ANOVA

	G	C	G x C	P	G x P	C x P	G x C x P
Mood	0	0.39	0.01	2.34 *	0.72	1.67	1.79
Irritable	2.21	2.59	2.37	1.13	0.79	0.43	0.55
Energy	0.04	4.04 *	1.67	0.92	0.65	0.43	0.88
Tense & anxious	0.27	1.49	0.002	0.25	0.91	0.65	0.95
Breast tenderness	0.02	0.32	0.52	5.96 **	0.44	1.17	1.06
Body swelling	0.20	2.29	3.07 T	2.89 **	0.47	1.75	2.24 *
Period pain	0.001	1.71	0.14	6.69 **	0.26	2.75 **	1.61
Sexual interest	2.59	1.68	0.07	2.48 *	1.42	1.87 T	0.94
DF	1	1	1	6	6	6	6

ii) Two-way ANOVA between normal cycles

	C	P	C x P	P@C1	P@C2
Mood	0.25	0.99	0.55	0.99	0.39
Irritable	0.005	3.06 **	0.32	2.00 T	2.05 T
Energy	0.61	0.28 *	1.55	1.62	2.48 *
Tense & anxious	1.59	0.94	0.45	0.61	1.21
Breast tenderness	0.03	5.13 **	0.91	2.61 *	4.54 **
Body swelling	0.16	4.71 **	0.55	3.73 **	3.29 **
Period pain	0.99	8.34 **	0.76	5.07 **	8.31 **
Sexual interest	1.53	2.65 *	1.37	2.39 *	1.44
DF	1	6	6	6,90(60)	

iii) Two-way ANOVA between normal and SLP cycles

	C	P	C x P	P@C1	P@C2
Mood	0.23	0.91	1.46	1.07	1.04
Irritable	8.83 *	0.42	0.58	0.65	0.03
Energy	4.51	0.95	0.51	0.73	0.49
Tense & anxious	1.06	0.72	1.46	0.75	1.46
Breast tenderness	2.72	1.57	2.39 T	1.04	2.15 T
Body swelling	0.88	1.21	1.49	1.26	2.22 T
Period pain	2.16	2.24 T	3.31 *	3.59 **	0.84
Sexual interest	0.41	1.41	1.65	0.93	2.82 T
DF	1	6	6	6,18(12)	

Key :- T - trend ($p < 0.10$) ; * - $p < 0.05$ ** - $p < 0.01$

G - Group ; C - Cycle ; P - Phase ; DF -Degrees of freedom .
(Numbers in brackets indicate DFe for sexual interest)

menstruation) than the normal cycle , and do show a slight upward trend in the luteal phase . Symptoms in the normal cycles show a rather more idiosyncratic pattern too - falling from a menstrual peak to a mid-luteal phase trough , but rising again in the late luteal phase . Tension and anxiety scores are essentially similar in both cycles , except in the early and late luteal phases in which the SLP data shows more and less tension than the normal data respectively . Similarly in the case of sexual interest , a slightly different profile is seen , with the midcycle peak and mid-luteal trough of sexuality being absent from SLP cycles .

The 2x2x7 ANOVA results reveal no significant group differences and only one GxCxP interaction - for body swelling . Two-way results indicate an overall cycle difference between normal and SLP in the case of irritability . Differences in phase effects between cycles occurred on measures of energy and sexual interest in the control group and on breast tenderness , body swelling , period pain and sexual interest in the comparison group .

As in the normal - anovulatory group , the imposition of a 28 day cycle on this data had little effect on its character .

b) Individual Comparison

Five subjects fall into the category of normal and short luteal phase cycle pairs. One of these also experienced an inadequate luteal phase , and hence will be discussed in both sections . The data are represented graphically in figures 5.13 to 5.17 inclusive , and the ANOVA results tabulated in table 5.9 .

Subject 002

In this subject , mood was the only symptom assessed . A clear premenstrual pattern was seen , with lowest levels occuring immediately before menstruation in both cycles . They did however begin to fall earlier in the SLP cycle and reached a lower level . Analysis of Variance reveals strong phase effects in both cycles , with a cycle x phase interaction . This latter would appear to be related to the slightly different symptom timing , since no difference is seen in the overall mean mood scores between the two cycles .

Subject 003

In this case , a short luteal phase was experienced before the first post-partum menstruation , followed by three normal cycles . Hence , the first cycle might be expected to be symptomatically different from the others . However , the potentially confounding psychological and physiological

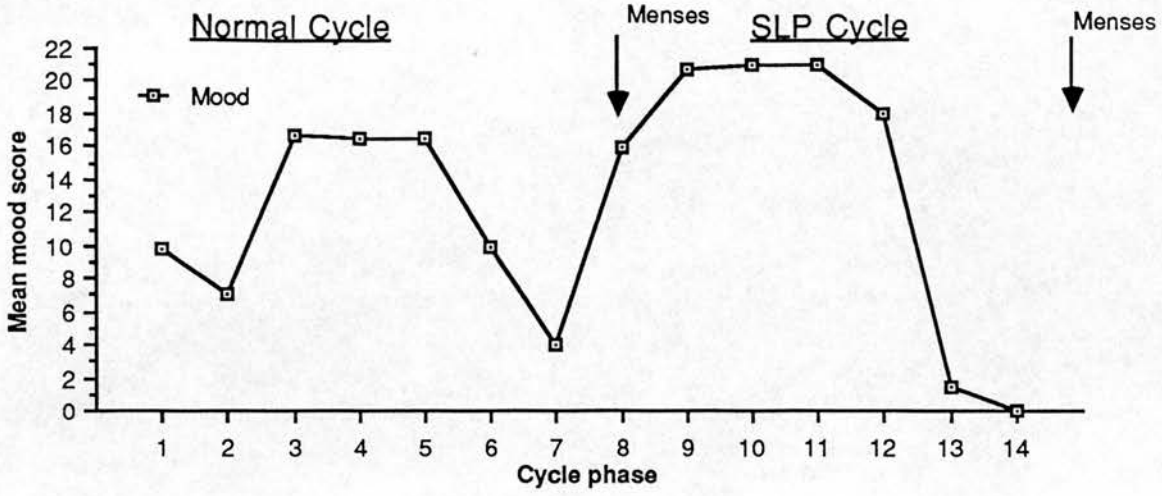


Figure 5.13 Changes in mood levels with time across 7 standardized cycle phases in one woman (002)

effects of being the first post-partum cycle should be borne in mind . In this case , physiological effects associated with the cessation of breast feeding may be involved . This is particularly true for the symptom of body swelling , high levels of which were experienced throughout lactation . After the first menstruation , however , the symptom diminishes and shows signs of becoming menstrually related in later cycles . Whether the high luteal levels in cycle one are a function of the short luteal phase diagnosis or of some other post lactational physiological change cannot be distinguished .

Some evidence for a difference between cycle one and the other three on the basis of phase effects is apparent on measures of breast tenderness and sexual interest . In the former case , breast tenderness is present in the early stages of cycle one , not the luteal phase , resulting in a significant phase effect . However, its presence is possibly more likely to be due to lactational cessation . Arguably , too , the phase effects seen in sexual interest in cycles two , three and four may have more to do with menstrual abstinence than hormonal events .

Hence , although cyclical changes are seen in some symptoms , with differences being apparent , potentially due to the presence of a short luteal phase cycle , other explanations related to the temporal association with lactation etc. are potentially more plausible .

Subject 022

In this subject a SLP cycle is preceded by two normal cycles , again suggesting a possible " odd one out " scenario . This would appear to be

TABLE 5.9

INDIVIDUAL ANOVA RESULTS FOR SUBJECTS 002 , 003 , 022 , 024 & 047 .

SUBJECT 002

	C	P	CxP	P@C1	P@C2
Mood	3.99	22.47**	14.78**	6.51**	53.96**
DF	1	6	6	6,18	

SUBJECT 003

	C	P	CxP	P@C1	P@C2	P@C3	P@C4
Mood	17.32**	3.09*	1.95*	1.37	1.45	6.00**	1.72
Irritable	1.73	1.31	2.28**	2.29T	2.51T	2.75*	1.20
Energy	5.57*	1.71	1.97*	2.09	4.20**	0.72	1.28
Breast tenderness	23.63**	10.12**	8.25**	19.40**	2.06	0.85	3.40
Body swelling	827.9**	34.04**	55.73**	3.19*	123.4**	9.50**	22.78**
Period pain	3.73*	10.29**	2.89**	0.87	10.73**	4.07**	2.99**
Sexual interest	1.97	3.77**	0.86	0.78	2.29T	5.10**	5.16**
DF	3	6	18	6,18			

C1v C2	C1v C3	C1v C4	C2v C3	C2v C4	C3v C4
*	*	ns	**	*	*
ns	ns	ns	ns	ns	ns
*	ns	*	ns	ns	ns
**	**	**	ns	ns	ns
**	**	**	**	**	ns
ns	ns	ns	ns	ns	ns
ns	ns	ns	ns	ns	ns

SUBJECT 022

	C	P	CxP	P@C1	P@C2	P@C3
Mood	40.49**	1.88	5.39**	6.46**	4.17**	1.99
Irritable	13.35**	3.16*	1.67	3.08*	2.36T	0.84
Energy	1.74	1.52	2.77**	2.39T	3.18*	0.03
Tense & anxious	21.94**	2.22T	3.83**	4.13**	1.46	2.91*
Breast tenderness	6.92*	2.95*	2.95**	2.95*	3.40	3.40
Body swelling	103.0**	3.58*	6.23**	9.14**	2.47T	3.40
Period pain	4.69T	7.06**	1.18	3.33*	4.65**	2.32T
Sexual interest	4.39T	1.56	3.32**	2.33T	3.16*	3.14*
DF	2	6	12	6,18		

C1vC2	C1vC3	C2vC3
**	ns	**
**	ns	*
ns	ns	ns
**	**	ns
*	*	ns
**	**	**
ns	ns	ns
ns	ns	ns

Table 5.9 Continued .

Subject 024

	C	P	CxP	P@C1	P@C2	P@C3	P@C4	C1 v C2	C1 v C3	C1 v C4	C2 v C3	C2 v C4	C3 v C4
Mood	68.77**	4.94**	6.37**	6.35**	6.80**	1.33	3.80**	**	**	*	**	**	**
Irritable	7.49**	3.03**	6.61**	5.48**	8.93**	0.84	9.09**	ns	*	ns	**	ns	ns
Energy	110.3**	8.55**	5.54**	10.34**	20.65**	0.60	7.07**	*	**	**	**	**	**
Tense & anxious	15.42**	6.42**	5.13**	3.95**	7.41**	1.00	6.25**	ns	*	*	**	**	ns
Breast tenderness	16.15**	25.40**	4.82**	7.73**	9.50**	21.91**	12.87**	**	**	**	ns	ns	ns
Body swelling	0.79	11.75**	6.08**	4.92**	19.99**	2.79**	14.02**	ns	ns	ns	ns	ns	ns
Period pain	4.28*	5.11**	6.28**	6.89**	4.67**	1.00	4.69**	ns	ns	ns	ns	ns	ns
DF	3	6	18	6,18									

Subject 047

	C	P	CxP	P@C1	P@C2	P@C3	P@C4	C1 v C2	C1 v C3	C1 v C4	C2 v C3	C2 v C4	C3 v C4
Mood	16.61**	9.23**	2.83**	5.59**	1.87	13.30**	3.34*	**	**	**	ns	ns	ns
Irritable	9.56**	9.42**	3.00**	1.02	3.75*	18.14**	5.98**	*	ns	**	ns	**	*
Energy	6.34**	3.97**	3.39**	3.19*	3.19*	6.80**	1.00	*	ns	**	ns	ns	*
Tense & anxious	88.10**	4.62**	2.67**	5.06**	2.67*	2.68*	2.34T	**	**	**	**	**	**
Breast tenderness	9.90**	7.06**	8.38**	1.75	3.40	50.73**	2.24T	*	*	ns	**	ns	**
Body swelling	111.2**	16.90**	22.88**	1.41	3.00*	28.84**	1.21	ns	**	ns	**	ns	**
Period pain	6.41*	3.29*	2.70**	1.01	5.57**	6.48**	1.39	ns	ns	*	ns	ns	**
Sexual interest	26.58**	2.14T	1.75T	1.10	1.75	3.29*	3.06*	**	**	**	*	**	ns
DF	3	6	18	6,18									

Key :- C - Cycle ; P - Phase ; ns - not significant ; T - trend ($p < 0.10$)

* - $p < 0.05$; ** - $p < 0.01$ DF - degrees of freedom .

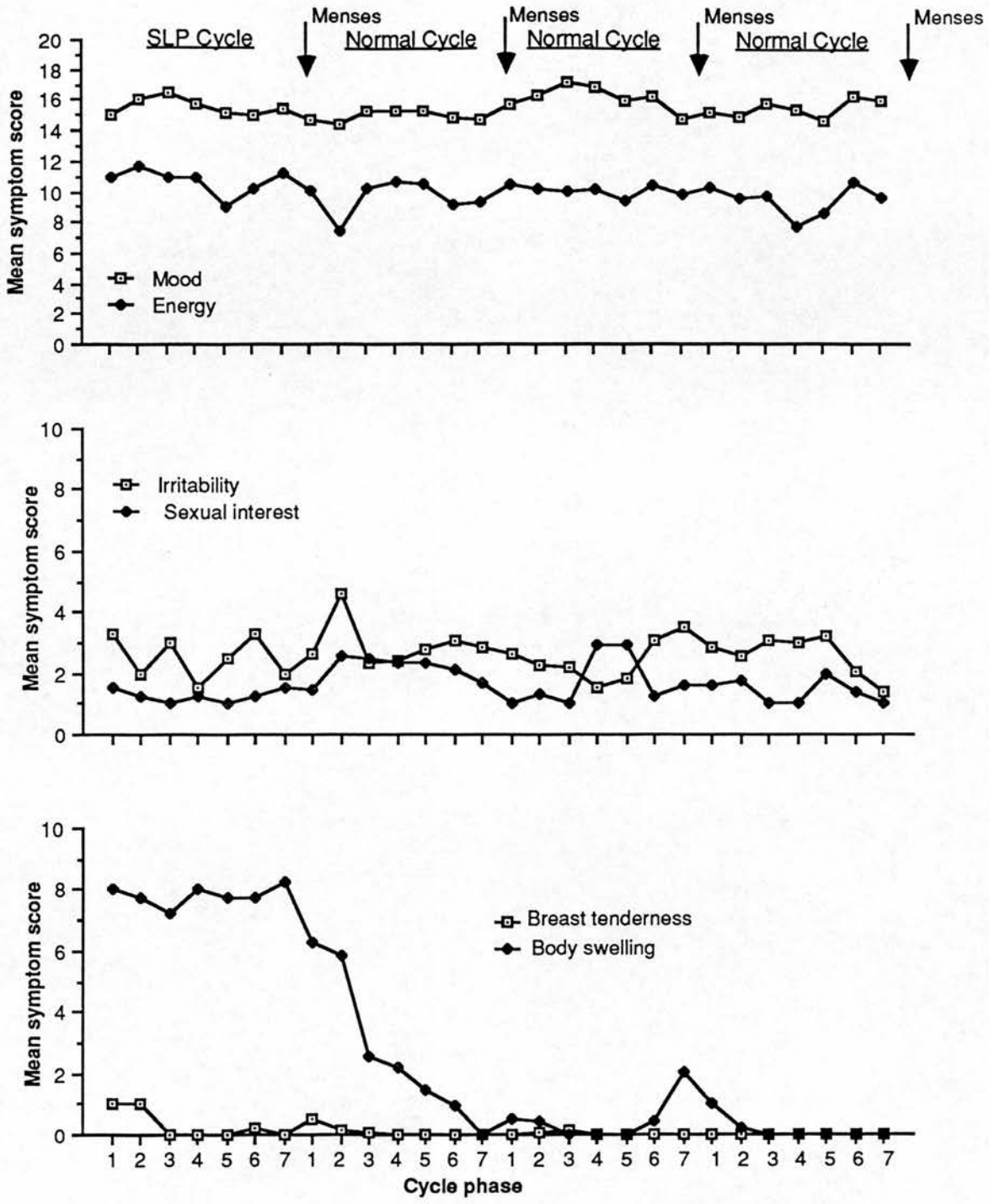


Figure 5.14 Changes in symptom levels with time over 7 standardized cycle phases in one woman (003)

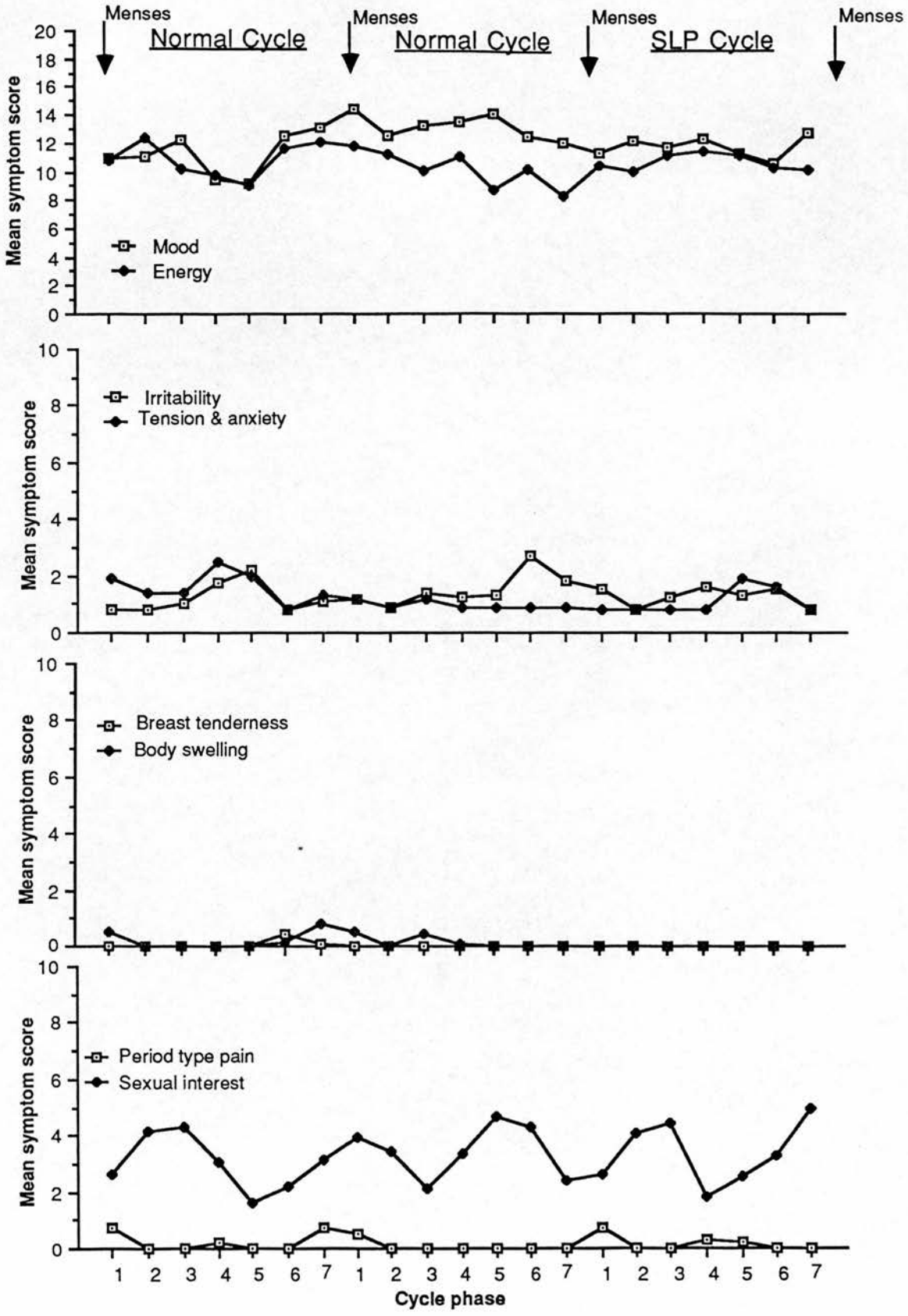


Figure 5.15 Changes in symptom levels with time across 7 standardized cycle phases in one woman (022)

the case with irritability , a much flatter picture being seen in the SLP cycle . Closer examination reveals however , that the peaks evident in cycles one and two are not coincident , with only the latter occurring premenstrually . The measures of mood and energy also reveal similarities between the first two cycles with cycle three being different on the basis of phase effects . However , the same observation applies , that while the SLP cycle may have a flatter profile than either of the others , the timing of symptom peaks in the first two cycles is asynchronous . Differences in overall mean symptom levels between cycles also do not appear to systematically suggest that the presence of a short luteal phase necessarily makes any difference to symptomatic experience .

One point of interest in this subject is the observation of cyclical changes in sexual interest . These cycles are quite clear , having a " wavelength " of approximately 4 - 5 phases (N.B. the x- axis in this case refers to standardized cycle phases , rather than " real time ") . Hence the cycles are shorter than the menstrual cycle and do not appear to be temporally linked to it . Although the presence of such a pattern in only one symptom for one woman reduces its theoretical significance , the possibility is raised that feelings and moods may fluctuate independently of both the menstrual cycle and each other .

Subject 024

A variety of endocrinological diagnoses are apparent for this subject . In this context , however , cycle one - the inadequate luteal phase cycle , will not be discussed . This leaves two short luteal phase cycles , which might be expected to be symptomatically similar , followed by a normal cycle . However , in this case a uterine polyp was removed under general anaesthesia during cycle two , causing some disruption of her normal lifestyle and leading to a great deal of tension and worry about the operation. Therefore cycle two cannot be considered to be typical and was not included in the group comparison . Hence a difference due entirely to the presence of a short luteal phase might be expected to be manifest between cycles three and four .

Very few differences in luteal symptom timing or severity are apparent between these two cycles . Mean overall levels of mood , energy and irritability are lower in the normal cycle . Phase effects are also present in cycle four but not in cycle three on these measures . This observation probably has more to do with the absence of a menstrually related drop in

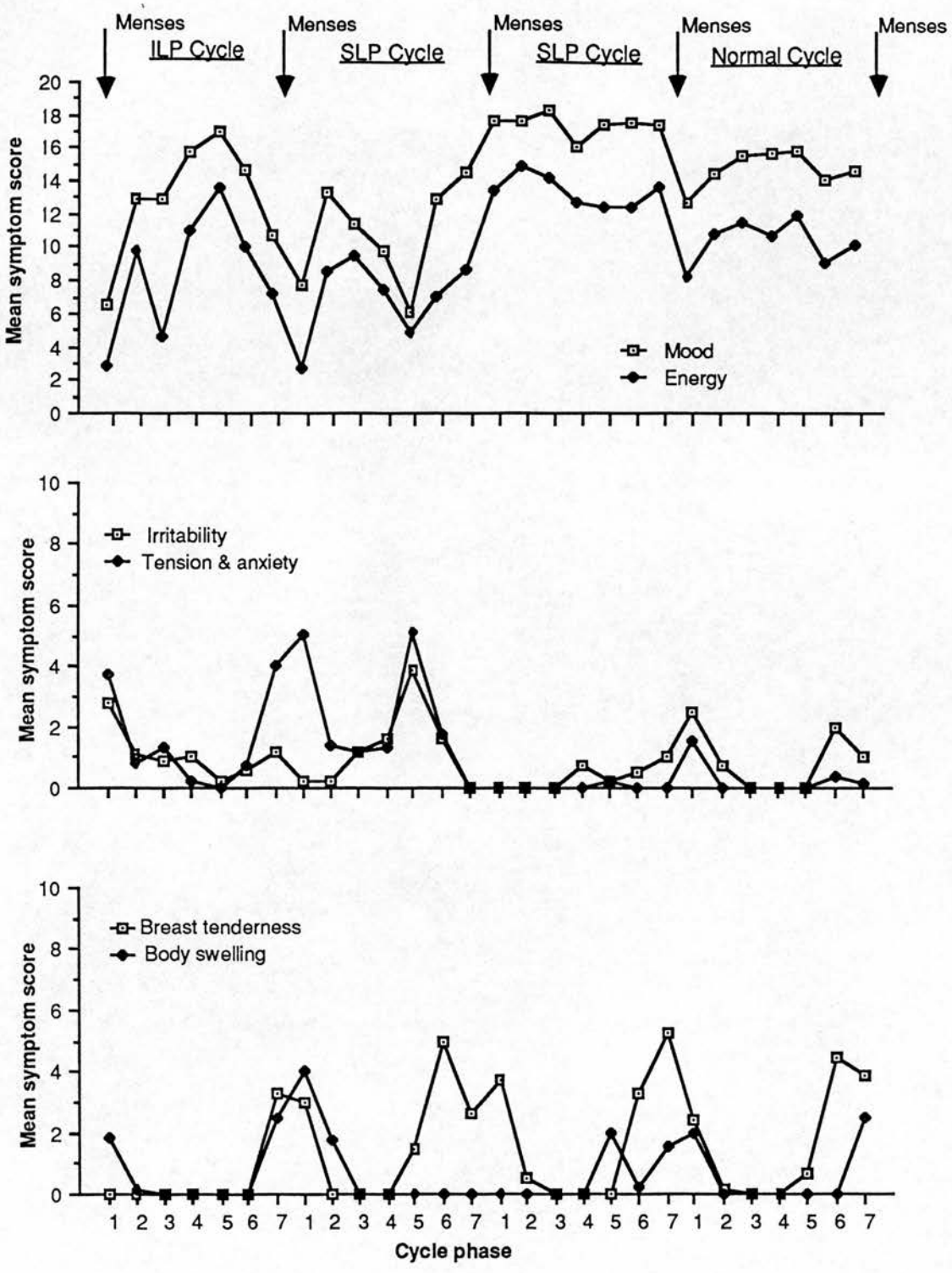


Figure 5.16 Changes in symptom levels with time across 7 standardized cycle phases in one woman (024)

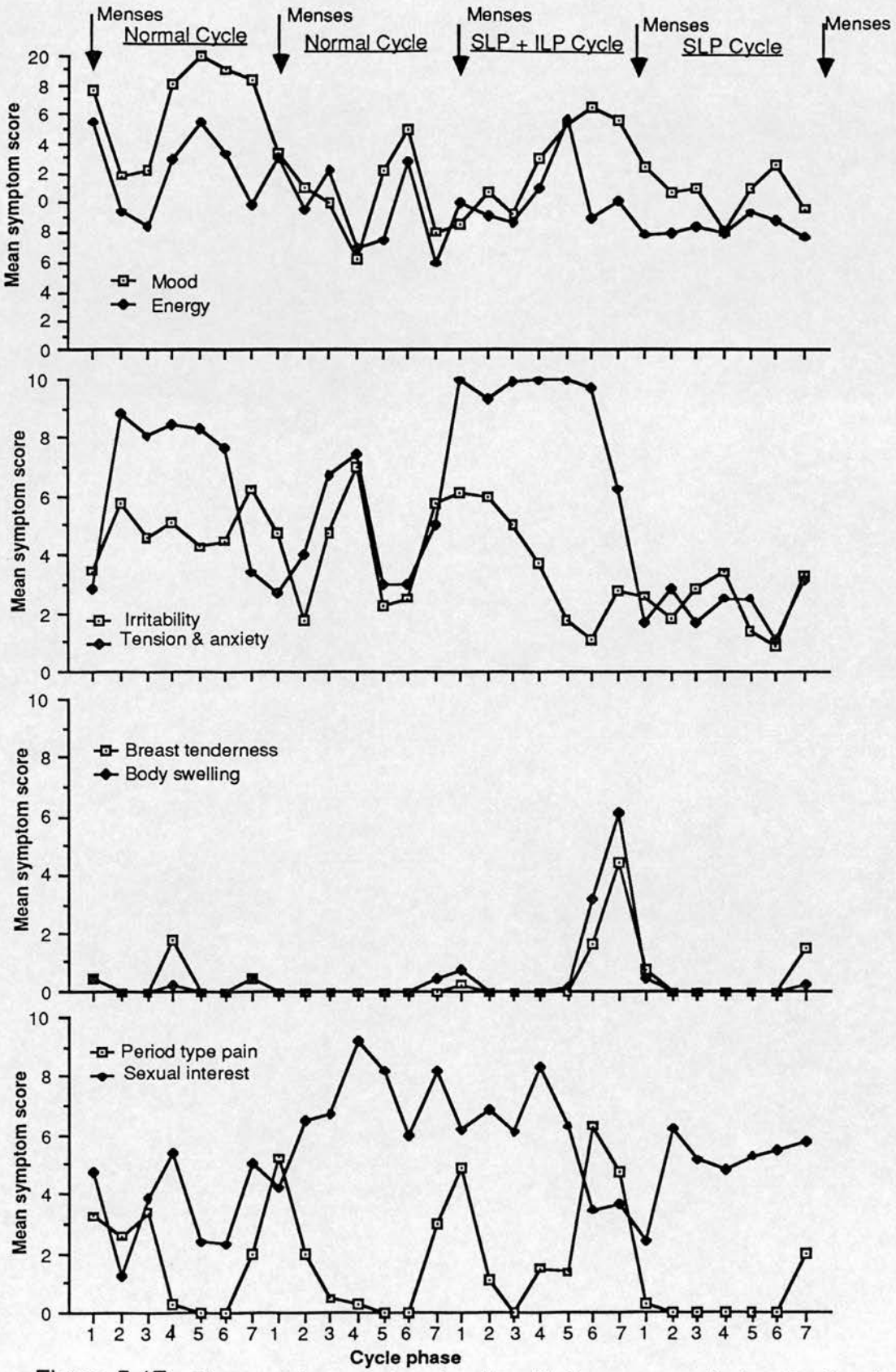


Figure 5.17 Changes in symptom levels with time across 7 standardized cycle phases in one woman (047)

mood and energy and rise in irritability during phase 1 of cycle three than any difference in luteal symptoms . Tension & anxiety shows a similar pattern although no difference occurs in mean levels . The physical symptoms of breast tenderness and body swelling are virtually indistinguishable .

Hence , there is a suggestion that this person may be happier and more energetic , but also more irritable and more tense in a short luteal phase cycle , although the symptoms experienced tend to be menstrually related rather than premenstrual .

Subject 047

Once more a variety of diagnoses are present in this subject , with two normal cycles being followed by a combined short and inadequate luteal phase cycle and a short luteal phase cycle.

The first striking observation is the difference in symptomatology , particularly with respect to mood , between the two normal cycles . The second is the marked difference in physical symptoms of breast tenderness and body swelling in cycle three , compared with the other cycles . The presence of these symptoms may perhaps be more closely related to the inadequacy of the luteal phase , since they are less severe in cycle four . Tension and anxiety levels are also higher in cycle three , although this would appear to be a chronic rather than a cyclical phenomenon .

ANOVA produces significant cycle , phase and cycle x phase effects for all parameters measured , except for sexual interest , in which the level of significance is narrowly missed . An examination of phase effects within each cycle emphasizes the lack of symptomatic concordance between consecutive normal cycles . Cycle three is distinguished by strongly significant phase effects on all measures . However , the patterns producing these effects are only "premenstrual " in the case of breast tenderness , body swelling and sexual interest .

In summary , the degree of variability between the two normal cycles in this subject makes data interpretation difficult . There seems to be little to suggest , however , that symptoms in the SLP cycle are any different from normal . The combination of SLP and ILP was however distinguished by the presence of premenstrual breast tenderness and body swelling , absent from other cycles .

c) Summary

The group comparison suggested that symptom profiles may be flatter in SLP cycles , although this is not necessarily associated with lower levels of symptom severity . In the case of body swelling , a suggestion appears of chronic symptoms throughout the SLP cycle . However , in the cases of energy and irritability , a rather more constant and preferential symptom level was observed (i.e. higher energy levels and lower irritability levels) .

The examination of individual data reveals no consistencies between subjects or symptoms . The presence of chronic body swelling (above) can be explained by the post-partum status of one particular subject , rather than by an effect of the SLP. There did not appear to be any suggestion that symptom duration was necessarily shorter or intensity less than in normal cycles in any subject .

iii) Normal vs Inadequate Luteal Phase Cycles

a) Group Comparison

In this case seventeen normal - normal pairs formed the control group , with four normal - inadequate luteal phase (ILP) pairs forming the comparison group. The mean scores for each symptom are described in figures 5.18 to 5.20 inclusive , with ANOVA results in tables 5.10 . Results of the standardized cycle phase analysis are presented in the Appendix . Any differences and similarities in the control group are essentially as described in section 5.3.2 i (a) .

The physical symptoms of breast tenderness and body swelling are reduced in the luteal phase of ILP cycles compared to controls . This does not however apply to period pain , which showed higher menstrual and late luteal levels in ILP cycles . Lower levels of sexual interest also occurred throughout the ILP cycles , although a very slight late follicular peak was still present . A slightly increasing level of interest was shown throughout the luteal phase in these cycles compared to the falling levels seen in the normal cycles . Levels of tension followed almost exactly the same pattern in both normal and ILP cycles , being slightly higher in the ILP cycles at all points except the early luteal phase .

In the case of mood and energy , no premenstrual decrease was observed in ILP cycles , this was also true for irritability , when no increase in irritability was seen premenstrually . In ILP cycles , low mood and energy and high irritability seemed to occur in the late follicular phase, i.e. at

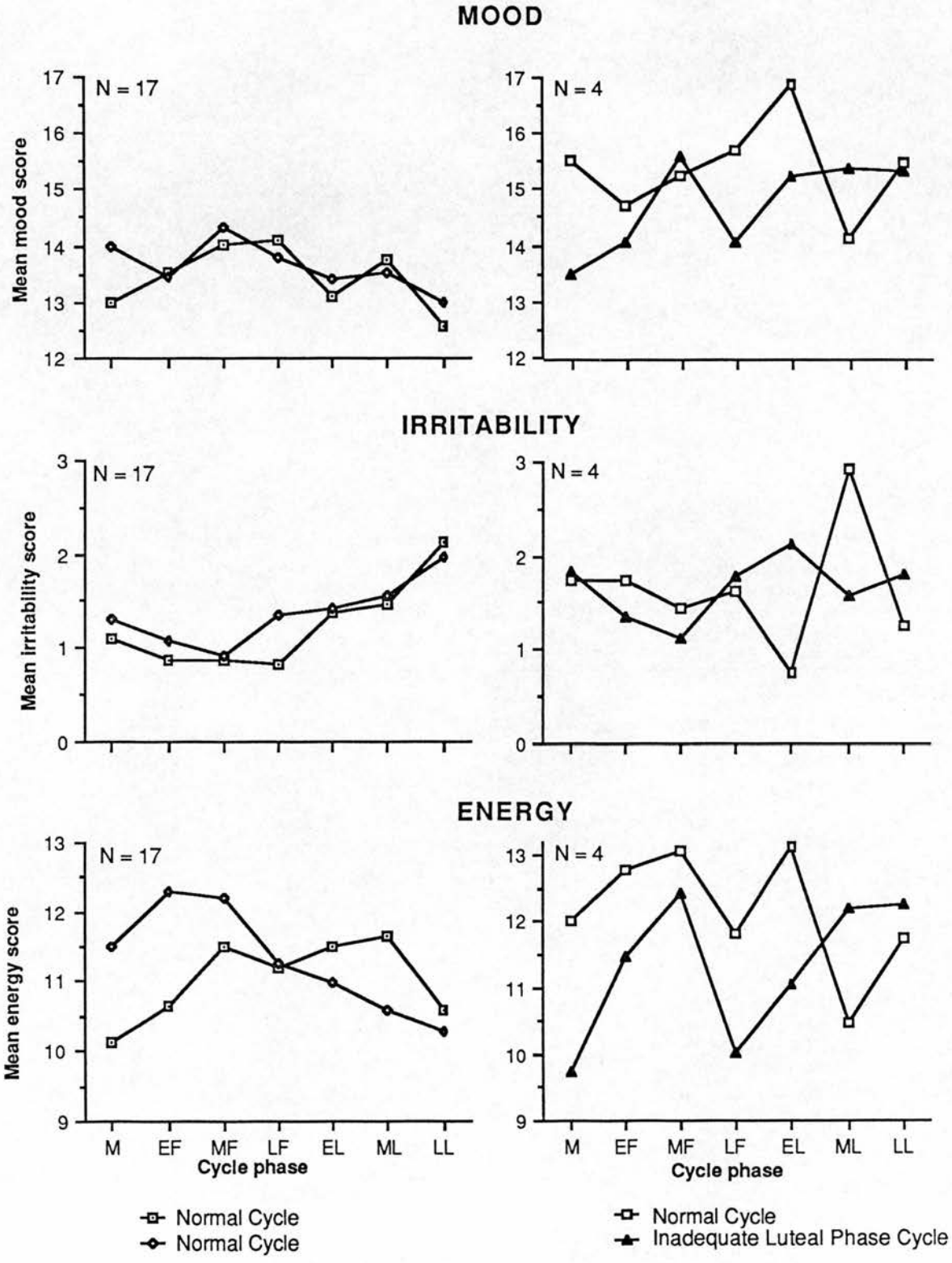


Figure 5.18 Comparison of mood , irritability and energy levels across 7 hormonally defined cycle phases in normal / normal cycle pairs and normal / inadequate luteal phase cycle pairs .

Key :- M = menses ; EF = early follicular ; MF = mid follicular ; LF = late follicular ; EL = early luteal ; ML = mid luteal ; LL = late luteal .

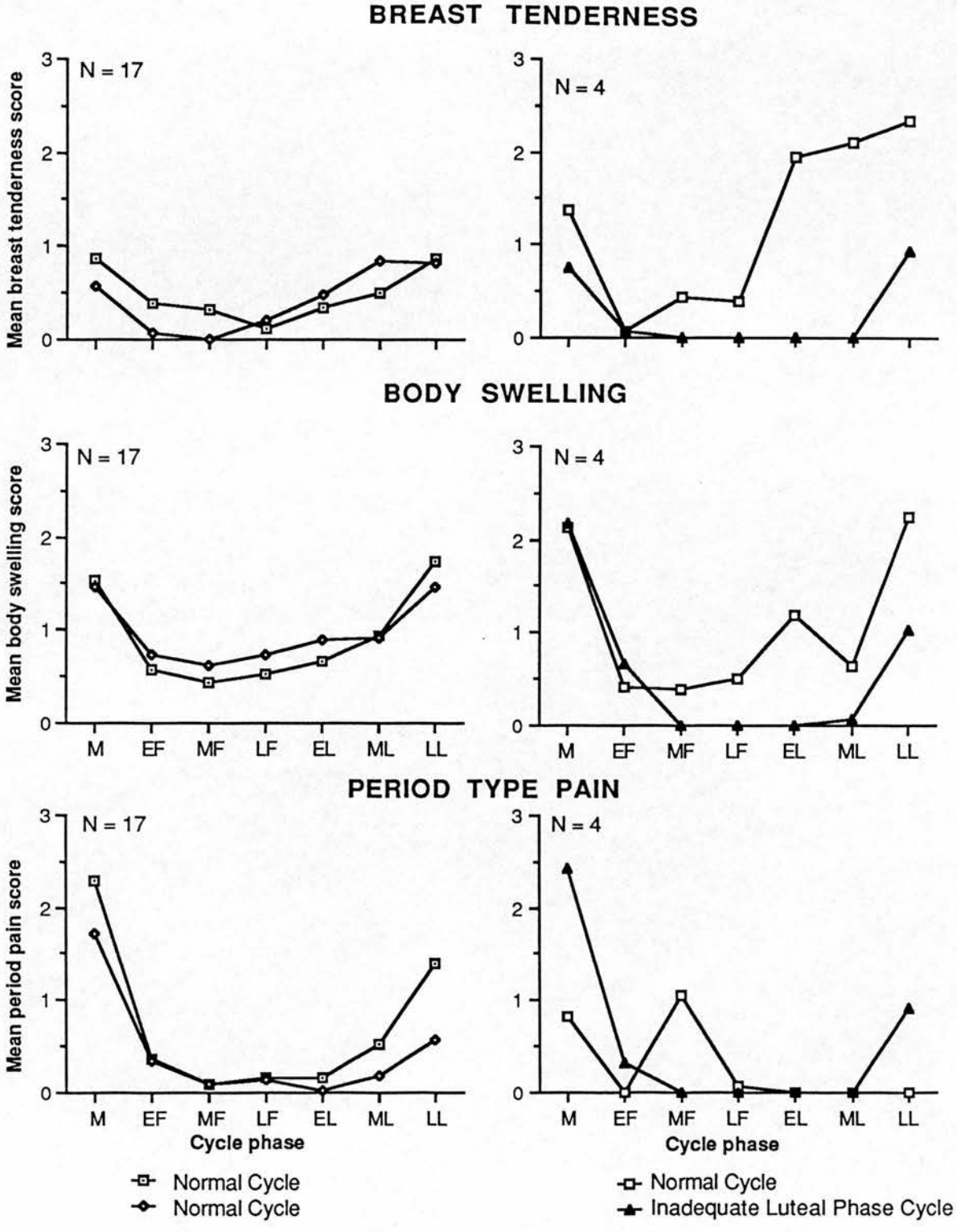


Figure 5.19 Comparison of breast tenderness , body swelling and period pain scores across 7 hormonally defined cycle phases in normal /normal cycle pairs and normal / inadequate luteal phase cycle pairs .

Key :- M = menses ; EF = early follicular ; MF = mid follicular ; LF = late follicular ; EL = early luteal ; ML = mid luteal ; LL = late luteal .

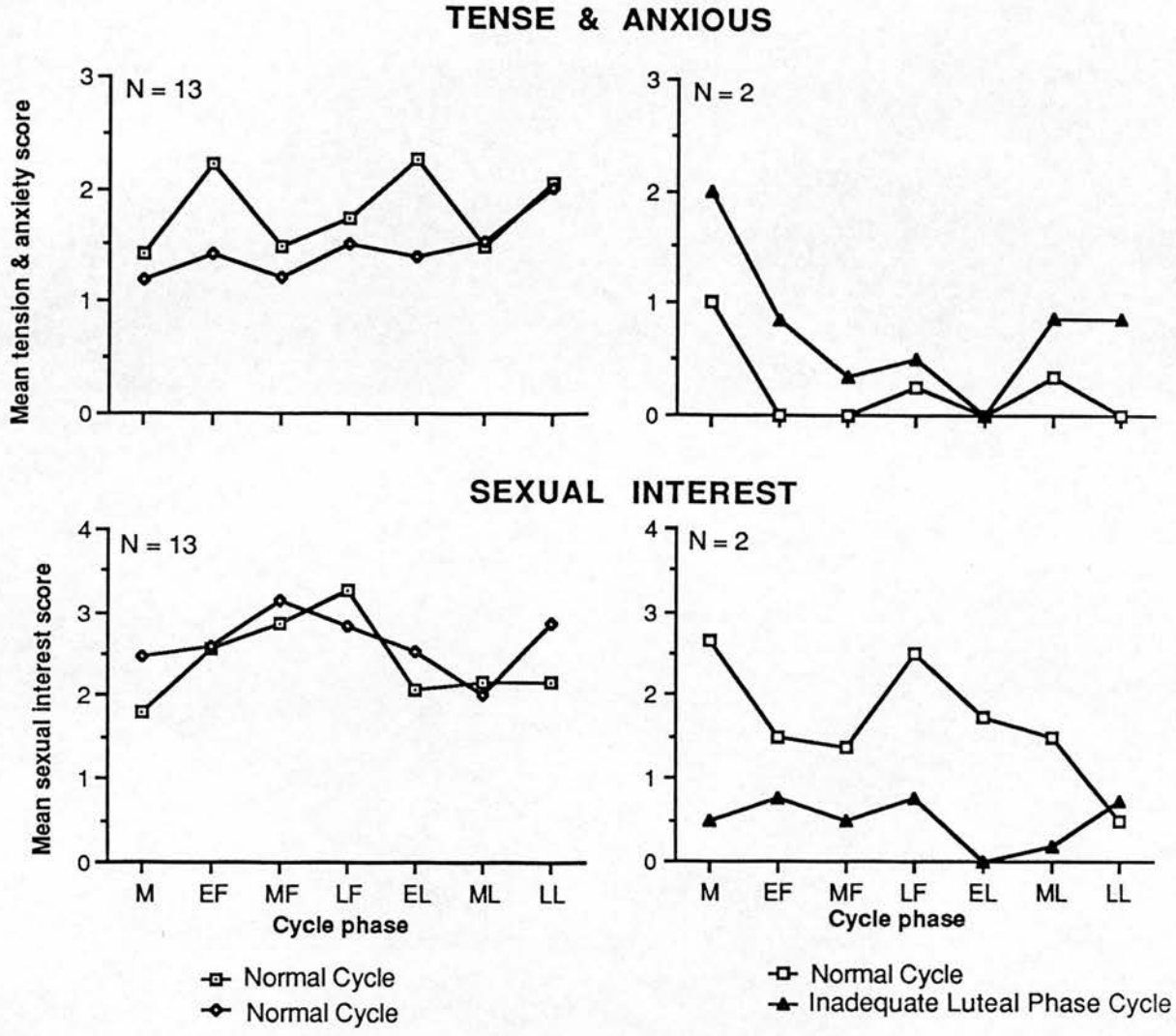


Figure 5.20 Comparison of tension & anxiety and sexual interest scores acrc 7 hormonally defined cycle phases in normal / normal cycle pair and normal / inadequate luteal phase cycle pairs .

Key :- M = menses ; EF = early follicular ; MF = mid follicular ; LF = late follicular ; EL = early luteal ; ML = mid luteal ; LL = late luteal .

TABLE 5.10

THREE-WAY AND TWO-WAY ANOVA RESULTS(F-VALUES) FOR NORMAL AND ILP CYCLES DIVIDED BY MENSTRUAL CYCLE PHASE

i) Three-way ANOVA .

	G	C	G x C	P	G x P	C x P	G x C x P
Mood	1.49	0.27	0.99	0.23	0.84	0.57	0.99
Irritable	0.23	0.09	0.06	1.43	0.93	1.15	1.35
Energy	0.13	0.46	1.79	1.39	0.54	0.76	2.56*
Tense & anxious	1.15	0.08	1.54	0.21	0.53	0.29	0.15
Breast tenderness	0.67	7.62**	5.94*	6.01**	0.88	1.07	2.86**
Body swelling	0.03	1.43	2.11	5.84**	0.69	1.05	0.77
Period pain	0.28	0.003	1.21	6.67**	0.41	0.79	2.37*
Sexual interest	1.32	0.89	2.05	1.06	0.66	0.47	0.26
DF	1	1	1	6	6	6	6

ii) Two-way ANOVA between normal cycles .

	C	P	C x P	P@C1	P@C2
Mood	0.07	1.24	0.28	0.91	0.92
Irritable	0.37	3.84**	0.55	3.32**	1.74
Energy	0.54	1.56	2.94**	1.32	3.26**
Tense & anxious	1.67	0.64	0.76	0.69	0.65
Breast tenderness	0.14	4.22**	1.25	2.68**	3.33**
Body swelling	0.08	3.78**	0.53	3.15**	2.47*
Period pain	1.56	10.27**	1.23	6.81**	10.11**
Sexual interest	0.43	3.20**	0.69	2.24*	1.02
DF	1	6	6	6,96(72)	

iii) Two-way ANOVA between normal and ILP cycles

	C	P	C x P	P@C1	P@C2
Mood	1.05	0.66	0.66	0.86	0.54
Irritable	0.004	0.50	0.76	0.91	0.29
Energy	1.77	0.69	1.09	1.40	0.67
Tense & anxious	1.19	0.85	0.57	0.84	0.79
Breast tenderness	6.37T	1.76	0.92	1.31	1.66
Body swelling	4.56	5.93**	0.89	2.74*	5.07**
Period pain	2.45	2.82*	0.86	1.02	1.85
Sexual interest	2.43	0.59	0.35	0.45	0.39
DF	1	6	6	6,18(6)	

Key :- DF- degrees of freedom; T - trend ($p < 0.10$); * - $p < 0.05$; ** - $p < 0.01$; G - Group ; C - Cycle ; P - Phase .

midcycle , rather than premenstrually . It is perhaps significant that maximal symptom occurence in the equivalent normal cycles was in the mid-luteal phase rather than the late luteal phase .

Three way ANOVA's give no evidence of group differences but do suggest GxCxP interactions on measures of energy , breast tenderness and period type pain . Two way ANOVA's suggest a cycle difference in the case of breast tenderness but otherwise no significant differences between normal and ILP cycles .

Standardization of cycles to a 28 day length , had little effect upon the differences between normal and ILP cycles . A tendency emerged for the normal cycles to show more variability in mood and the ILP cycles to have lower mood scores premenstrually .

b) Individual Comparison

Four subjects fall into the category of normal and inadequate luteal phase cycle pairs . One of these also experienced a short luteal phase , discussed above . The mean scores for these subjects are represented in figures 5.16 , 5.21, 5.22 and 5.23 with ANOVA results in tables 5.9 and 5.11 .

Subject 013

Two cycles of data are available for this subject , the first being normal whilst the second has an inadequate luteal phase . Premenstrual changes are more evident in the normal than the ILP cycle on measures of mood , irritability , energy and sexual interest . The physical symptoms of breast tenderness and body swelling would appear to be more closely related to menstruation , rather than the premenstruum , however these symptoms are present throughout the early and mid luteal phases in the normal cycle , being absent in the ILP cycle .

In terms of phase effects , cycle two is clearly different from cycle one on all symptoms measured except energy . However , these effects do not seem to relate to the luteal phase , but rather to symptoms in the follicular phase , or at midcycle . Generally , the presence of an inadequate luteal phase appears to reverse the premenstrual symptoms , with an improvement in mood etc. during the latter half of the cycle . It should be mentioned , however , that cycle one in this subject represents the first cycle after childbirth , the relatively high levels of breast tenderness and body swelling

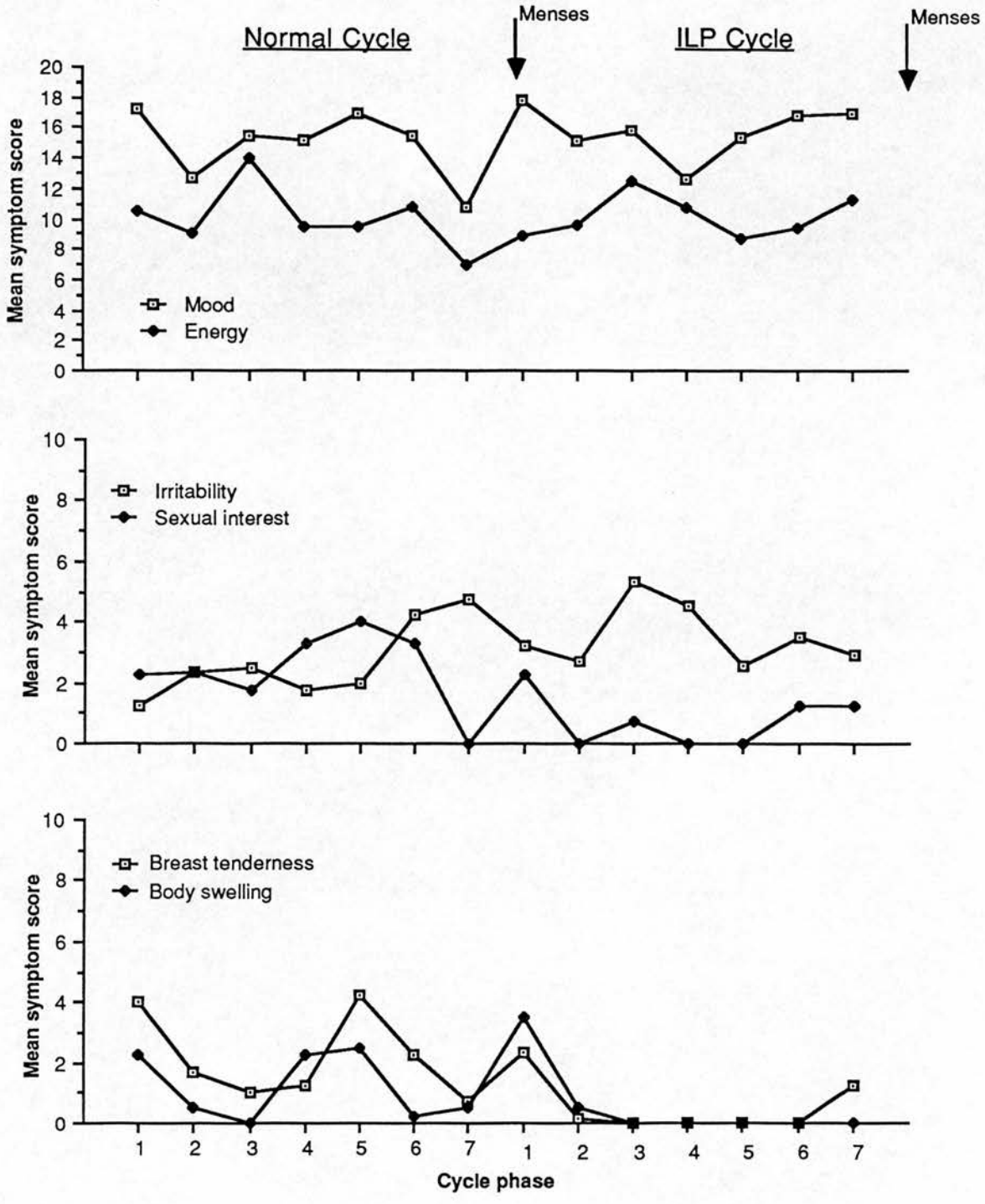


Figure 5.21 Changes in symptom levels with time across 7 standardized cycle phases in one woman (013)

TABLE 5.11

INDIVIDUAL ANOVA RESULTS FOR SUBJECTS 013 , 025 AND 026 .

Subject 013

	C	P	CxP	P@C1	P@C2
Mood	7.39	2.90*	1.49	1.75	2.73*
Irritable	10.06*	1.44	1.90	1.35	2.71*
Energy	0.07	2.11	1.29	1.91	1.37
Breast tenderness	9.93*	2.17	1.23	1.42	3.24*
Body swelling	3.42	4.61**	1.78	1.84	6.32**
Period pain	5.07	5.34**	7.14**	1.70	19.76**
Sexual interest	7.84	0.48	1.20	0.59	3.28*
DF	1	6	6	6,18	

Subject 025

	C	P	CxP	P@C1	P@C2	P@C3	C1vC2	C1vC3	C2vC3
Mood	370.8**	6.43**	3.43**	2.01	6.18**	5.80**	**	**	**
Irritable	6.31*	5.00**	2.38*	2.74*	3.07*	9.37**	*	*	ns
Energy	242.0**	3.46*	2.52*	2.41T	4.52**	1.37	**	**	**
Tense & anxious	1.04	0.94	1.08	0.79	1.55	2.28*	ns	ns	ns
Breast tenderness	87.98**	19.32**	19.33**	3.40	3.40**	19.33**	**	**	ns
Body swelling	96.83**	10.45**	4.17**	2.46T	6.33**	7.24**	**	ns	**
DF	2	6	12	6,18					

Subject 026

	C	P	CxP	P@C1	P@C2	P@C3	C1vC2	C1vC3	C2vC3
Mood	6.25*	2.46T	2.94**	3.58*	1.37	4.66**	*	ns	ns
Irritable	58.45**	2.76*	4.49**	4.42**	3.03*	4.96**	**	**	*
Energy	8.31*	2.01	4.37**	3.94**	1.13	6.99**	ns	*	ns
Breast tenderness	30.44**	14.86**	3.31**	4.95**	1.21	8.77**	**	**	ns
Body swelling	62.85**	20.06**	5.17**	9.42**	17.83**	19.04**	**	**	ns
Period pain	2.55	2.59*	2.55**	3.40	3.05*	2.11	ns	ns	ns
Sexual interest	110.1**	3.27*	2.40*	3.58*	0.27	0.84	**	**	ns
DF	2	6	12	6,18					

Key :- C - Cycle ; P - Phase ; DF - Degrees of freedom ; ns - not significant ; T - Trend ($p < 0.10$)
* - $p < 0.05$; ** - $p < 0.01$

may therefore be related to lactation rather than ovarian hormone levels *per se* (see discussion of subject 003) .

Subject 024

Four cycles are available for this subject , three of which have been discussed before due to the presence of short luteal phases . In this case , cycles one and four will be compared , the former being an ILP cycle whilst the latter is normal .

Large differences can be seen between these cycles in terms of mood , energy and tension & anxiety . In each of these cases , the symptoms are more pronounced in cycle one , the ILP cycle . However , they seem to be maximal during menstruation rather than during the premenstrual phase .

Breast tenderness is also significantly different between the two cycles in terms of overall levels . This difference is manifest by a later onset in the ILP cycle, accompanied by slightly less severe levels .

As discussed in relation to the short luteal phase cycles , the removal of a uterine polyp during cycle two may have been the cause of lower than normal mood and higher than normal tension & anxiety i.e. an exacerbation of menstrually related emotional symptoms due to stress . In this context , the findings of less severe and prolonged breast tenderness in the ILP cycle than the post-operative normal cycle may take on more significance . The possibility that in this case , luteal phase adequacy was more closely associated with breast symptoms than external events were must be considered .

Subject 025

In this subject , the inadequate luteal phase cycle is followed by two normal cycles . Hence cycle one might be expected to be the odd one out . This would appear to be the case with respect to two symptoms, irritability and breast tenderness . Levels of irritability are higher in the ILP cycle whilst breast tenderness is absent . This latter observation is in contrast to the resonably high levels of breast symptoms seen in the normal cycles . On both of these measures, significant differences are seen between the cycles in terms of overall mean levels . Phase effects are absent in cycle one with respect to breast tenderness , but present in cycles two and three . There are no differences between the three cycles in terms of phase effects on the measure of irritability , since here the difference is one of severity rather than

symptom timing . Mood also shows no phase effects in cycle one , suggesting a slightly flatter picture in the ILP cycle .

As with other subjects , it should be borne in mind that some variability is seen between normal cycles , particularly in the case of energy, hence some caution must be exercised in the attribution of symptom occurrence to hormonal variability . However , fairly strong evidence emerges from this subject that the occurence of some symptoms i.e. breast tenderness and irritability , may be associated with luteal phase adequacy .

Subject 026

Three cycles are also available for this subject , two normal cycles followed by an ILP cycle . Little evidence is seen here of cyclical changes on any of the parameters measured . A biphasic mood pattern is seen in cycle one , with low levels premenstrually and at midcycle . This pattern is not present in cycle three , but neither is it present in cycle two . Generally variations in symptom levels appear to become less marked with time , rather than in relation to the endocrine environment . Hence cycle one tends to be odd rather than cycle three.

Breast tenderness and body swelling do show menstrually related variations. The former would appear to be present premenstrually in cycle one but not in cycle three . However as with mood , the symptom is also much reduced in cycle two , suggesting that hormonal variations may not be the key factor in this case .

In summary , this subject does not appear to show a consistent premenstrual pattern , but rather gradually decreasing symptoms with time . Although differences are seen in symptomatology between normal and ILP cycles , the large differences observed between consecutive normal cycles invalidate any obvious hormonal hypothesis .

c) Summary

Group comparisons suggest that ILP cycles may be chatacterized by lower luteal levels of breast tenderness and body swelling , and the presence of emotional symptoms at mid-cycle rather than in the premenstruum . Of all the differences , breast tenderness appears to be the most marked .

Three of the individual analyses tend to support the observation of reduced breast symptoms in ILP cycles , although in one of these alternative explanations could be offered i.e. the potential exacerbation of breast

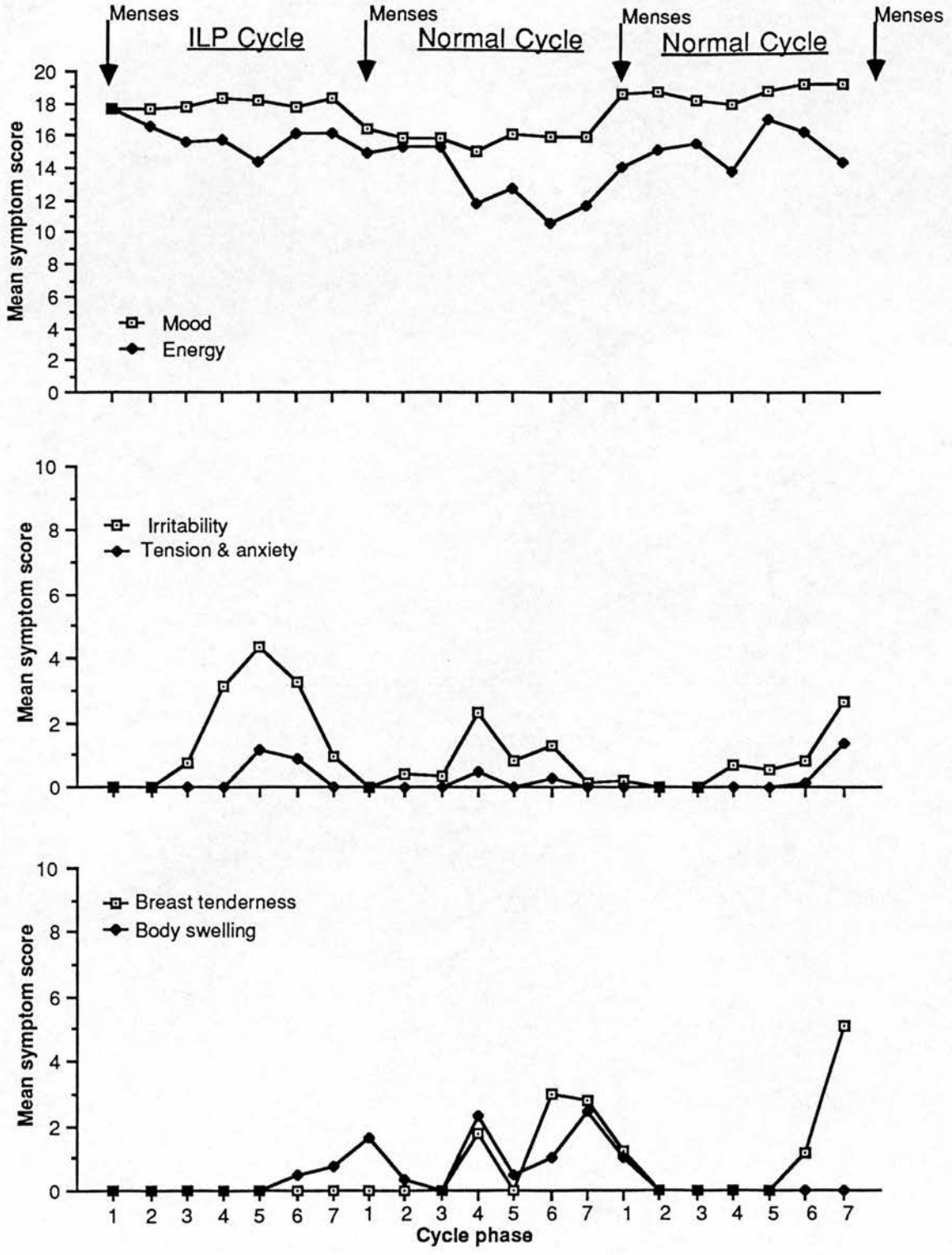


Figure 5.22 Changes in symptom levels with time across 7 standardized cycle phases in one woman (025)

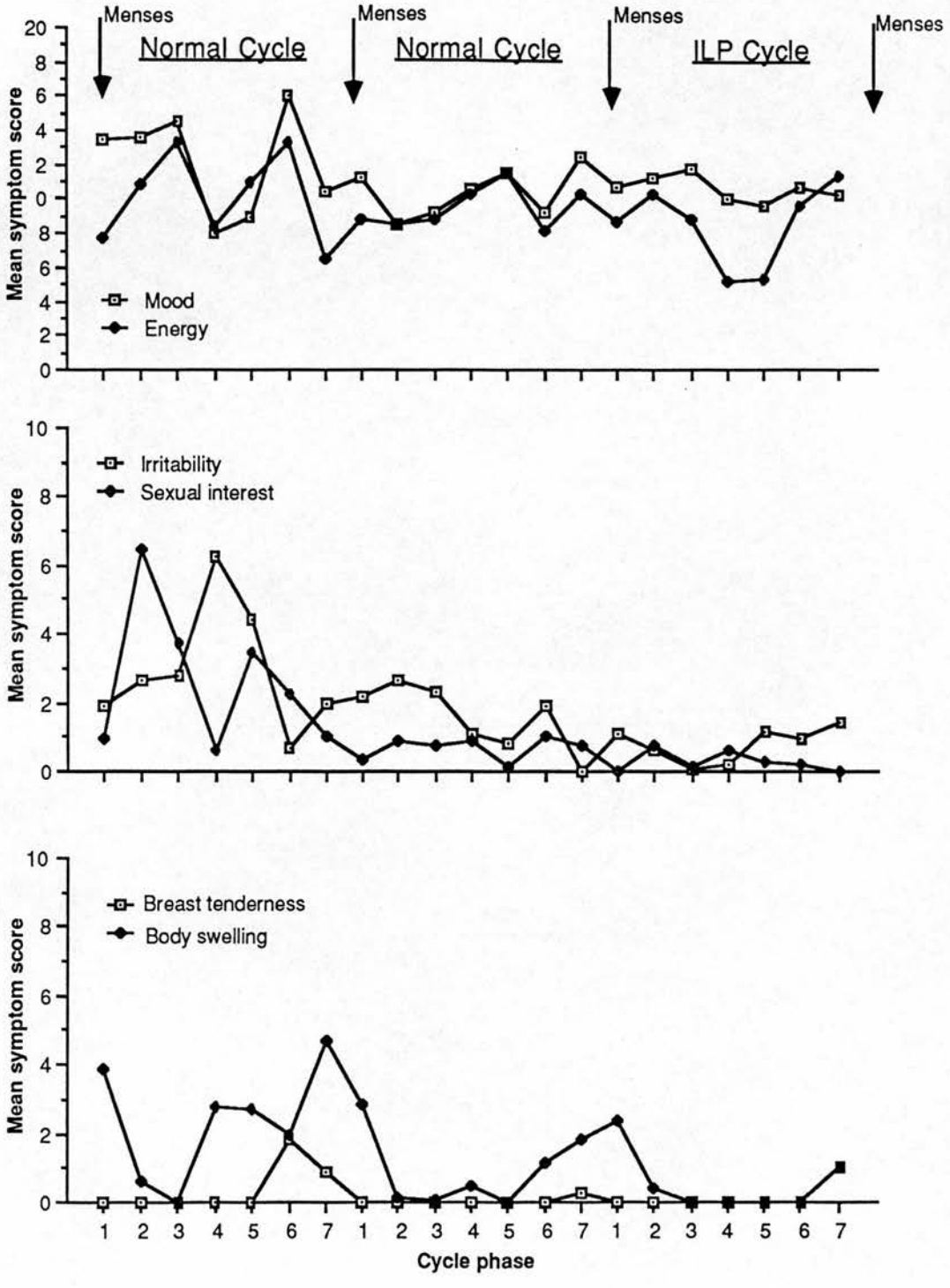


Figure 5.23. Changes in symptom levels with time across 7 standardized cyc phases in one woman (026)

symptoms in the normal cycle due to lactation . The fourth subject , whilst showing reduced breast tenderness levels in an ILP cycle , also demonstrated some variability across normal cycles and therefore cannot be said to show changes which can be related to luteal phase adequacy . None of the other symptoms showed any degree of consistency across subjects , although the suggestion of a premenstrual exacerbation of irritability in ILP cycles was raised by one subject .

iv) Summary of Section 5.3.2

In summary - there is little statistical evidence to suggest any greater variability between normal and abnormal cycles than between consecutive normal cycles in terms of overall symptom severity or differential phase effects for most of the symptoms studied .

The major exception to this would appear to be the measure of breast tenderness . This symptom tended to be diminished or absent in ILP cycles , compared to normal cycles . A trend towards this was also seen in anovulatory cycles .

Several points should be made , arising from the data which may however reduce the validity of any observations . Firstly - a large degree of variability was seen between consecutive normal cycles on all parameters measured , and particularly the emotional ones . Secondly - none of the subjects can be said to demonstrate cyclical changes which might be diagnosed as PMS , despite being self-diagnosed sufferers . This point may not be important if the same aetiology is assumed for premenstrual symptoms as the PMS , however caution should be exercised before generalizations are made . Thirdly - the statistical methodology used in this section is arguably inappropriate to this type of data , leading to difficulties in the interpretation of results , and fourthly - the imposition of gynaecological definitions of luteal phase adequacy etc. may not be meaningful in the behavioural context . In the next section , an attempt is made to accommodate for the latter two points .

5.3.3 CROSS CORRELATIONAL DATA ANALYSIS

The data analysis used in the previous section makes several assumptions about the nature of hormone - behaviour relationships . The major one of these is that a gynaecological diagnosis should be meaningful in behavioural terms . For example , the diagnosis of inadequate luteal phase is a purely arbitrary one , based on the description of a " normal " range . A hypothesis could be put forward that premenstrual symptoms are more common in ILP cycles . Hence all the ILP cycles would be expected to be symptomatic , whilst the normal cycles were relatively symptom free . Consider then the case of an individual who tends to have either very high or normal range luteal progesterone levels, with the latter cycles being symptomatic . In the analysis above , all of her data would be included in the normal cycle category , tending to lead to a conclusion of no symptomatic difference between cycles of differing luteal progesterone levels . In short - the assumption has been made that group statistics are meaningful in the individual case . The division of mood and symptom data into phases , dependent upon hormonal parameters could be similarly criticized , since the current state of knowledge about premenstrual changes is arguably inadequate to make the assumption that all women will respond in the same way to hormonal events . This type of manipulation can produce distortions in the data by grouping together different individual symptom patterns . For example - if a four day premenstrual phase is considered , then a woman who scores 4 on the day before menstruation will appear to show the same pattern as one who scores 1 on each of the four premenstrual days . As yet we have no information about the possibility that different symptom patterns have different aetiologies , hence some caution should be exercised in the interpretation of results using this type of methodology .

The other major reason for caution in the interpretation of the analysis presented in the previous section is the dubious applicability of the statistical methodology used . The data collected falls into the category known as "Time Series " i.e. data which is collected serially at equal time intervals for an extensive period . The statistical analysis of this type of data is as yet a young science . Several characteristics of such data are known however to increase the risks of erroneous results if conventional statistics are applied . Examples of this are autocorrelation (the tendency for consecutive data points to be highly correlated) , trend and seasonality . The statistical field of Time Series Analysis (TSA) has developed , largely from the

requirements of economists and financial analysts , to enable this type of data to be mathematically modelled , with the ultimate aim of producing an accurate forecast of future trends and variations in measures such as the Share Index . However , little work has been done to demonstrate the applicability of "pure", Box-Jenkins type TSA to physiological and psychological data , where the purpose is vested in the analysis of responses made to certain events , rather than the prediction of future outcomes . The aim in this case was to find a statistically valid form of analysis which would allow conclusions to be drawn with some degree of confidence about the association between each of the symptomatic variables and hormonal changes .

One form of bivariate analysis , which would appear to be appropriate in this case is cross-correlation . In this form of analysis , two sets of data , collected at equal time intervals over the same period are correlated together using conventional correlational methods . The method , however , also lags one set of data allowing correlations to be made between , for instance , mood and oestrone levels from one to twenty days beforehand with an identical lag being incorporated in the opposite direction . Hence it is possible to detect relationships between two variables at various temporal distances . This form of analysis is most applicable to long term time series biological data and is recommended by Sollberger (1965) , although it is seldom used . The method has also found use in psychology , in the analysis for instance of the interaction between members of a couple during marital therapy (Revenstorf , Kunert , Hahlweg & Schindler 1982) .

Several factors should be borne in mind before this method is applied however . These largely fall into two categories - those relating to the caution required in the interpretation of any type of correlational analysis , and those relating to the appropriate filtering techniques which should be used before the data is analysed . The former are addressed by Kendall (1976) , who points out that the number of correlations performed in the analysis of any bivariate data set of reasonable length (i.e. not less than 35 data points per variable) , rapidly becomes very large , with the attendant increased probability of randomly occurring significant results by chance .

The potential pitfalls of inappropriate filtering are addressed by Chatfield (1984) . As with all TSA , the data must be rendered " stationary" before any analysis can be conducted i.e. any existing trend must be removed . This can be achieved in a number of ways with perhaps the most intuitively

obvious method being known as " differencing " . In this technique , each data point is subtracted from its predecessor , in order to remove the trend . An example of this would be in the case of the data set - 5,4,3,2,1 - which , when differenced produces - 1,1,1,1 - a detrended series . This method has the advantage of retaining any cyclicity in the data . Care should also be taken to remove any seasonal components in data covering several years , and to account for autocorrelation within the data . Chatfield recommends the removal of all of these types of variability by forming the approprate Box-Jenkins model , removing it from the data and performing the analysis on the residuals , in order to avoid spurious correlations . However , in this case , the examination of several data sets suggested that autocorrelation and seasonality were not major sources of variability in this type of data . Hence , only the trend was removed .

In this analysis , all the hormonal data was logarithmically transformed , to stabilise the variance . Three hormonal variables were assessed , derived from the hormone - creatinine ratios resulting from urinalysis . These were :- Log 10 Oestrone (Log 10 E1G) ; Log 10 Pregnanediol (Log 10 PdG) ; and the logarithmic transformation of the oestrone - pregnanediol ratio (Log 10 (E/P)) . This latter variable had been implicated in previous research studies of PMS (e.g. Backstrom et al 1976 ; Munday et al 1981) . These data were then differenced and cross correlated with each of the differenced symptom variables to a lag of 19 places in most cases . Hence a potential total of 24 (eight symptoms with each of three hormonal variables) cross correlations were conducted for each subject . These analyses were performed for all of those women who had provided daily data over at least 50 days and for whom no more than 10 % of any of the variables was missing . This led to the exclusion of all of the clinic patients and one other subject with inadequate amounts of data , but the inclusion of those subjects whose menstrual cycles were absent or incomplete . Hence a total N of 24 was achieved . A significant result , it was anticipated , would be shown by a peak in the cross correlation preceded and followed by gradually decreasing values . In this type of analysis , a reasonably high frequency of spurious high single correlations was expected .

Each woman was assessed individually , since there was no reason to suppose that they would all show the same correlational patterns . The data from a typical example are presented in tables 5.12 , 5.13 and 5.14 . This particular subject was selected as an example since the previous analysis

suggested that some of her symptoms may be hormonally related (i.e. irritability and breast tenderness) . It can be seen that apart from the occasional potentially spurious correlation , no association would appear to emerge between any of the hormonal variables and any of the symptoms assessed . The data here are presented only up to lag 15 , taking in any possible relationship between premenstrual symptoms and hormone levels around the time of ovulation , however , no higher correlations were seen up to lag 19 . Only one woman showed very high correlations on measures of breast tenderness and body swelling at lag -1 with all the hormonal variables . However , these were not supported by the expected rise and fall in value of the surrounding coefficients . Hence , it must be suggested that the most likely explanation for these results is the occurence of "outliers " , i.e. one-off unusually high or low values on one or more of the measures assessed . None of the other women studied showed any sign of the expected pattern , no matter what type of hormonal cycle was experienced .

The correlations were so low that the possibility of a pure curvilinear relationship at one or more of the lags was raised . Statistical tests for such a relationship were not available , hence the possibility was examined by plotting data selected from various subjects and lags at random (Time factors precluded the the examination of graphs for each subject at all the possible lags - a potential total of 912 graphs per subject). The resulting scattergraphs for subject 025 at lag -1 are presented in figures 5.24 , 5.25 and 5.26 . Once more , little evidence is seen of any kind of curvilinear relationship in this case, and this was true of all the subjects assessed . The observation does not of course preclude the possibility of such a relationship occurring in the subjects or at the lags not assessed .

In summary - the method of cross correlation would appear to be the most appropriate for data of this type if applied with caution . The results of the analysis suggest an almost unbelievable degree of concordance between women , showing very low levels of association between absolute hormonal measures and absolute symptom measures at any of the lags assessed . The explanation for this would not appear to be vested in anykind of curvilinear relationship , although this possibility has not been fully examined .

TABLE 5.12

CROSS CORRELATIONS BETWEEN SYMPTOMS AND LOG 10 E1G

FOR SUBJECT 025

LAG	Mood	Irritable	Energy	Tense & anxious	Breast tenderness	Body swelling
-15	-0.05	-0.03	-0.04	-0.03	-0.009	0.12
-14	-0.01	0.02	-0.08	0.05	0.19	0.005
-13	0.095	-0.04	0.08	-0.07	-0.15	0.04
-12	-0.18	-0.03	0.04	0.06	0.09	0.07
-11	0.15	0.08	-0.104	0.04	0.15	0.06
-10	-0.18	0.04	-0.06	-0.08	0.002	-0.115
-9	0.16	-0.09	0.20	0.08	-0.02	-0.09
-8	0.03	0.04	-0.04	0.03	0.08	-0.05
-7	0.009	-0.05	-0.05	-0.07	-0.17	0.04
-6	0.02	0.08	0.04	0.006	0.005	0.05
-5	0.095	-0.002	-0.11	0.017	0.003	0.03
-4	-0.102	0.07	0.13	-0.001	0.04	-0.08
-3	0.03	-0.097	-0.17	0.102	-0.03	0.14
-2	0.05	0.107	0.14	-0.23	0.16	0.09
-1	0.015	0.002	-0.20	0.16	0.004	-0.12
0	-0.12	-0.07	0.01	-0.004	-0.096	0.19
1	0.06	0.002	0.14	-0.13	0.35	-0.14
2	-0.08	0.08	-0.09	0.21	-0.17	0.08
3	-0.02	0.102	-0.04	-0.16	0.07	-0.14
4	0.02	-0.22	0.14	0.23	-0.18	0.03
5	0.03	0.10	-0.101	-0.17	0.04	-0.16
6	0.06	0.008	0.19	0.004	-0.16	-0.008
7	-0.03	-0.08	-0.16	0.008	-0.19	0.02
8	-0.11	0.06	0.20	0.06	0.03	-0.01
9	0.116	-0.03	-0.05	-0.05	0.003	0.011
10	0.05	-0.03	-0.15	-0.16	-0.13	0.07
11	-0.195	-0.03	0.12	0.08	0.097	0.016
12	0.19	-0.04	-0.18	-0.04	0.09	0.066
13	-0.21	0.09	0.07	0.07	0.07	0.032
14	0.17	0.011	0.105	-0.02	0.03	-0.24
15	-0.17	-0.06	-0.04	-0.007	-0.08	0.30

TABLE 5.13
CROSS CORRELATIONS BETWEEN SYMPTOMS AND LOG 10 PdG
FOR SUBJECT 025

LAG	Mood	Irritable	Energy	Tense & anxious	Breast tenderness	Body swelling
-15	-0.02	-0.07	0.15	0.03	-0.18	-0.01
-14	-0.07	-0.03	0.03	-0.05	-0.009	-0.06
-13	0.09	-0.006	-0.07	0.01	-0.03	0.07
-12	-0.12	-0.04	0.03	-0.13	-0.14	-0.015
-11	0.07	0.06	-0.004	0.17	0.06	-0.05
-10	-0.16	0.03	-0.06	-0.015	-0.04	-0.09
-9	0.17	-0.01	0.14	-0.112	-0.12	0.04
-8	-0.11	-0.07	-0.05	0.111	0.10	-0.07
-7	0.12	-0.03	-0.03	-0.21	-0.108	0.09
-6	-0.02	-0.102	0.08	0.07	0.12	-0.05
-5	0.101	0.19	-0.17	0.17	0.04	0.18
-4	-0.09	-0.07	0.21	-0.25	0.26	-0.07
-3	0.03	0.02	-0.28	0.298	-0.06	0.16
-2	-0.02	0.09	0.07	-0.22	0.23	-0.06
-1	0.06	-0.16	-0.05	0.17	-0.07	-0.04
0	0.08	0.03	-0.03	-0.09	0.05	0.26
1	0.06	0.17	0.11	0.02	0.18	-0.23
2	0.02	-0.24	-0.04	0.05	-0.09	0.09
3	-0.13	0.22	-0.09	-0.09	0.07	0.08
4	0.10	-0.07	0.15	0.13	-0.108	0.01
5	-0.07	0.11	-0.18	-0.02	0.09	-0.15
6	-0.07	-0.005	0.15	-0.007	-0.08	0.04
7	0.16	-0.05	-0.09	-0.02	-0.102	-0.06
8	-0.16	0.13	0.04	0.09	0.04	0.02
9	0.001	-0.09	-0.06	-0.106	-0.09	0.03
10	-0.02	0.05	0.008	0.04	-0.07	-0.07
11	-0.09	0.05	0.115	0.01	0.05	-0.07
12	0.09	-0.12	-0.05	-0.14	-0.22	0.005
13	-0.12	-0.06	0.06	0.08	0.05	0.09
14	0.15	0.09	0.12	-0.01	-0.009	-0.18
15	-0.07	-0.14	-0.15	-0.06	-0.07	0.08

TABLE 5.14

CROSS CORRELATIONS BETWEEN SYMPTOMS AND LOG 10 (E/P) FOR SUBJECT 025

LAG	Mood	Irritable	Energy	Tense & anxious	Breast tenderness	Body swelling
-15	-0.01	0.05	-0.19	-0.05	0.19	0.114
-14	0.06	0.05	-0.09	0.08	0.16	0.07
-13	-0.03	-0.02	0.13	-0.07	-0.09	-0.04
-12	-0.02	0.02	0.001	0.19	0.22	0.07
-11	0.04	0.001	-0.08	-0.16	0.06	0.095
-10	0.02	-0.002	0.02	-0.04	0.04	0.001
-9	-0.06	-0.06	0.009	0.18	0.11	-0.11
-8	0.14	0.104	0.02	-0.10	-0.04	0.03
-7	-0.12	-0.01	-0.003	0.17	-0.02	-0.07
-6	0.04	0.17	-0.06	-0.07	-0.13	0.095
-5	-0.03	-0.20	0.098	-0.17	-0.04	-0.17
-4	0.016	0.13	-0.13	0.27	-0.24	0.02
-3	-0.002	-0.097	0.17	-0.24	0.04	-0.06
-2	0.056	-0.014	0.04	0.06	-0.12	0.13
-1	-0.05	0.17	-0.105	-0.06	0.08	-0.06
0	-0.18	-0.08	0.041	0.09	-0.13	-0.12
1	-0.02	-0.18	-0.009	-0.13	0.08	0.13
2	-0.08	0.32	-0.03	0.116	-0.04	-0.03
3	0.13	-0.16	0.07	-0.03	-0.01	-0.19
4	-0.09	-0.101	-0.06	0.04	-0.02	0.01
5	0.10	-0.04	0.114	-0.12	-0.06	0.03
6	0.12	0.01	-0.006	0.011	-0.05	-0.05
7	-0.19	-0.009	-0.04	0.03	-0.05	0.08
8	0.09	-0.09	0.115	-0.05	-0.02	-0.03
9	0.09	0.07	0.02	0.08	0.10	-0.02
10	0.06	-0.08	-0.13	-0.17	-0.03	0.13
11	-0.06	-0.08	-0.03	0.05	0.02	0.09
12	0.05	0.097	-0.09	0.115	0.31	0.05
13	-0.04	0.14	-0.006	-0.04	0.004	-0.08
14	-0.03	-0.09	-0.05	0	0.04	0.009
15	-0.06	0.105	0.13	0.06	0.01	0.15

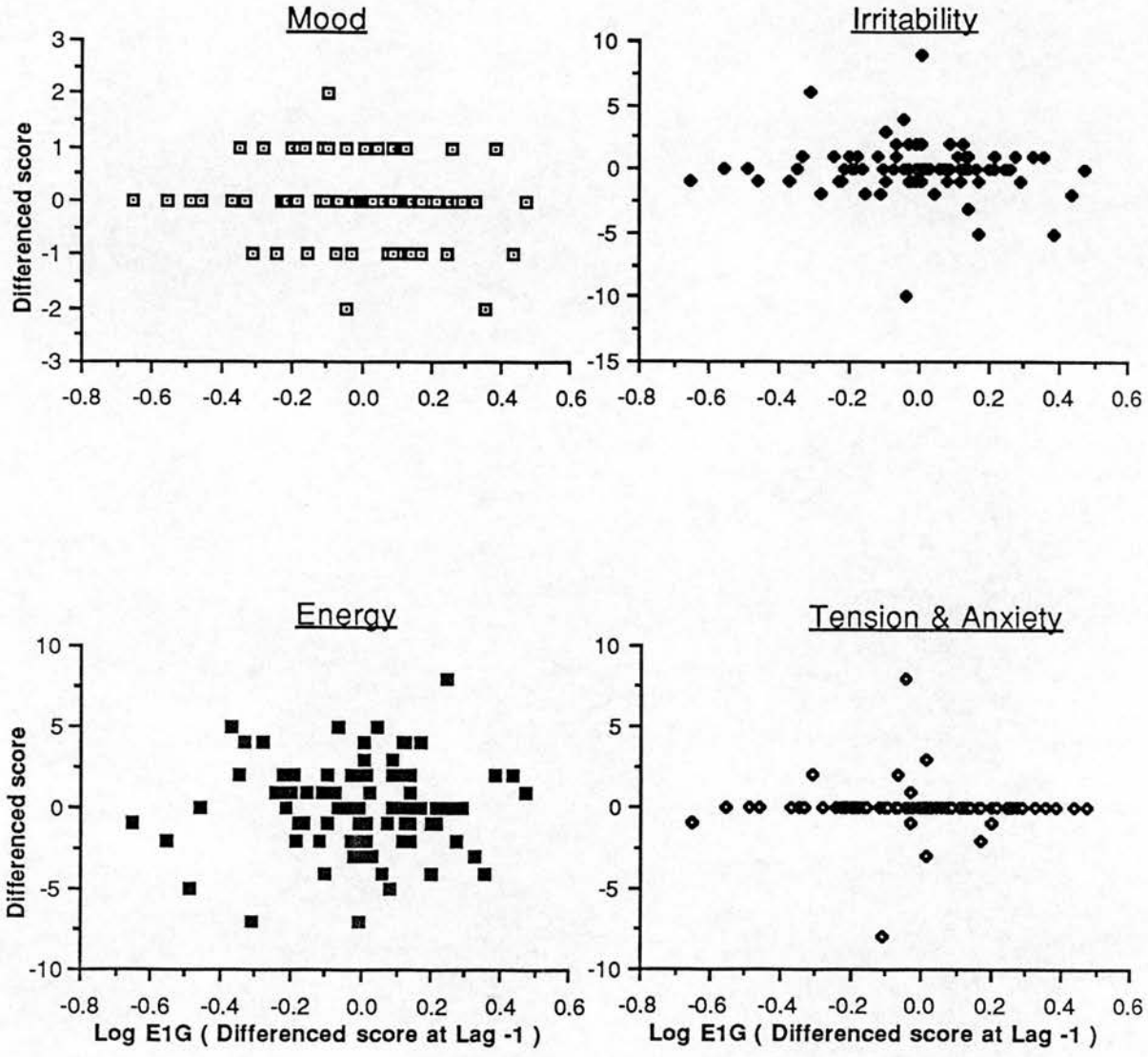


Figure 5.24 (a) The relationship between mood , irritability , energy , tension & anxiety and Log 10 Oestrone Glucuronide using differenced scores at lag -1 for subject 025

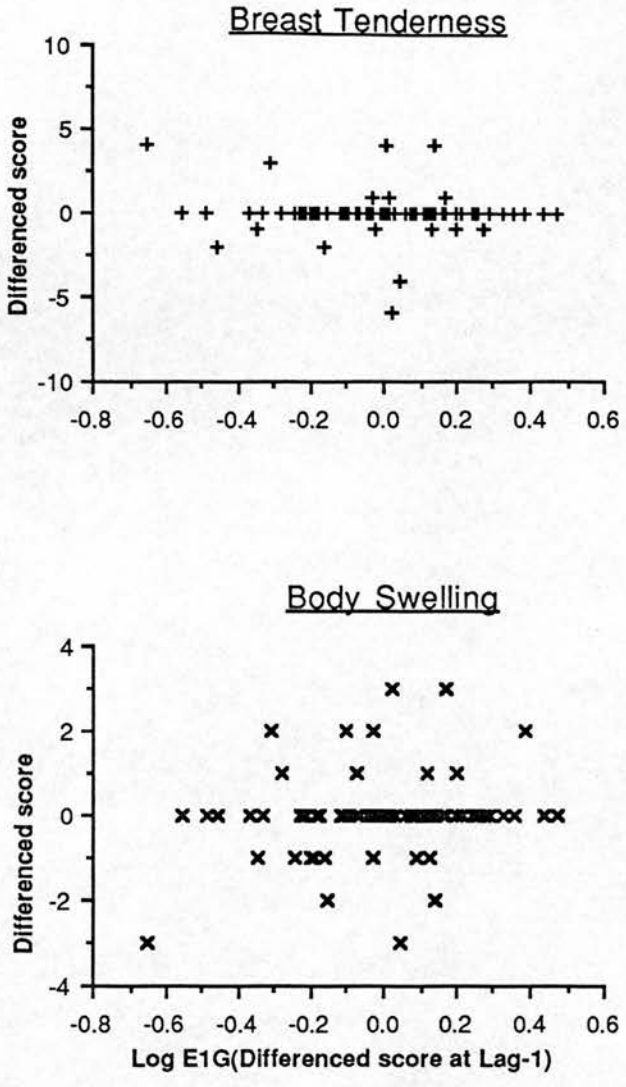


Figure 5.24 (b) The relationship between breast tenderness , body swelling and Log 10 Oestrone glucuronide , using differenced scores at lag -1 , for subject 025 .

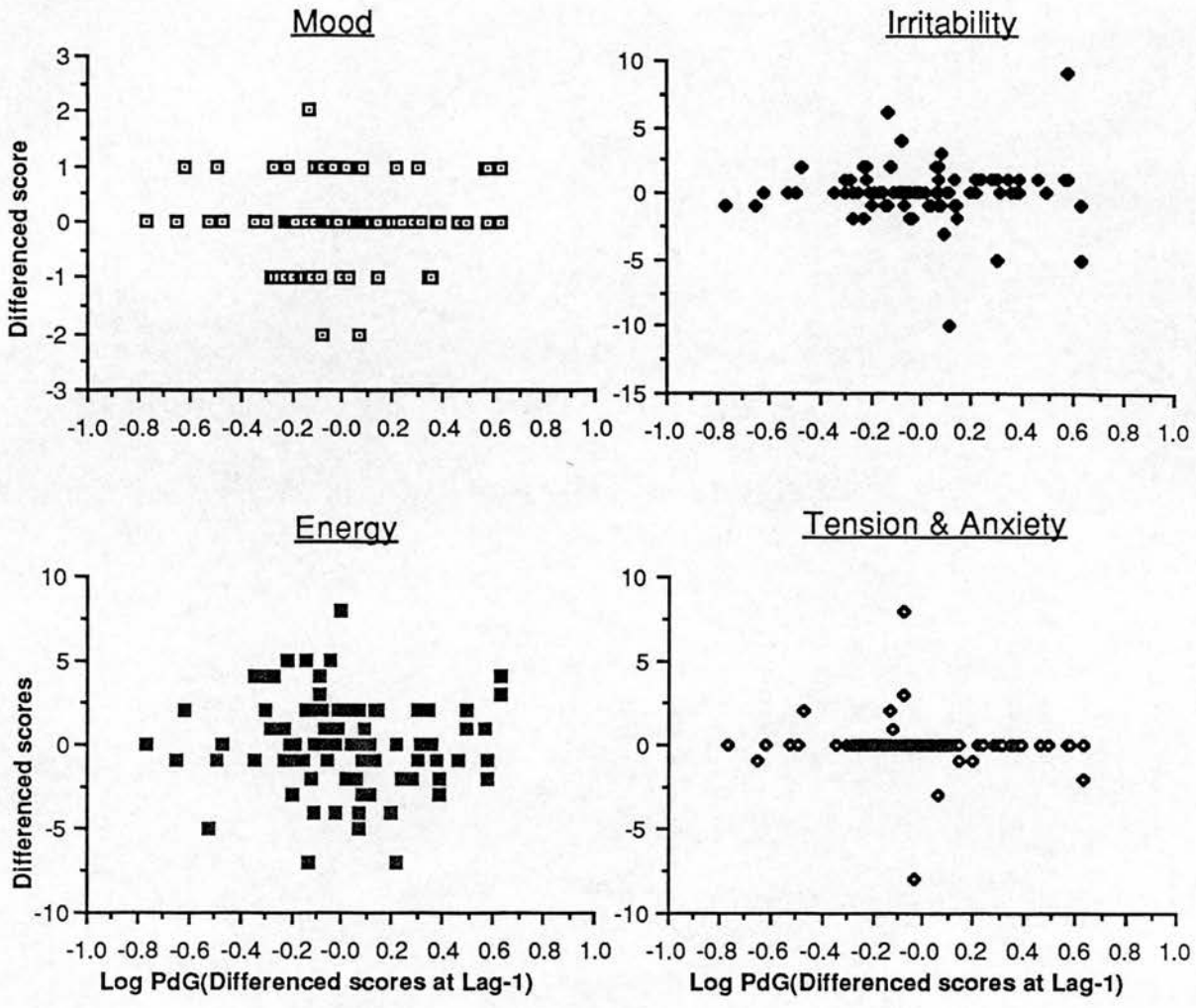


Figure 5.25 (a) The relationship between mood , irritability , energy , tension & anxiety and Log 10 Pregnanediol glucuronide using differenced scores at Lag -1 , for subject 025

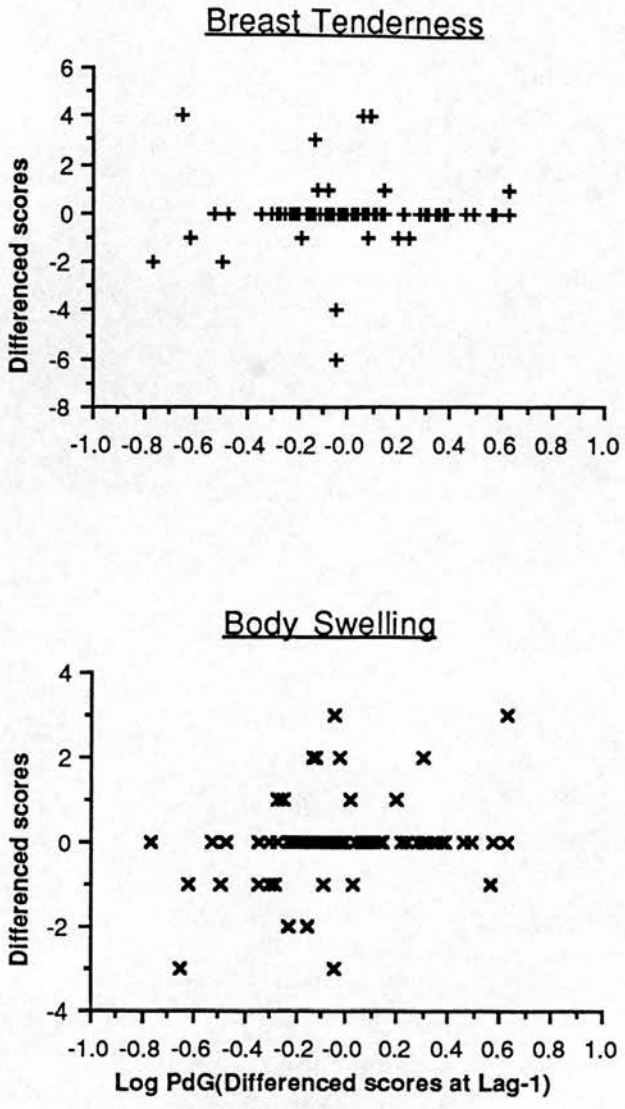


Figure 5.25 (b) The relationship between breast tenderness , body swelling and Log 10 Pregnanediol glucuronide , using differenced scores at Lag -1 , for subject 025 .

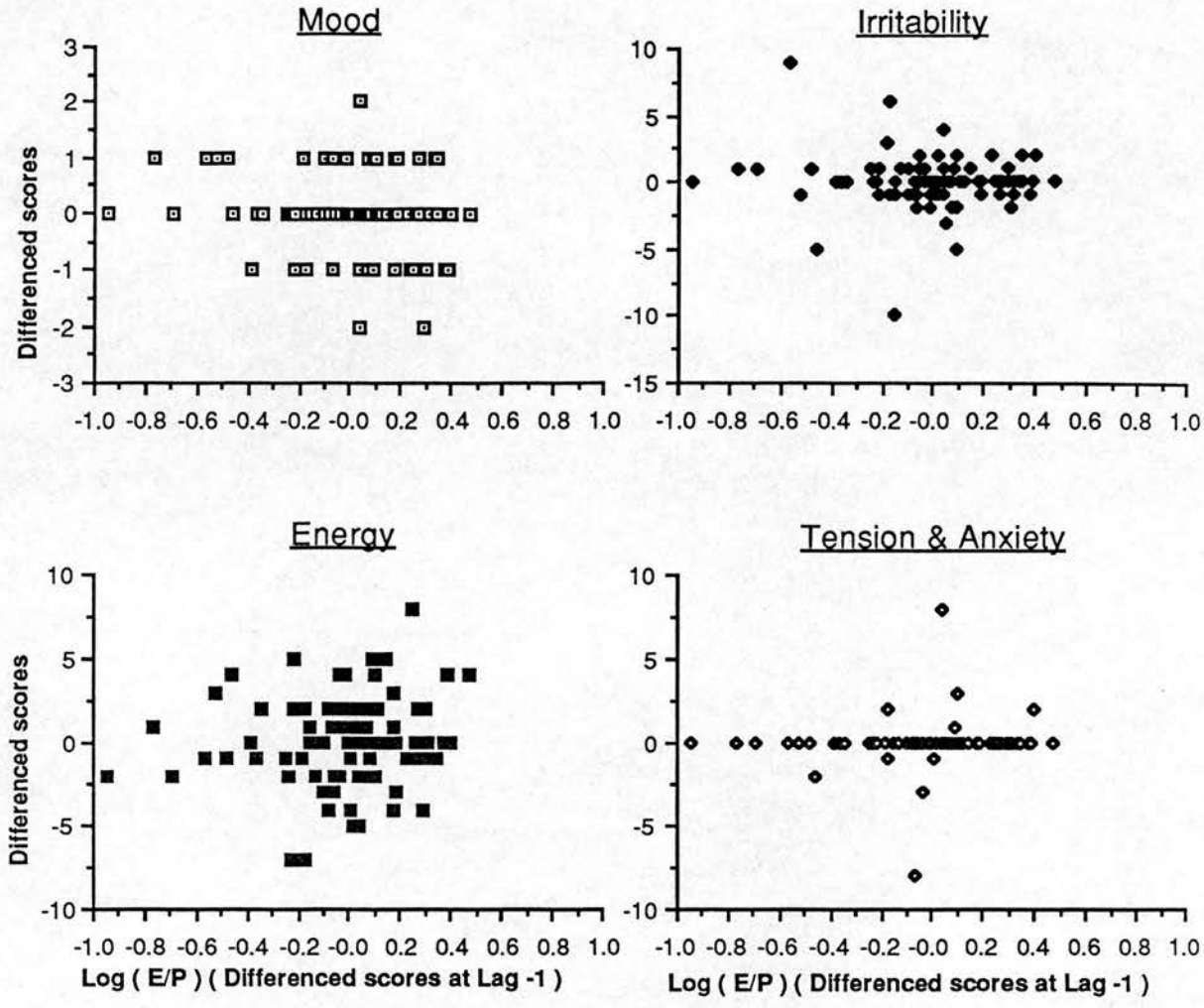


Figure 5.26 (a) The relationship between mood , irritability , energy tension & anxiety and Log 10 (E / P) , using differenced scores at Lag -1 , for subject 025 .

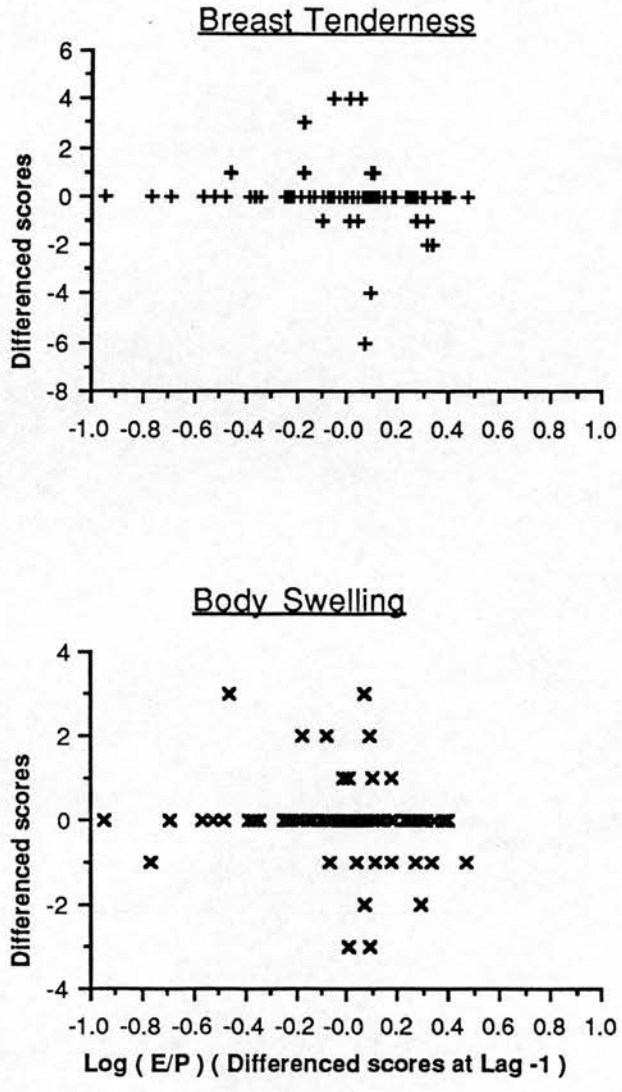


Figure 5.26 (b) The relationship between breast tenderness , body swelling and Log 10 (E / P) using differenced scores at Lag -1 , for subject 025 .

5.4 DISCUSSION

The study described in this chapter utilised an observational "eliminationist " approach to the relationship between premenstrual symptoms and the ovarian cycle . In this case , the factor to be eliminated was ovulation . Hence an attempt was made to recruit subjects in whom anovulatory cycles might occur . One of the confounding factors associated with the removal of ovulation is the absence of luteal phase hormones , in particular progesterone . In order to attempt to tease out the relative components of these factors , normal cycles and cycles with deficient luteal phases were studied . Hence , if the endocrine event of ovulation were associated with symptom occurence , we would expect anovulatory cycles to be different from normals and deficient luteal phases . If luteal phase hormones are related to symptoms , then both anovulatory and deficient luteal phase cycles should be different from normal cycles . The presence of two sub-diagnoses of deficient luteal phase allows the hypotheses to be extended . Hence , if absolute levels of luteal phase hormones are important , then inadequate luteal phase cycles should be different from normals whilst short but adequate luteal phase cycles should not - in terms of severity (although symptom timing may be expected to be altered) . An assessment of the time of onset of symptoms in SLP cycles might also provide evidence against a role for either ovulation or luteal phase hormones , if that onset were before the endocrine event i.e. symptoms began > 9 days before menstruation .

The small number of abnormal cycles observed in this study requires that some caution must be exercised in the interpretation of the results . However, it would appear , from the first analysis that only one of the symptoms measured shows any systematic variation with luteal phase adequacy . This symptom is breast tenderness , levels of which were reduced in both anovulatory and ILP cycles compared to normals , but not in SLP cycles . (N.B. One subject (047) showed higher than normal levels of breast tenderness in a cycle whose luteal phase was both short and inadequate , although not in a SLP cycle suggesting that the inadequacy of the luteal phase may be a key factor , and may have a stimulatory rather than an inhibitory effect on breast tenderness in some women) . No tendency emerged for symptoms in SLP cycles to begin later or to be less severe than symptoms in normal cycles . Hence , it would appear from this

analysis , that the presence or absence of ovulation is not associated with symptom occurence . However , in the case of breast tenderness , a relationship with luteal phase adequacy does appear .

The cross-correlational analysis showed no relationship between any of the symptoms and absolute levels of oestrone or pregnanediol , or the E/P ratio . This result held true for subjects showing all types of ovarian cycle , ranging from anovulatory to normal . In this case , breast tenderness did not emerge as an exception . Hence , the possibility arises that premenstrual breast tenderness may be related to some other aspect of luteal phase adequacy than the ovarian steroids . The possibility that the breast is responsive to the same physiological events which produce an ILP in the ovary should be considered .

Two hormones which may be involved are LH and FSH (luteinizing hormone and follicle stimulating hormone) . FSH is involved in follicular growth whilst LH is important in the endocrine mechanism of ovulation (see Chapter Two) .Both of these are still present in the circulation during the luteal phase , where their function is largely unknown . Recent evidence from work with sheep suggests that adequate luteal function is dependent upon adequate gonadotrophic stimulation of the developing follicle (Stirling 1986) . However , LH levels during the luteal phase may also be involved (Niswender et al 1985) . These aspects have been little investigated in the human context .

Prolactin has also been implicated in the human luteal phase . Hunter (1984) showed that prolactin significantly enhances hCG stimulation of oestrogen and progesterone synthesis from human luteal tissue in vitro, although it is not effective alone . Hence , prolactin may play a permissive role in the control of steroidogenesis by the corpus luteum . This work is supported by the observation that in most species , the maintenance of luteal function in early pregnancy is dependent on a "luteotrophic hormone complex" , whose chief components are prolactin and LH (see Heap & Flint 1984) . The suggestion has arisen from work with rats , that a normal range of prolactin levels are required for maintenance of CL function , with both high and low levels acting to decrease steroidogenesis (Rajkumar , Couture & Murphy 1985 ; Lee 1987) . Hence , the possibility arises of two groups of women , both with inadequate luteal phases , but one having higher than normal prolactin levels, and the other lower than normal .

Prolactin , as its name implies , is involved in milk secretion during lactation . However it is present at reasonable levels throughout the normal menstrual cycle (McNeilly & Chard 1974) . It can be inhibited by the action of bromocriptine , a dopamine agonist . This latter drug has been successfully used in the treatment of cyclical breast pain (Mansel , Preece & Hughes 1980) and has shown favourable results on premenstrual breast symptoms when prescribed for PMS (Anderson & Larsen 1979 ; Kullander & Svanberg 1979 etc.) Hence , the possibility exists that premenstrual breast tenderness is associated with prolactin , or some other aspect of luteal function , rather than the ovarian steroids .

5.5 SUMMARY

The study described in this chapter involved the observation of naturally occuring abnormal menstrual cycles in order to investigate the relative effects of ovulation and luteal phase adequacy on premenstrual symptoms . Only a small number of abnormal cycles were observed in women who did not show very strong cyclical symptoms . However , for the majority of symptoms studied , no greater variation was seen between normal and abnormal cycles than between consecutive abnormal cycles . Breast tenderness was different in this respect , being generally less severe in anovulatory and inadequate luteal phase cycles . Cross correlation of the symptoms with each of the hormonal measures indicates that none of them are associated with absolute ovarian steroid levels .

Hence , premenstrual symptoms can occur in the absence of ovulation and do not appear to be dependent upon luteal hormone levels . In the case of breast tenderness , differential levels , either higher or lower than normal , are associated with an absent or deficient luteal phase . It is possible that some other factor associated with luteal function may be involved for this symptom . The implication of prolactin in this respect , plus the use of a prolactin inhibitor, bromocriptine , to relieve cyclical breast pain , suggests that this hormone may be worthy of study in this regard .

CHAPTER SIX
PREMENSTRUAL SYMPTOMS IN ARTIFICIALLY MANIPULATED ANOVULATORY CYCLES

6.1 INTRODUCTION

The relationship between the Premenstrual Syndrome and ovulation can be investigated in two ways . Firstly , observations can be made of naturally occuring anovulatory cycles for comparison with ovulatory cycles , and secondly , manipulations of the natural menstrual cycle can be undertaken to induce a state of anovulation . The natural anovulatory cycle has been discussed in Chapter 5 , in this section artificially manipulated cycles will be considered .

The oral contraceptive pill (oc) is the most widely used inhibitor of ovulation in Western society . The physiological effects of oc's on the menstrual cycle have been discussed elsewhere (Section 2 .4) as have the reported effects of oc's on mood and PMS (Section 3 .4.2) . Several distinctions should however be borne in mind when considering the actions of oc's on PMS .

1) As Cullberg (1972) points out - the oc has two effects , its pure pharmacological effect of ovulation inhibition and its psychological effects due to the prevention of conception . This latter " placebo " effect may be involved in studies finding therapeutic effects of oc's on PMS .

2) A distinction should be made between the effects of oc's in an individual and the characteristics of oc users as a whole compared to non-oc users . A finding of similarity in PMS symptoms between users and non-users does not imply that any one individual will not experience changes in cyclical symptoms with oc use .

3) A distinction should be made between menstrual cycles immediately after the beginning or end of a course of oc and those cycles within a long-term oc regime . In the former case the effects of the exogeneous cycle will be either unestablished or still present whilst in the latter they will be a dominant influence . Present knowledge about chronobiological and endocrinological adaptations to the oc does not allow any precise definition of the time at which their effects become dominant .

The fundamental question in this study is whether ovulation is a necessary prerequisite for premenstrual symptomatology to occur . If ovulation and luteal function are necessary then pill-taking women reporting " PMS " would be expected to differ from non pill-taking complainers when compared on the basis of prospective daily ratings . The hypothesis would be that pill users are attributing random mood changes to the premenstruum

TABLE 6.1

HORMONAL DIFFERENCES BETWEEN GROUPS

(N.B. Changes during the pill free week are not considered)

	HORMONAL PARAMETER				
GROUP	LH Surge	Ovulation	Cyclical FSH	Cyclical Oestrogen	Cyclical Progesterone
CONTROL	+	+	+	+	+
TRIPHASIC PILL	–	–	?	+	+
MONOPHASIC PILL	–	–	?	–	–

Key + = present – = absent ? = uncertain

in retrospective reports . The current availability of a triphasic oral contraceptive designed to mimic the natural cycle allows a further comparison which might be expected to differentiate between the effects of ovulation *per se* and the effects of cyclical ovarian steroids .

Hence an experimental design utilizing the two pill-using groups and a matched control group can be visualized . The differences between these groups being on the basis of the presence or absence of the LH surge and ovulation , cyclical FSH , oestrogen and progesterone (Table 6.1) . If ovulation and luteal function are both necessary for PMS to occur , then the two pill groups would be expected to behave in a similar way , but differently from the control group . If ovulation itself is not essential , but luteal hormones are - then the triphasic and control groups might be expected to act in a similar fashion with the monophasic users behaving differently .If neither ovulation nor luteal function are important , then the three groups will produce similar data .

Three major contaminating factors should however be borne in mind :-

1) The relative biological activity of endogeneous and exogeneous hormones . It may be that synthetic oestrogens and progestagens will not have the same physiological activity as those produced by the body itself .

2) Most of the oral contraceptives currently prescribed are " low dose " (i.e ≤ 30 μg ethinyloestradiol) . The level of residual follicular activity in users of these preparations is uncertain and may have some influence on the expression of mood states etc. .

3) Further to the above - the presence of a " pill free week " during which endogeneous ovarian activity can occur may have a bearing on symptom development .

6.2 STUDY DESIGN

6.2.1 SUBJECT SELECTION

The insertion of a Menstrual Health Questionnaire in a national women's magazine , " Woman " , in August 1985 , produced a large response with approximately 7500 women returning completed questionnaires (Bancroft & Warner 1987) . The respondents were invited to volunteer their services for further research work , producing a research " pool " of about 5000 women . Although epidemiological studies cannot be undertaken on this group because of the biased nature of the original questionnaire and the readership characteristics of the magazine , the presence of a large group of volunteers on whom some descriptive data is available makes subject selection on various criteria a possibility . All subjects in this study were selected from this pool with the major criterion being their contraceptive use . Several exclusions were made however before the selection was undertaken .

1) Age - all respondents below the age of 18 years and above the age of 35 years were excluded from the selection . In this way the possible contaminating factors of puberty and the climacteric were minimized . This age group is also the peak range for oral contraceptive use , the pill being rarely prescribed over the age of 35 for fear of long term side effects or under the age of 16 for legal reasons .

2) Stress - all women who reported " a great deal of stress " or a relationship which was " not at all happy " at the time of the original questionnaire were excluded from the selection .

3) PMS - since the concern in this study is the potential difference between pill-users and non users in respect to their premenstrual symptoms - only those women who responded yes or maybe to the question " Do you have PMS ? " were included.

4) Relationship - as sexual interest and sexual activity were to be assessed , women were only included if they reported stable heterosexual relationships at the time of the original questionnaire .

5) Contraception - pregnant , lactating and hysterectomized women were excluded from the selection .

After making these exclusions , three groups of women were chosen on the basis of oral contraceptive use , one group using triphasic pills , one using monophasic (combined) pills and one group using non-steroidal contraception . These groups were matched for age , parity (i.e. with or without children) and occupation (i.e. full time work , part time work or no paid work outside the home) . The distribution within each group is described in Table 6.2 . The numbers within each cell took advantage of the maximum number of available pill users in each category . Since the overall number of pill users in the pool was small - this was a limiting factor in deciding the number of women approached .

6.2.2 PROCEDURE

The study procedure followed a series of steps :-

1) All 422 selected women were contacted by post and asked to complete a further questionnaire , the Menstrual Health Questionnaire Part II (see Appendix) , an example diary form , and to indicate their willingness to participate in a prospective study . This step allowed an assessment to be made of potentially crucial changes in the subjects' oral contraceptive use and / or personal circumstances since the first questionnaire , due to a gap of about 6 months . Further data was also collected , a check made that the diary instructions were sufficiently clear for postal use and a " let-out " clause made available to those women who were uncertain about their participation .

2) Those women who responded and expressed willingness to continue were then sent sufficient diary forms for 84 days (three 28 day cycles) and instructed to start the diaries on the first day of their next menstrual period , completing one each day until the end of the series . They were asked to indicate on the diaries their current pill brand and the days on which they began and ended each pill packet . A modified Moos MDQ (MMDQ) was also included , to be completed before the diaries were started, and in a subgroup another copy of the Menstrual Health Questionnaire (MHQ) was sent . The diaries were returned in fortnightly

TABLE 6.2

FREQUENCIES OF WOMEN SELECTED

AGE	WITHOUT CHILDREN			WITH CHILDREN			TOTAL
	F/T	P/T	NPW	F/T	P/T	NPW	
20	10	1	0	0	0	0	11
21	13	0	2	0	0	0	15
22	10	0	2	0	0	0	12
23	11	0	1	0	2	0	14
24	13	0	1	0	1	1	16
25	5	1	1	0	1	1	9
26	7	1	0	1	1	2	10
27	3	0	0	1	2	3	9
28	5	0	0	0	1	4	10
29	7	0	0	1	3	3	14
30	2	0	0	0	1	3	6
31	1	0	0	0	3	1	5
32	3	0	0	1	1	1	6
33	0	0	0	0	3	0	3
34	0	0	0	1	0	0	1
35	1	0	0	0	0	0	1
TOTAL	91	3	7	5	19	19	144
	101			43			

Key F / T - full-time work ; P / T - part-time work ; NPW - no paid work outside the home .

Each cell represents the number of women selected in each experimental group (i.e. the triphasic , monophasic and control groups) who satisfied the various criteria of age , parity and occupation . For example 10 full-time working , nulliparous 20 year olds were approached in each experimental category . In this way the groups were matched on the various parameters whilst allowing maximum usage of the pill-users available .

batches (the MMDQ and MHQ were to be included with the first batch) in Freepost envelopes .

3) At the end of the study - all women were sent a Thank-you letter and a leaflet describing self-help strategies for coping with PMS . The subgroup who received the second MHQ completed a further copy at the end of the study to assess its relevance to prospective data . The results of this study will be reported seperately (Bancroft & Walker) .

All subjects were encouraged to contact the researcher by telephone or letter at any point during the study if they had queries about or problems with the research - and this many of them did . No assessment of the hormonal status of the control subjects was made at any point , due to logistic difficulties . The assumption being that a high proportion of cycles in this age group will be ovulatory . In addition no assessment was made of the personality characteristics of the three groups due to the absence of a suitable instrument for postal administration .

6.3 RESULTS

As outlined in the introduction , the purpose of this study was to assess the importance of ovulation *per se* and natural or synthetic luteal function on cyclical symptoms associated with menstruation . The hypotheses generated by the experimental design were tested by three analytical techniques . Firstly , each subject's data were divided according to "menstrual cycle " phase and " pill cycle" phase . This analysis tested the relative effects of menstruation as such and the " pill free week " on symptom presentation , and allowed for comparison between groups directly on the basis of the underlying hormonal milieu . Secondly, a non-parametric analysis was performed to reduce errors due to inter individual differences in scale usage . This analysis was conducted on a daily basis across each cycle , allowing a more sensitive index of symptom onset to be obtained . Thirdly , symptom patterns were further assessed within each of the three groups by means of a crude comparison of premenstrual , menstrual and postmenstrual score ratios . On the basis of several criteria , each subject was categorized according to symptom pattern , and differences between the frequencies of occurrence of different subtypes were assessed between the three groups . Hence the two major variables of symptom expression , timing and severity have been analysed between the three groups .

6.3.1 RESPONSE RATES AND DEMOGRAPHIC DATA

Approximately half of the women originally contacted returned the Menstrual Health Questionnaire Part II , with almost all of these agreeing to participate in the research (see Table 6.3) . The reasons for this low response rate in a group of apparently highly motivated volunteers are not immediately obvious . The time lapse between the original magazine survey and this study , of about six months , may have been a contributory factor in that some proportion of the sample may have moved house and become uncontactable. The differences between a one-off questionnaire and a long term daily study may also be important .

TABLE 6.3

RESPONSE RATES WITHIN THE THREE GROUPS

	TRIPHASIC	MONOPHASIC	CONTROL
Number Contacted	146	146	146
Number returning First Questionnaire	74	81	85
Number Agreeing To Participate	72	81	85
Number returning Some Diaries	43	41	79
Number Providing Usable Data	30	35	57

The majority of those who responded favourably did in fact return some proportion of the daily diary series , however this proportion is much higher in the control group than in either of the pill using groups . Once more the reasons for this are not immediately evident . Arguably if the pill users overall are experiencing fewer or less severe premenstrual changes than the control group , then they may be less well motivated to continue with the study . The lack of personal contact with the researcher in a postal study may also be a contributory factor , although no evidence is available to

support this contention . Data were selected for analysis from that collected on several criteria . Firstly , an unbroken set of data covering at least two

TABLE 6.4

REASONS FOR UNUSABLE DATA

	TRIPHASIC	MONOPHASIC	CONTROL
< 2 Cycles data	10	6	15
Diaries uncodable	1	0	0
Changed pill brand	2	0	0
Became pregnant	0	0	3
Cycles <23 or >35 days	0	0	4
TOTAL	13	6	22

menstrual cycles was considered necessary for the study to be meaningful . Therefore any data set covering less than this time period was excluded . Specific cycles were excluded if they were shorter than 23 or longer than 35 days in the case of the control group , to maintain comparability with the pill using groups , or if pregnancy occured .

Data were also excluded if the respondent changed pill brand partway through or if the diaries were uncodable . The proportion of data falling into these categories is described in Table 6.4 .

Despite the relatively low response rates , the distribution of women within the three analysed groups does not differ significantly from that in the selected groups on the basis of the three selection criteria - age , parity and occupation (Figures 6.1 & 6.2) .

Demographic data was obtained from the three groups from the Menstrual Health Questionnaire Part II (Table 6.5) . The three groups of women are very similar in age and social class . Perhaps surprisingly when classed on their own present or previous occupations , the majority of women fell into class III . However classification on the basis of partner's occupation increased the numbers in classes I & II in all groups sufficiently to cause a significant difference to arise between the triphasic group and the others . The majority of women reported themselves to be in good health , with few chronic medical conditions . Some of the stable relationships used as an inclusion criterion had broken down since the original questionnaire .

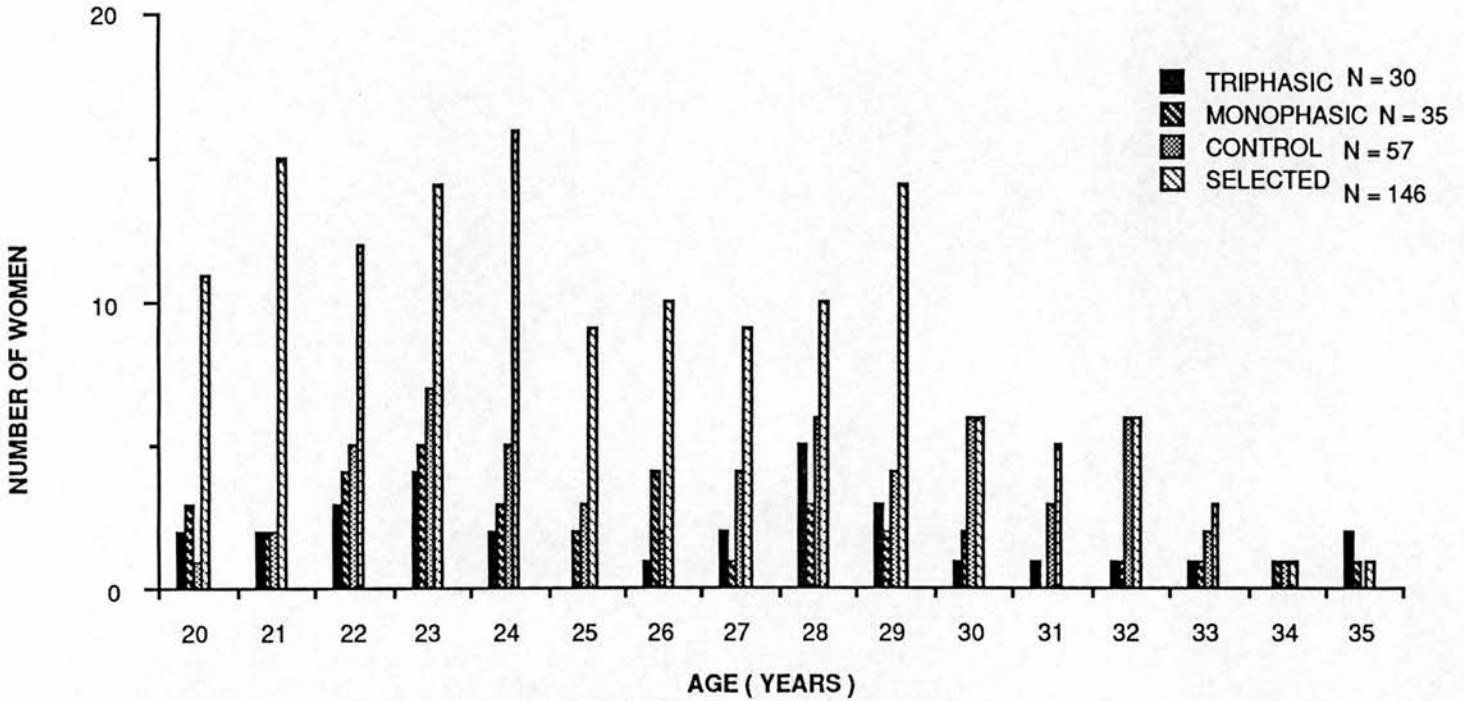


Figure 6.1 Comparison of age distribution in the original subject selection with that in the final study groups .

(N.B. Identical selections were made in each experimental group , final differences reflect response variability .)

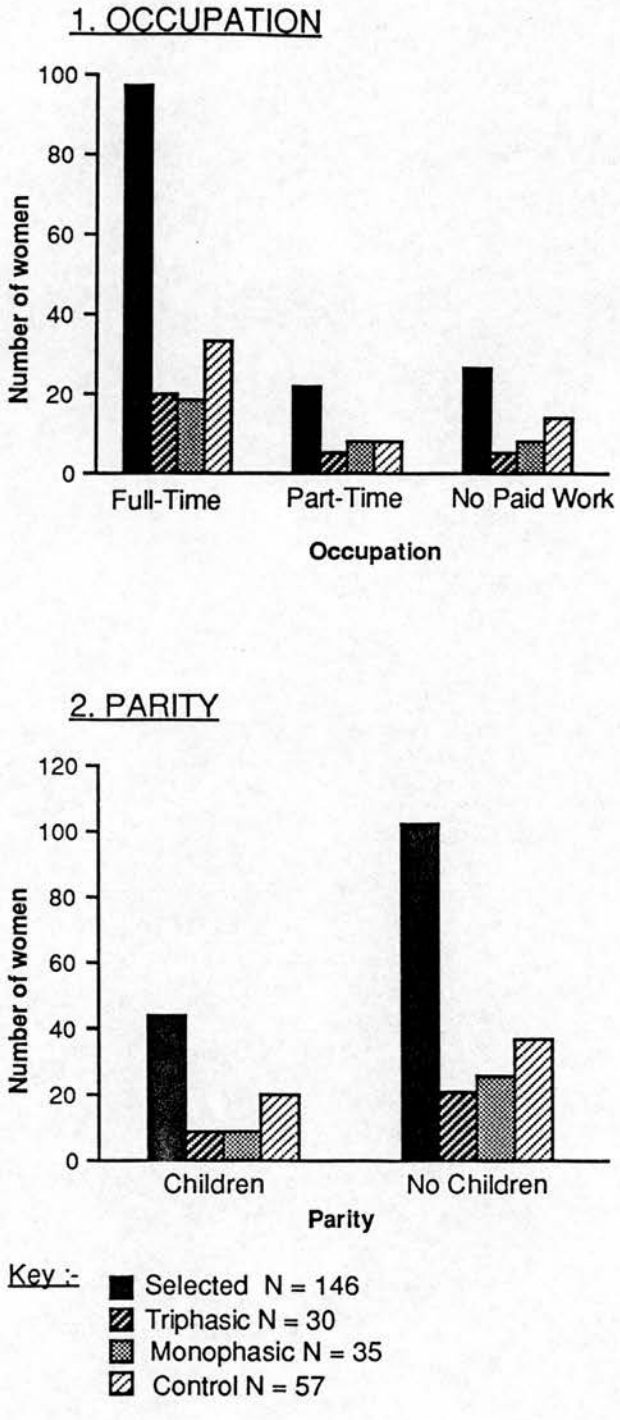


Figure 6.2 Comparison of parity and occupation distributions in the original selection with the final study groups

TABLE 6.5

DEMOGRAPHIC DATA OF PILL STUDY PARTICIPANTS

PARAMETER		TRIPHASIC	MONOPHASIC	CONTROL	STATISTICS
N		30	35	57	–
MEAN AGE (SD)		26.46 (4.28)	25.57 (4.17)	26.95(3.82)	F = 0.68 ns
SOCIAL CLASS (SELF)	I & II	10 (33.3%)	5 (14.3%)	15 (26.3 %)	Chi-square = 7.94 ns
	III	18 (60%)	24 (68.6%)	39 (68.4%)	
	IV & V	2 (6.7%)	5 (14.3%)	1 (1.7%)	
	UNCLASS	0	1 (2.8%)	2 (3.5%)	
SOCIAL CLASS (PARTNER)	I & II	14 (46.7%)	7 (19.6%)	20 (34.0%)	Chi-square =18.05 p < 0.01
	III	10 (33.3%)	15 (42.0%)	23 (39.1%)	
	IV & V	0	10 (28.0%)	3 (5.1%)	
	UNCLASS	6 (19.8%)	3 (8.4%)	11(18.7%)	
GENERAL HEALTH	POOR	1 (3.3%)	0	2 (3.5%)	Chi-square =1.46 ns
	MODERATE	8 (26.7%)	8 (22.8%)	13 (22.8%)	
	GOOD	21 (70.0%)	27 (77.2%)	42 (73.7%)	
CHRONIC MEDICAL CONDITION	NO	23 (76.7%)	29 (82.8%)	43 (75.5%)	Chi-square =0.73 ns
	YES	7 (23.3%)	6 (17.2%)	14(24.5%)	
RELATIONSHIP	N/A	3 (10%)	1 (2.8%)	7 (12.3%)	Chi-square = 6.85 ns
	UNHAPPY	2 (6.6%)	1 (2.8%)	5 (8.7%)	
	FAIRLY HAPPY	9 (30%)	13 (37.1%)	10 (17.5%)	
	VERY HAPPY	16 (53.3%)	20 (57.1%)	34 (59.6%)	
PRESENT STRESS	NO	13 (43.3%)	12 (34.3%)	25 (43.9%)	Chi-square =0.91 ns
	YES	17 (56.6%)	23 (65.4%)	32 (56.1%)	
PREVIOUS EPISODE	UNHAPPY NO	2 (6.7%)	4 (11.4%)	8 (14.0%)	Chi-square =2.72 ns
	YES/REASON	26 (86.7%)	27 (77.1%)	43 (75.4%)	
	YES NO REASON	1 (3.3%)	4 (11.4%)	6 (10.5%)	
DID YOU SEE YOUR DOCTOR ABOUT IT ?	N/A	2 (6.7%)	4 (11.4%)	7 (12.3%)	Chi-square = 3.34 ns
	NO	10 (33.3%)	14 (40.0%)	22 (38.6%)	
	YES/NO TREATMENT	4 (13.3%)	3 (8.6%)	10 (17.5%)	
	YES/TREATMENT	14 (46.7%)	14 (40.0%)	18 (31.6%)	

Key SD - standard deviation N/A - not applicable ns - not significant

TABLE 6.6

MENSTRUAL CYCLE CHARACTERISTICS AND REPRODUCTIVE HISTORY OF ALL PILL STUDY PARTICIPANTS

PARAMETER	TRIPHASIC	MONOPHASIC	CONTROL	STATISTICS
MEAN AGE AT MENARCHE (SD) (Years)	12.80 (1.58)	12.00 (1.31)	12.47(1.44)	F=3.01 ns
ADOLESCENT DYSMENORRHEA				Chi-square = 9.73 $p < 0.05$
YES	12 (40.0%)	13 (37.1%)	38 (66.7%)	
NO	18 (60.0%)	22 (62.9%)	19 (33.3%)	
CURRENT CYCLE LENGTH (SD) (Days)	27.90 (0.74)	27.26 (2.16)	28.09 (3.33)	
CYCLE REGULARITY				
REGULAR	29 (96.7%)	32 (91.4%)	49 (85.9%)	
IRREGULAR	1 (3.3%)	2 (5.7%)	8 (14.1%)	
VERY IRREGULAR	0	1 (2.8%)	0	
CURRENT DYSMENORRHEA				Chi-square =7.38 ns
YES	1 (3.3%)	4 (11.4%)	14 (24.6%)	
NO	29 (96.7%)	31 (88.6%)	43 (75.4%)	
NUMBER OF PREGNANCIES				Chi-square = 2.46 ns
0	19 (63.4%)	22 (62.8%)	28 (49.1%)	
1	4 (13.3%)	5 (14.3%)	11 (19.2%)	
2	4 (13.3%)	5 (14.3%)	11 (19.2%)	
≥3	3 (10.0%)	3 (8.5%)	7 (12.3%)	
NUMBER OF CHILDREN				Chi-square =2.41 ns
0	22 (73.3%)	26 (74.3%)	37 (64.9%)	
1	3 (10.0%)	2 (5.7%)	5 (8.8%)	
2	4 (13.3%)	6 (17.1%)	14 (24.6%)	
≥3	1 (3,3%)	1 (2.8%)	1 (1.7%)	
PREGNANCY COMPLICATIONS				
N/A	22 (73.3%)	25 (71.4%)	37 (64.9%)	
NONE	6 (6.7%)	2 (5.7%)	9 (15.8%)	
HBP	0	2 (5.7%)	3 (5.3%)	
DEP	2 (6.7%)	2 (5.7%)	3 (5.3%)	
MS	2 (6.7%)	2 (5.7%)	3 (5.3%)	
TM	1 (3.3%)	2 (5.7%)	1 (1.7%)	
COMBINATION	! (3.3%)	0	1 (1.7%)	
BIRTH COMPLICATIONS				
N/A	22 (73.3%)	26 (74.3%)	37 (64.9%)	
NONE	4 (13.3%)	3 (8.6%)	11 (19.3%)	
BREECH/ FORCEPS	1 (3.3%)	3 (8.6%)	1 (1.7%)	
CAESARIAN	1 (3.3%)	1 (2.8%)	2 (3.5%)	
IND/EPID/EPIS	0	1 (2.8%)	4 (7.0%)	
OTHER/COMBINATION	1(3.3%)	0	2 (3.5%)	
BREAST FEEDING				Chi-square = 5.13 ns
N/A	22 (73.3%)	26 (74.3%)	37 (64.9%)	
<2 MONTHS	5 (16.6%)	8 (22.9%)	9 (15.8%)	
>2MONTHS	3 (10.0%)	1 (2.8%)	10 (17.5%)	
COMBINATION	0	0	1 (1.7%)	

Table 6.6 Continued

PARAMETER		TRIPHASIC	MONOPHASIC	CONTROL	STATISTICS
POST-PARTUM DEPRESSION	N/A	22 (73.3%)	26 (74.3%)	37 (64.9%)	Chi-square
	NO	4 (13.3%)	4 (11.4%)	11 (19.3%)	=1.43
	YES	4 (13.3%)	5 (14.3%)	9 (15.8%)	ns
GYNAECOLOGICAL DISORDERS	NONE	11 (36.7%)	15 (42.8%)	18 (31.6%)	
	MENORRHAGIA	0	2 (5.7%)	0	
	AMENORRHEA	1 (3.3%)	1 (2.8%)	0	
	OLIGOMENORRHEA	1 (3.3%)	0	0	
	DYSMENORRHEA	1 (3.3%)	3 (8.6%)	10 (17.5%)	
	THRUSH etc.	11 (36.7%)	9 (25.7%)	19 (33.3%)	
	VENEREAL DISEASE	1 (3.3%)	0	1 (1.7%)	
	OTHER	0	1 (2.8%)	1 (1.7%)	
	COMBINATION	4 (13.3%)	4 (11.4%)	8 (14.0%)	

Key SD - standard deviation ; ns - not significant ; N/A - not applicable HBP - high blood pressure ; DEP - depression ; MS - morning sickness ; TM - threatened miscarriage ; IND - induction ; EPID - epidural anaesthesia ; EPIS - episiotomy .

However this number was reasonably small and consistent across all three groups. Although the number reporting themselves to be under some stress is apparently high , a very small proportion of these fell into the category " a great deal of stress " and hence their data was included . The majority had suffered some degree of depression in the past , although this was usually related to an external event such as a broken relationship or a bereavment . The majority of treatments given were sleeping tablets or minor tranquilizers such as valium .

The reproductive history of the three groups is described in table 6.6 . All three showed a slightly younger than expected age of menarche , ranging from an average of 12 to 12.8 years . However since this was a retrospective questionnaire, little weight can be attached to this . A higher proportion of the control group suffered painful periods during adolescence , although this factor was not present when current dysmenorrhea was considered . The numbers of pregnancies and children were consistent across the groups . The number of pregnancies resulting in abortions or miscarriages was also consistent at about 30 % of the total number of pregnancies in each group .

The majority were nulliparous but the proportion of parous women having suffered at least one episode of post partum depression was approximately 50 % in all groups . No comment can be made about the relationship between PMS and post natal depression on the basis of this due to the absence of a non PMS group , however the incidence seems higher than would be expected . Few of the women had experienced any serious gynaecological problems although a fairly high incidence of vaginal infections e.g. thrush (candida albicans) was reported .

The contraceptive history of the subjects is described in table 6.7. The most popular form of contraception amongst the control women was the sheath although most of them had used an oral contraceptive at some time . The majority in all groups used the oc purely for contraception , however a substantial proportion of the women currently using the pill also found it helpful for dysmenorrhea or cycle regulation . Most of the women had experienced side effects of one sort or another from the oc . The most common of these being headaches , weight gain and loss of libido . Although the triphasic group had been using their current brand of pill for slightly longer than the monophasic group , this difference was not statistically significant . A very small number had experienced " post - pill amenorrhea " , however the majority of the pill using groups had never stopped taking the pill , although they had changed brands . The different pill brands used in the study are outlined in table 6.8 , the most frequent being the hormonally correspondent microgynon ™ and logynon™ . All pills used can be described as " low - dose " with respect to oestrogen content .

Each of the women completed a modified Moos Menstrual Distress Questionnaire at the beginning of the study . This questionnaire was scored and its scales categorised on the basis of Moos' original Factor Analysis . The scores on each scale were then subjected to one-way analysis of variance between the three groups to assess any differences in their retrospective reporting of premenstrual symptoms (Table 6.9) . Scores were indistinguishable between the three groups on any of the scales , although water retention scores were less marked in the monophasic group. Interactions between the scales were not assessed .

Overall , then , a picture emerges of three groups of reasonably well matched women , differing only on their choice of contraception.

TABLE 6.7

CONTRACEPTIVE HISTORY OF PILL STUDY PARTICIPANTS

PARAMETER		TRIPHASIC	MONOPHASIC	CONTROL	STATISTICS
CONTRACEPTION	NONE	0	0	9 (15.8 %)	
	SHEATH	0	0	26 (45.6%)	
	CAP	0	0	8 (14.0%)	
	IUD	0	0	10 (17.5%)	
	OC	30 (100 %)	35 (100%)	0	
	WITHDRAWAL	0	0	2 (3.5 %)	
	FEMALE STERn	0	0	1 (1.7 %)	
	MALE STERn	0	0	1 (1.7 %)	
EVER USED OC	NOW	30 (100%)	35 (100%)	0	
	< 6m AGO	0	0	12 (21 %)	
	6m - 2y AGO	0	0	10 (17.5%)	
	2y - 5y AGO	0	0	14 (24.6%)	
	> 5y AGO	0	0	14 (24.6%)	
	NEVER	0	0	7 (12.3%)	
MEAN AGE FIRST STARTED OC (SD) (Years)		18.36 (2.18)	18.03 (2.55)	17.94 (2.34) N = 50	
REASON FOR USING OC	N/A	0	0	7 (12.3%)	
	CONTRACEPTION ONLY	18 (60.0%)	19 (54.3%)	35 (61.4%)	
	DYSMENORRHEA	2 (6.7%)	4 (11.4%)	5 (8.8%)	
	MENORRHAGIA	1 (3.3%)	1 (2.8%)	1 (1.7%)	
	IRREGULARITY	0	0	1 (1.7%)	
	PMS	0	0	2 (3.5%)	
	OTHER	0	0	0	
	COMBINATION	9 (30.0%)	11 (31.4%)	6 (10.5%)	
SIDE EFFECTS	N/A	0	0	7 (12.3%)	
	NO	9 (30.0%)	19 (54.3%)	6 (10.5%)	
	YES	21 (70.0%)	16 (45.7%)	44 (77.2%)	
ALWAYS SAME BRAND	N/A	0	0	7 (12.3%)	
	NO	28 (93.3%)	26 (74.3%)	36 (63.2%)	
	YES	2 (7.7%)	9 (25.7%)	13 (22.8%)	
MEAN TIME ON CURRENT BRAND (SD) (Years)		4.03 (3.37)	3.30 (2.47)	–	t = 1.01 ns
POST-PILL AMENORRHEA	N/A	0	0	7 (12.3%)	
	NO	1 (3.3%)	5 (14.3%)	48 (84.2%)	
	NEVER STOPPED	27 (90.0%)	28 (80.0%)	0	
	YES	2 (6.7%)	2 (5.7%)	1 (1.7%)	
EFFECT ON PMS	N/A / UNSURE	5 (16.7%)	8 (22.8%)	16 (28.1 %)	
	NO PMS THEN	1 (3.3%)	1 (2.8%)	8 (14.0%)	
	WORSE	5 (16.7%)	3 (8.6%)	10 (17.5%)	
	NO EFFECT	7 (23.3%)	10 (28.6%)	7 (12.3%)	
	BETTER	11 (36.7%)	13 (37.1%)	15 (26.3%)	
	OTHER / COMBINATION	0	0	1 (1.7%)	

TABLE 6.8

FREQUENCY OF PILL BRANDS USED IN STUDY

PILL TYPE	BRAND NAME	CONSTITUENTS	NUMBER IN STUDY
TRIPHASIC	LOGYNON / TRINORDIOL	6 X Levenorgestrel 50 µg /EE 30 µg 5 x Levenorgestrel 75 µg/ EE 40 µg 10 x Levenorgestrel125 µg /EE 30µg	22
	TRINOVUM	7 x Norethisterone 500µg /EE 35µg 7 x Norethisterone 750 µg/EE 35µg 7x Norethisterone 1mg/EE 35 µg	8
MONOPHASIC	MICROGYNON / OVRANETTE	21 X Levenorgestrel 150 µg Ethinyloestradiol 30 µg	21
	MARVELON	21 x Desorgestrel 150 µg Ethinyloestradiol 30 µg	6
	OVRAN 30 / EUGYNON 30	21 X Levenorgestrel 250 µg Ethinyloestradiol 30 µg	3
	CONOVA 30	21 X Ethynodiol diacetate 2 mg Ethinyloestradiol 30 µg	1
	NORIMIN	21 x Norethisterone 1mg Ethinyloestradiol 35 µg	1
	OVYSMEN	21 x Norethisterone 500 µg Ethinyloestradiol 35 µg	1

Key:- EE = Ethinyl-oestradiol

TABLE 6.9

MODIFIED MOOS MDQ RESULTS OF PILL STUDY PARTICIPANTS

(MEAN SCORES - STANDARD DEVIATIONS IN BRACKETS)

SCALE	TRIPHASIC	MONOPHASIC	CONTROL	STATISTICS
PAIN (Headache , Fatigue , General aches & pains)	7.17 (2.91)	6.73 (3.96)	6.71 (3.39)	F = 0.20 ns
CONCENTRATION (Insomnia , Difficulty in concentrating , More accidents)	4.21 (2.96)	3.55 (3.38)	4.50 (4.18)	F = 0.66 ns
WATER RETENTION (Swelling , Weight gain , Breast tenderness)	8.03 (4.21)	6.0 (4.20)	7.58 (4.04)	F = 2.13 ns
NEGATIVE AFFECT (Anxiety , Restlessness , Irritability , Tension , Feeling down , Nervousness)	13.55 (5.18)	14.24 (6.89)	14.94 (5.78)	F = 0.48 ns
AROUSAL (Overactivity , Bursts of energy , Excitement)	2.59 (3.83)	2.18 (3.37)	1.49 (2.52)	F = 1.46 ns
CONTROL (Palpitations)	0.38 (1.16)	0.24 (0.85)	0.17 (0.82)	F = 0.41 ns
APPETITE (Appetite change)	2.38 (1.77)	2.27 (1.85)	2.38 (1.94)	F = 0.2 ns
REPEATED ILLNESSES (Repeated illnesses)	0.48 (1.25)	0.76 (1.63)	0.31 (0.93)	F = 1.18 ns
TOTAL	38.86 (12.52)	35.97 (14.97)	37.92 (14.28)	F = 0.34 ns
N	29	33	48	

6.3.2 CYCLE DIVISION ON THE BASIS OF MENSTRUAL CYCLE PHASE

The phenomena under investigation in this study are the cyclical changes in female mood and well-being coincident with the menstrual cycle. One of the most obvious effects of oc's is an alteration of the physical parameters of the menstrual cycle . Usually they induce a state of regular , predictable , light and generally pain-free menstruation . The first method of analysis then , is an attempt to distinguish between the three groups on the basis of menstrual cycle phase - investigating the relationship between menstruation itself and the classic timing of PMS in these groups . In order to do this , a mean score for each of four arbitrarily defined menstrual cycle phases was calculated for each woman . The four phases being :-

i) The menstrual phase - including all days on which bleeding occured.

ii) The premenstrual phase - seven days immediately before the onset of menstruation .

iii) The postmenstrual phase - seven days immediately after the end of menstruation .

iv) The intermenstrual phase - the rest of the menstrual cycle .

All usable data were amalgamated for each woman to produce one score for each phase for each subject .These scores were then averaged within the groups , and the resultant means are represented graphically in figures 6.3 and 6.4 , and numerically in table 6.10 . Although the data were reduced to four points per symptom , they are here "double-plotted " , i.e. the same data are repeated , to emphasize the cyclical nature of the phenomenon . The data points are plotted at the mid-point of the phase they represent in relation to the menstrual cycle to allow visual comparisons to be made across different forms of analysis . Two-way analyses of variance for repeated measures were carried out to determine the relative effects of experimental group and menstrual cycle phase . The results of these are summarized in tables 6.11 , 6.12 and 6.13 .

All three groups exhibited their lowest mood , energy and sexual interest , and highest irritability , tension & anxiety , breast tenderness , body swelling and period pain scores in either the premenstrual or menstrual phases .The timing of peak symptom occurence between these two phases was more often congruent between the triphasic and control groups and different in the monophasic group . For instance , in the cases of body swelling , irritability and tension & anxiety , maximal monophasic scores occur during

TABLE 6.10

MEAN MENSTRUAL CYCLE PHASE SCORES

(Standard deviations in brackets)

TRIPHASIC GROUP

PARAMETER	POST	INTER	PRE	MENS	N of Women
Mood	14.81 (2.16)	14.76 (2.09)	13.49 (2.40)	13.68 (2.56)	29
Irritable	1.72 (1.28)	2.07 (1.47)	2.93 (1.69)	2.85 (1.73)	29
Energy	13.11 (2.84)	12.39 (2.84)	11.01 (2.94)	11.05 (3.19)	29
Tense & anxious	1.85 (1.70)	1.92 (1.73)	2.70 (1.86)	2.46 (1.69)	29
Breast tenderness	0.09 (0.19)	0.72 (1.00)	2.50 (1.96)	1.24 (1.32)	29
Body Swelling	0.43 (0.96)	0.81 (0.94)	2.78 (1.95)	2.41 (1.22)	29
Period Pain	0.05 (0.14)	0.10 (0.22)	0.65 (0.99)	2.27 (1.45)	29
Sexual Interest	3.81 (1.82)	3.10 (1.47)	2.86 (1.57)	2.82 (1.59)	24
DAYS	7	All other days	7	All menstrual days	

MONOPHASIC GROUP

PARAMETER	POST	INTER	PRE	MENS	N of Women
Mood	14.08 (2.62)	13.82 (3.08)	12.72 (3.39)	12.11 (2.26)	35
Irritable	1.47 (1.24)	1.70 (1.71)	2.34 (1.84)	2.78 (1.68)	35
Energy	12.53 (2.72)	12.10 (2.71)	11.38 (2.54)	10.16 (2.17)	35
Tense & anxious	1.61 (1.64)	1.88 (2.04)	2.46 (2.67)	2.59 (1.94)	35
Breast tenderness	0.13 (0.30)	0.34 (0.62)	1.12 (1.34)	1.02 (1.18)	35
Body Swelling	0.51 (0.99)	0.91 (1.64)	2.27 (2.17)	2.64 (1.81)	35
Period Pain	0.11 (0.25)	0.17 (0.39)	0.65 (1.09)	2.08 (1.48)	35
Sexual Interest	3.71 (1.97)	2.94 (1.67)	2.76 (1.83)	2.50 (2.07)	30
DAYS	7	All other days	7	All menstrual days	

CONTROL GROUP

PARAMETER	POST	INTER	PRE	MENS	N of Women
Mood	15.88 (2.04)	15.00 (2.11)	13.78 (2.53)	13.40 (2.58)	57
Irritable	1.19 (1.16)	1.54 (1.32)	2.69 (1.64)	2.64 (1.80)	57
Energy	14.12 (2.53)	12.98 (2.52)	11.50 (2.56)	10.89 (2.95)	57
Tense & anxious	1.29 (1.22)	1.53 (1.42)	2.23 (1.73)	2.22 (1.69)	57
Breast tenderness	0.12 (0.32)	0.68 (1.04)	2.71 (2.32)	1.22 (1.17)	57
Body Swelling	0.23 (0.54)	0.66 (1.03)	2.45 (1.82)	1.94 (1.65)	57
Period Pain	0.05 (0.22)	0.06 (0.23)	0.46 (0.7)	2.11 (1.58)	57
Sexual Interest	4.25 (1.96)	3.46 (1.94)	2.52 (1.95)	2.79 (1.92)	49
DAYS	7	All other days	7	All menstrual days	

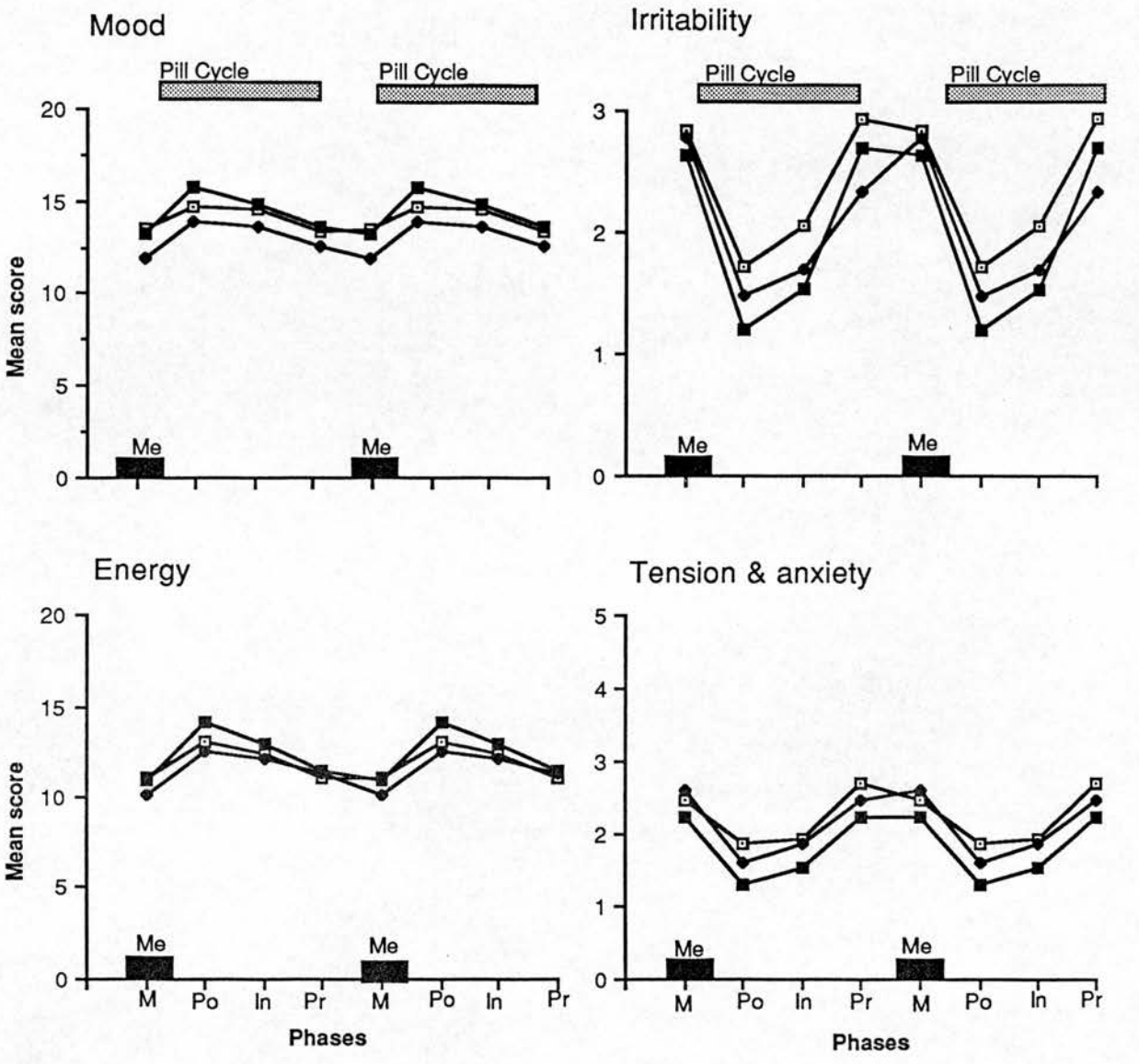


Figure 6.3 Comparison of monophasic , triphasic and control groups on measures of mood , irritability , energy and tension & anxiety divided by menstrual cycle phase (double plotted) . .

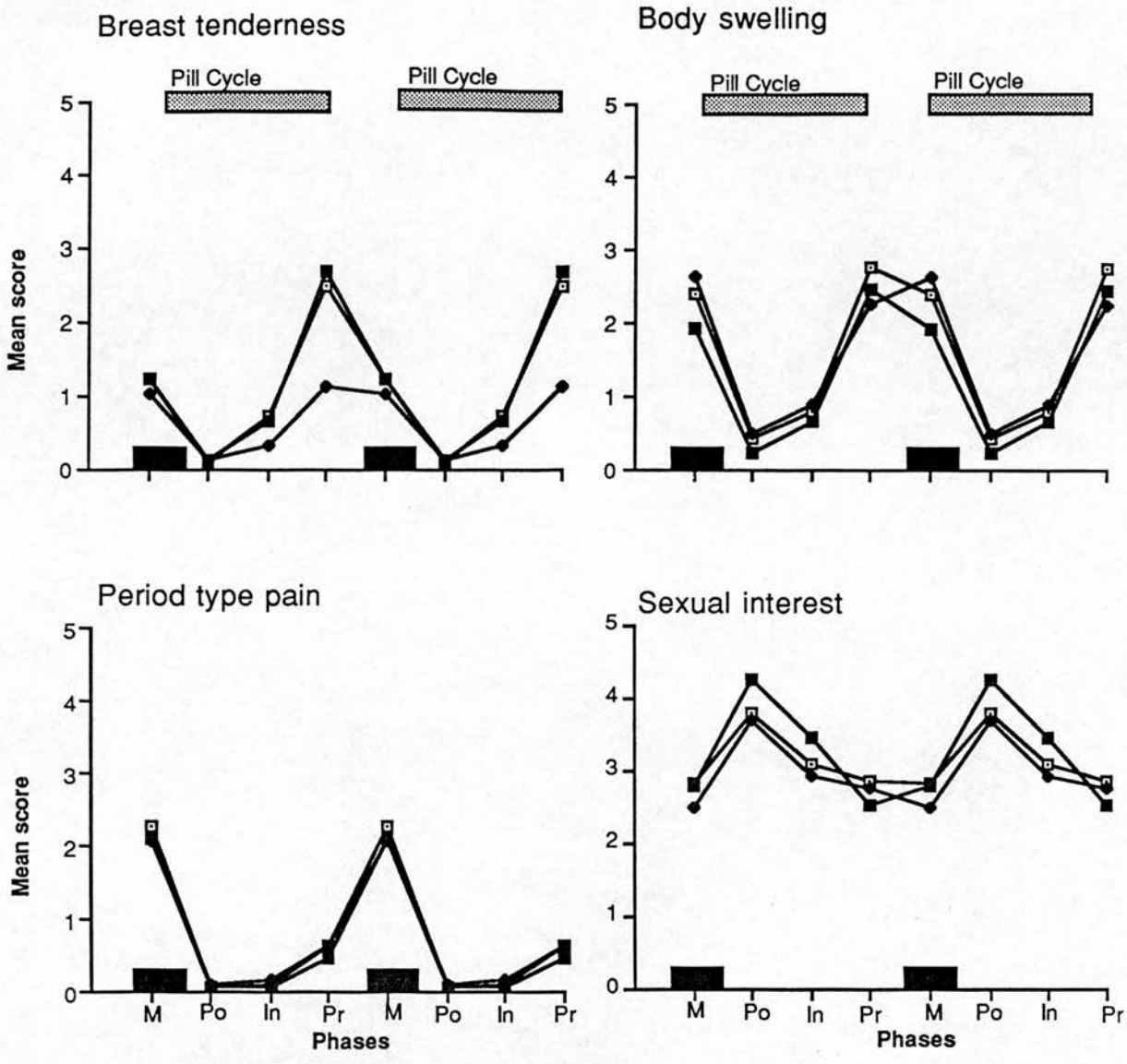


Figure 6.4 Comparison of monophasic , triphasic and control groups on measures of breast tenderness , body swelling , period type pain and sexual interest divided by menstrual cycle phase (double plotted)

TABLE 6.11

OVERALL ANALYSIS OF VARIANCE SUMMARY TABLE (F VALUES)

FOR DATA DIVIDED BY MENSTRUAL CYCLE PHASE

PARAMETER	GROUP EFFECT	PHASE EFFECT	INTERACTION
MOOD	3.70 *	33.78 **	1.72
IRRITABLE	0.78	41.08 **	0.79
ENERGY	1.28	15.45 **	1.64
TENSION & ANXIETY	0.75	20.89 **	0.32
BREAST TENDERNESS	4.26 **	72.34 **	5.00 **
BODY SWELLING	0.70	94.55 **	1.22
PERIOD TYPE PAIN	0.33	147.34 **	0.27
SEXUAL INTEREST	0.22	24.34 **	1.09
Degrees of Freedom	2	3	6

Key * - $p < 0.05$; ** - $p < 0.01$

menstruation whilst peak triphasic and control scores occur before menstruation . This also applies in the case of energy and sexual interest , where the lowest monophasic scores occur during menstruation , whilst the lowest triphasic and control group scores occur during the premenstrual week . The parameters of period pain , breast tenderness and mood do not differ in this respect . However a large difference in absolute scores of breast tenderness is seen , with monophasic users producing scores suggestive of much milder degrees of breast tenderness .

The overall analysis of variance results (Table 6.11) show highly significant phase effects for all measures , suggesting that the groups can safely be considered to experience cyclical changes in well-being .

TABLE 6.12

THE EFFECT OF MENSTRUAL CYCLE PHASE WITHIN EACH GROUP

PARAMETER	Triphasic	Monophasic	Control
MOOD	7.71**	9.97**	23.39**
IRRITABLE	9.17**	10.37**	30.14**
ENERGY	7.13**	2.97*	9.74**
TENSION & ANXIETY	4.59**	7.07**	12.34**
BREAST TENDERNESS	26.30**	7.35**	61.81**
BODY SWELLING	28.93**	27.54**	46.56**
PERIOD TYPE PAIN	43.05**	40.33**	75.69**
SEXUAL INTEREST	3.90**	6.30**	22.79**
Degrees of Freedom	3, 351 (297)		

Key * - $p < 0.05$; ** - $p < 0.01$

(Figures in brackets indicate DFe for sexual interest)

Significant group effects were also found in respect of mood , energy and breast tenderness .

An examination of pairwise comparisons between the groups (Table 6.13) reveals that the monophasic group is significantly different from the other two groups on measures of mood and breast tenderness and significantly different from the control group for energy scores . The only significant interaction between group and phase occured on the measure of breast tenderness , however a difference in symptom timing by this analysis does not appear to account for this , but rather an absolute difference between the monophasic group and the other two , reflecting perhaps a difference in scale usage , or a larger proportion of the monophasic group experiencing very mild or noncyclical breast tenderness .

TABLE 6.13

PAIRWISE COMPARISONS BETWEEN GROUPS ON THE BASIS OF MENSTRUAL CYCLE DATA , ASSESSED BY TUKEY (hsd) TEST

PARAMETER	Triphasic vs Monophasic	Triphasic vs Control	Monophasic vs Control
MOOD	ns	ns	* *
IRRITABLE	ns	ns	ns
ENERGY	ns	ns	ns
TENSE & ANXIOUS	ns	ns	ns
BREAST TENDERNESS	*	ns	* *
BODY SWELLING	ns	ns	ns
PERIOD TYPE PAIN	ns	ns	ns
SEXUAL INTEREST	ns	ns	ns

Key ns - not significant ; * - $p < 0.05$; * * - $p < 0.01$

An examination of the phase effects (i.e a measure of cyclicity) within each group symptom by symptom (Table 6.12) , reveals no further points of divergence between them . Significant phase effects are present for all groups on all symptoms.

In summary then , group differences would appear to be small and symptom specific when the data were analysed according to the menstrual cycle. Examination of trends in the data suggests that the triphasic and control groups tend to experience maximal symptoms during the premenstrual phase , whilst monophasic users peaked during menstruation . This pattern did not hold for all symptoms . Mood , breast tenderness and period pain scores revealed a close similarity between the groups on the

basis of peak symptom occurrence .On measures of mood and breast tenderness the triphasic and control groups appear
to be convergent in terms of absolute symptom scores , with the monophasic group being significanylt divergent .These findings are particularly clear in the case of breast tenderness , with a markedly lower level of severity occurring in the monophasic group despite a similar pattern of symptom timing . The possibility that these findings are not related to the real or perceived menstrual cycle , but in fact to the constituents of the oral contraceptive pill is examined in the next section .

6.3.3 CYCLE DIVISION ON THE BASIS OF PILL CYCLE PHASE

The data analysis outlined in the previous section makes no allowance for the potential physiological and psychological effects of the pill free week (pfw) on symptom manifestation . The changing levels of exogeneous hormone in the triphasic pill are similarly unaccounted for . In order to examine any differences reflecting these variables , each menstrual cycle was divided into five phases according to the changing levels of hormone in the triphasic pill following the method outlined by Bancroft , Sanders , Warner & Loudon (1987) (see figure 6.5). All cycles in the control group were standardized to 28 days to allow for comparison with the pill groups following the method outlined in section 4.4 . An arbitrary pfw was assigned to each control cycle by counting the first day of menstruation as day 3 of the pfw . This assignment was made on the basis of the most common lag between ending a course of oc and starting to bleed in the pill using groups . The data were averaged within each phase for each woman and then collected for each group . Graphical representations of the data form figures 6.6 and 6.7 . The data are double - plotted to emphasize cyclical effects (see Section 6.3.2) . The data are represented numerically in table 6.14 .Two-way analyses of variance for repeated measures were performed on the group data (Tables 6.15 , 6.16 and 6.17) .

Seven of the eight variables show a similar pattern , with peaks of irritability , tension & anxiety , body swelling and period pain , and troughs in mood and energy occuring during the pfw whilst the converse was true in the first five days of the pill cycle . This pattern holds for the control women too , suggesting an independence from exogeneous hormone levels . On these parameters , the women felt at their worst during the pill free week and at their best immediately after recommencing the pill . The rest of the cycle

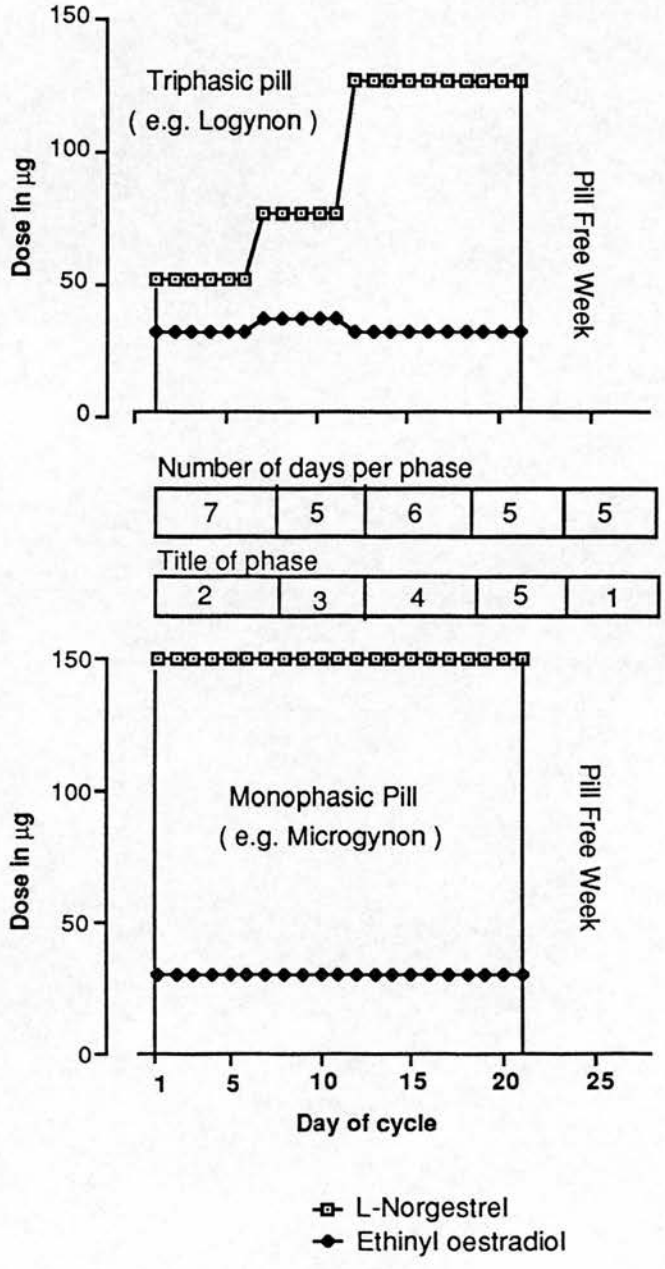


Figure 6.5 The doses of L-Norgestrel and ethinyl oestradiol in the most common triphasic and monophasic pill with the division of the cycle into five phases according to " pill cycle phase " . (Day 1 = first day of pill regime)

(Adapted from : Bancroft , Sanders , Warner & Loudon (1987))

TABLE 6.14

MEAN PILL CYCLE PHASE SCORES

(Standard Deviations in brackets)

TRIPHASIC GROUP

PARAMETER	P1	P2	P3	P4	P5
Mood	13.39 (2.35)	14.80 (2.22)	14.99 (2.30)	14.43 (2.39)	13.80 (2.36)
Irritable	3.02 (1.76)	1.71 (1.34)	1.74 (1.26)	2.18 (1.70)	2.62 (1.67)
Energy	10.73 (3.12)	13.19 (2.53)	12.70 (2.95)	12.40 (2.99)	11.33 (2.97)
Tense & Anxious	2.77 (1.80)	1.76 (1.74)	1.67 (1.67)	2.08 (1.92)	2.36 (1.84)
Breast tenderness	1.92 (1.47)	0.05 (0.15)	0.19 (0.42)	0.95 (1.44)	2.15 (1.96)
Body Swelling	3.08 (1.44)	0.41 (0.87)	0.35 (0.66)	1.03 (1.26)	2.24 (1.83)
Period Pain	2.04 (1.31)	0.14 (0.29)	0.03 (0.09)	0.13 (0.28)	0.42 (0.72)
Sexual Interest	2.75 (1.55)	3.88 (1.63)	3.61 (1.82)	2.67 (1.35)	2.72 (1.43)
DAYS	5	7	5	6	5
PILL CYCLE		ACTIVE PILL			

MONOPHASIC GROUP

PARAMETER	P1	P2	P3	P4	P5
Mood	12.06 (2.61)	14.17 (2.41)	13.98 (3.04)	13.88 (2.84)	12.97 (3.56)
Irritable	2.71 (1.57)	1.39 (1.11)	1.51 (1.57)	1.76 (1.68)	2.20 (1.89)
Energy	10.42 (2.09)	12.47 (2.50)	12.34 (2.75)	12.23 (2.55)	11.37 (2.89)
Tense & Anxious	2.56 (2.08)	1.46 (1.47)	1.74 (1.99)	1.97 (2.04)	2.48 (2.57)
Breast tenderness	1.22 (1.31)	0.14 (0.38)	0.17 (0.36)	0.47 (0.84)	0.95 (1.34)
Body Swelling	2.76 (1.89)	0.53 (0.90)	0.64 (1.34)	1.12 (1.88)	2.01 (2.26)
Period Pain	1.79 (1.38)	0.23 (0.54)	0.09 (0.23)	0.19 (0.40)	0.56 (1.08)
Sexual Interest	2.61 (2.02)	3.89 (1.97)	3.28 (1.84)	2.75 (1.67)	2.51 (1.67)
DAYS	5	7	5	6	5
Pill Cycle		ACTIVE PILL			

CONTROL GROUP

PARAMETER	P1	P2	P3	P4	P5
Mood	12.83 (2.86)	15.57 (2.81)	15.69 (2.30)	14.90 (2.51)	14.12 (2.84)
Irritable	3.11 (1.78)	1.44 (1.40)	1.24 (1.19)	1.70 (1.52)	2.45 (1.73)
Energy	10.47 (2.74)	13.67 (3.19)	13.64 (2.59)	12.77 (2.73)	11.80 (2.94)
Tense & Anxious	2.63 (1.76)	1.55 (1.42)	1.28 (1.34)	1.70 (1.61)	2.06 (1.83)
Breast tenderness	2.09 (1.71)	0.11 (0.31)	0.19 (0.37)	0.93 (1.56)	2.40 (2.30)
Body Swelling	2.64 (1.81)	0.28 (0.60)	0.23 (0.46)	0.80 (1.06)	2.08 (1.81)
Period Pain	2.02 (1.39)	0.22 (0.93)	0.03 (0.10)	0.12 (0.38)	0.36 (0.68)
Sexual Interest	2.47 (1.77)	4.27 (2.33)	3.86 (1.82)	3.37 (2.01)	2.64 (2.05)
DAYS	5	7	5	6	5

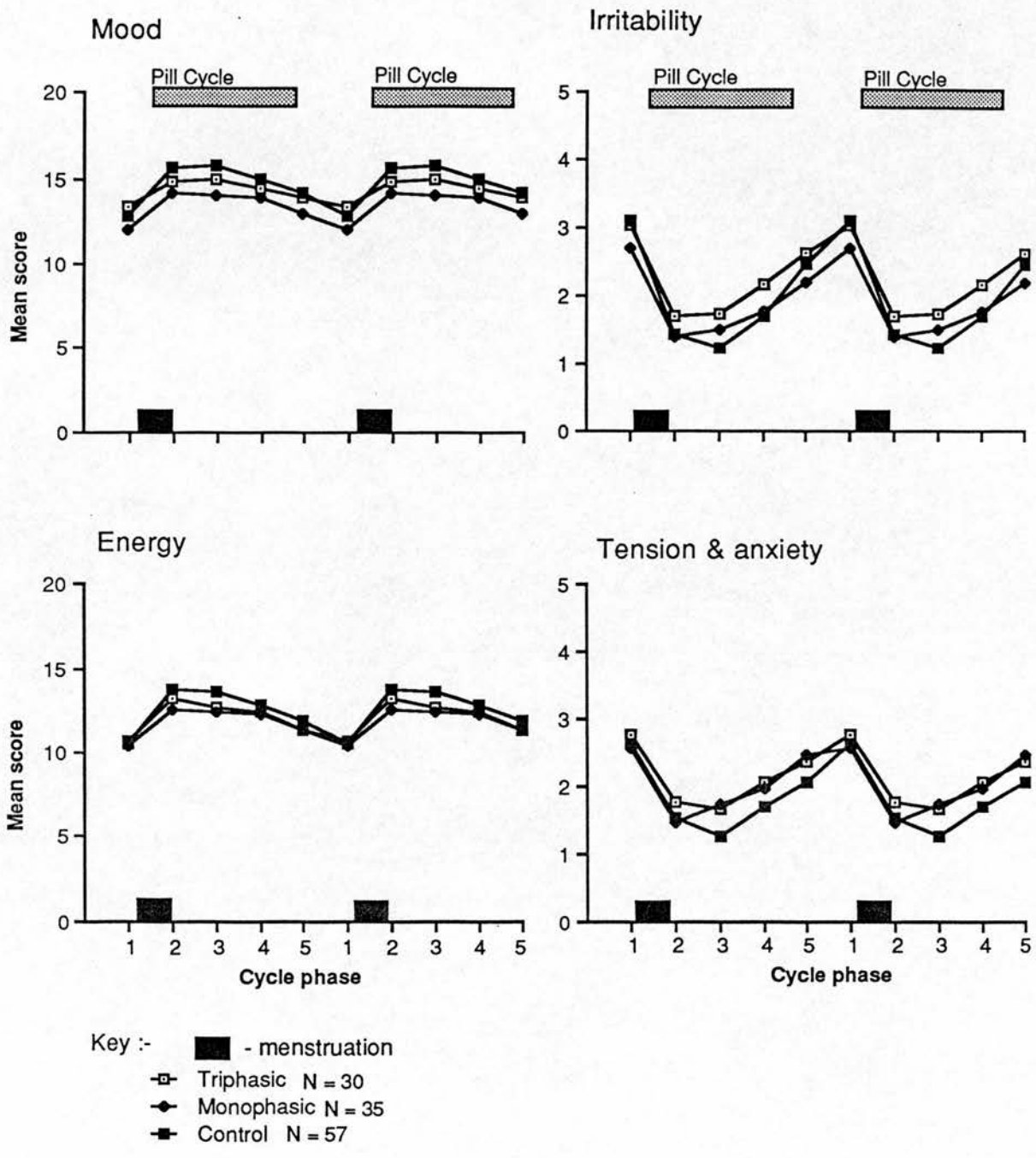


Figure 6.6 Comparison of monophasic , triphasic and control groups on measures of mood , irritability , energy and tension & anxiety divided by pill cycle phase (double plotted) .

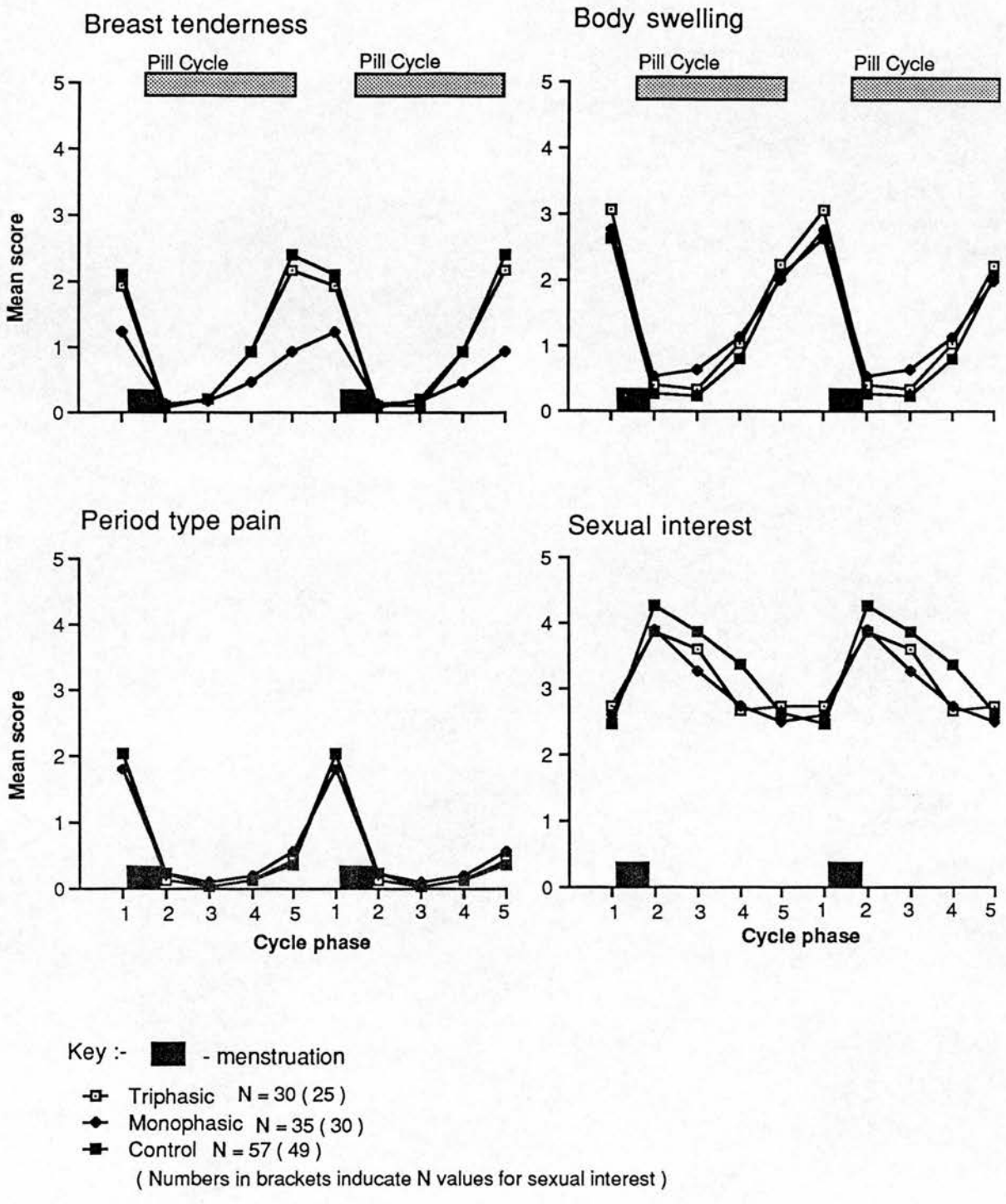


Figure 6.7 Comparison of monophasic , triphasic and control; groups on measures of breast tenderness , body swelling , period type pain and sexual interest divided by pill cycle phase (double plotted)

TABLE 6.15

OVERALL ANOVA SUMMARY TABLE (F-VALUES) FOR DATA DIVIDED BY PILL CYCLE PHASE

PARAMETER	GROUP	PHASE	INTERACTION
MOOD	2.64	25.60**	1.44
IRRITABLE	0.72	43.67**	0.83
ENERGY	0.85	42.16**	1.12
TENSE & ANXIOUS	0.34	21.47**	0.60
BREAST TENDERNESS	4.00*	68.03**	3.72**
BODY SWELLING	0.48	114.38**	0.65
PERIOD PAIN	0.03	136.83**	0.61
SEXUAL INTEREST	0.33	27.85**	1.05
Degrees of Freedom	2	4	8

Key :- * - $p < 0.05$; ** - $p < 0.01$.

TABLE 6.16

THE EFFECT OF PILL CYCLE PHASE IN EACH GROUP

(F-VALUES FROM TWO-WAY ANOVA WITH REPEATED MEASURES)

PARAMETER	TRIPHASIC	MONOPHASIC	CONTROL
MOOD	2.76*	7.83**	24.97**
IRRITABLE	9.54**	10.10**	33.86**
ENERGY	10.06**	8.56**	33.95**
TENSE & ANXIOUS	5.27**	6.68**	13.32**
BREAST TENDERNESS	24.45**	7.06**	55.96**
BODY SWELLING	37.34**	27.52**	58.87**
PERIOD PAIN	41.31**	33.38**	75.53**
SEXUAL INTEREST	6.04**	7.49**	21.78**
Degrees of Freedom	4,476 (404)		

Key :- * $p < 0.05$; ** $p < 0.01$

(Figures in brackets indicate DFe for sexual interest)

TABLE 6.17

PAIRWISE COMPARISONS BETWEEN GROUPS ASSESSED BY TUKEY (hsd) TEST

PARAMETER	TRIPHASIC vs MONOPHASIC	TRIPHASIC vs CONTROL	MONOPHASIC vs CONTROL
MOOD	ns	ns	*
IRRITABLE	ns	ns	ns
ENERGY	ns	ns	ns
TENSE & ANXIOUS	ns	ns	ns
BREAST TENDERNESS	*	ns	**
BODY SWELLING	ns	ns	ns
PERIOD PAIN	ns	ns	ns
SEXUAL INTEREST	ns	ns	ns

Key :- ns - not significant ; * $p < 0.05$; ** $p < 0.01$.

shows a gradual decline in well-being. The symptom of breast tenderness , however reveals a slightly different pattern , with maximal scores occuring before the pfw in both the control and triphasic groups whilst the monophasic group exhibit peak scores during the pfw . Minimal values occured during the first pill phase in all three groups .

Analyses of variance reveal highly significant overall phase effects on all parameters , and no differences between the three groups on any measure except breast tenderness . This the only parameter for which a significant interaction between group and phase is seen reflecting the difference in timing of maximal symptoms between the groups , as well as a difference in absolute levels of severity .

Examination of phase effects within each group (table 6.16) reveals that a strong cyclical pattern was indicated overall on all parameters.

On none of these measures were the triphasic group different from the control group (table 6.17) . However differences were apparent between the monophasic and control groups on measures of mood and breast tenderness . The latter of these parameters demonstrated a similar difference between triphasic and monophasic groups .

Overall , then it can be said that no consistent differences have been observed between the three groups on any of the parameters except mood

and breast tenderness . In both cases the triphasic and control groups are similar whilst the monophasic group is different from both .

6.3.4 NON-PARAMETRIC ANALYSIS

One of the major sources of error in estimating differences between groups on the basis of symptom severity assessed by prospective subjective data is the possibility of differential scale use between subjects and across the study . In other words , a score of 6 on any 0 - 10 scale may represent a severe symptom
experience to one subject but a relatively minor experience to another . This source of error could conceivably explain apparent differences in severity on parameters discussed in section 6.3.3 . An alternative way of examining the data would be from a non-parametric standpoint , not involving the use of absolute values but rather assigning scores to categories indicating an average , better than average or worse than average experience of a particular symptom on a particular day . Collective data within each group would then demonstrate the proportion of the sample experiencing symptoms or not at any timepoint . The practicalities of such a method involve the imposition of a " baseline " or measure of central tendency onto cyclical data and a definition of points to be considered as " peaks " or " troughs " of experience . (For a fuller discussion of cycle analysis in the context of PMS research see Chapter Four). In this case , the baseline used was the mean score over all usable data (complete cycles only and standardized to 28 days in the control group) for each symptom for each subject .The normal range of scores was defined as the mean plus or minus one standard deviation for each symptom , all scores falling outwith this range being classed as worse than normal or better than normal . Semantic difficulties arise in the description of this analysis in that high scores on three parameters i.e. mood , energy and sexual interest imply a better than normal experience , that is a peak could be defined as " good " whereas a high score on other parameters (irritability , tense & anxious , breast tenderness , body swelling , period pain) indicates a worse than normal experience , i.e. a peak could be described as " bad " . The converse of this being true of any troughs in the data . In order to reduce confusion the data is described in two ways - as " good " days and " bad " days , where the assignment of a good day for instance implies a better than normal experience - or no experience -

of a particular symptom rather than a peak or trough in the data . This concept is described diagrammatically in figure 6.8 .

The frequencies of occurence of good days and bad days for each parameter across the three groups is shown in figures 6.9 to 6.16 . All the measured variables show frequency patterns which might be expected from women reporting PMS . Bad days tended to occur before and during menses, with good days peaking after menstruation .Several important features may be extracted from an examination of these graphs :-

1) The three experimental groups are indistinguishable on the majority of variables considered , that is the percentage of cycles which were good or bad on a particular day is apparently unaffected by being an oral contraceptive user . The major exceptions to this are breast tenderness and sexual interest . In the former case , the monophasic group whilst exhibiting the same pattern as the others , shows consistently lower frequencies of both good days and bad days throughout the menstrual cycle . This might suggest a larger subgroup of monophasic users who experience either no breast tenderness or noncyclical breast tenderness than appears in the other groups . In the case of sexual interest , the two pill using groups show a very similar and almost flat pattern , although a peak of good days is apparent at the beginning of the menstrual cycle . However the control group show a rather more marked cyclical pattern , with a peak of bad days occuring during menstruation .Thus it would appear that a postmenstrual increase in sexual interest is present in all groups but that its presence is less marked in the pill using groups due to the absence of a substantial menstrual decrease in sexual interest . This phenomenon may be related to a stronger menstrual sex taboo in the control subjects , or differing attitudes towards menstruation in the three groups due to oc induced changes in the heaviness and duration of menstrual bleeding (N.B. there is no evidence from either the non-parametric analysis or the previous analyses of any differences between the groups in either the absolute severity or timing of occurence of dysmenorrhea) .

2) The pattern of occurence of each symptom is not necessarily congruent with all other symptoms . In this respect there appears to be a dichotomy between those variables which might be described as physical i.e. breast tenderness , body swelling and period type pain , and those which might be described as psychological i.e. mood , irritability , energy and tension & anxiety . The physical parameters appear to be more closely

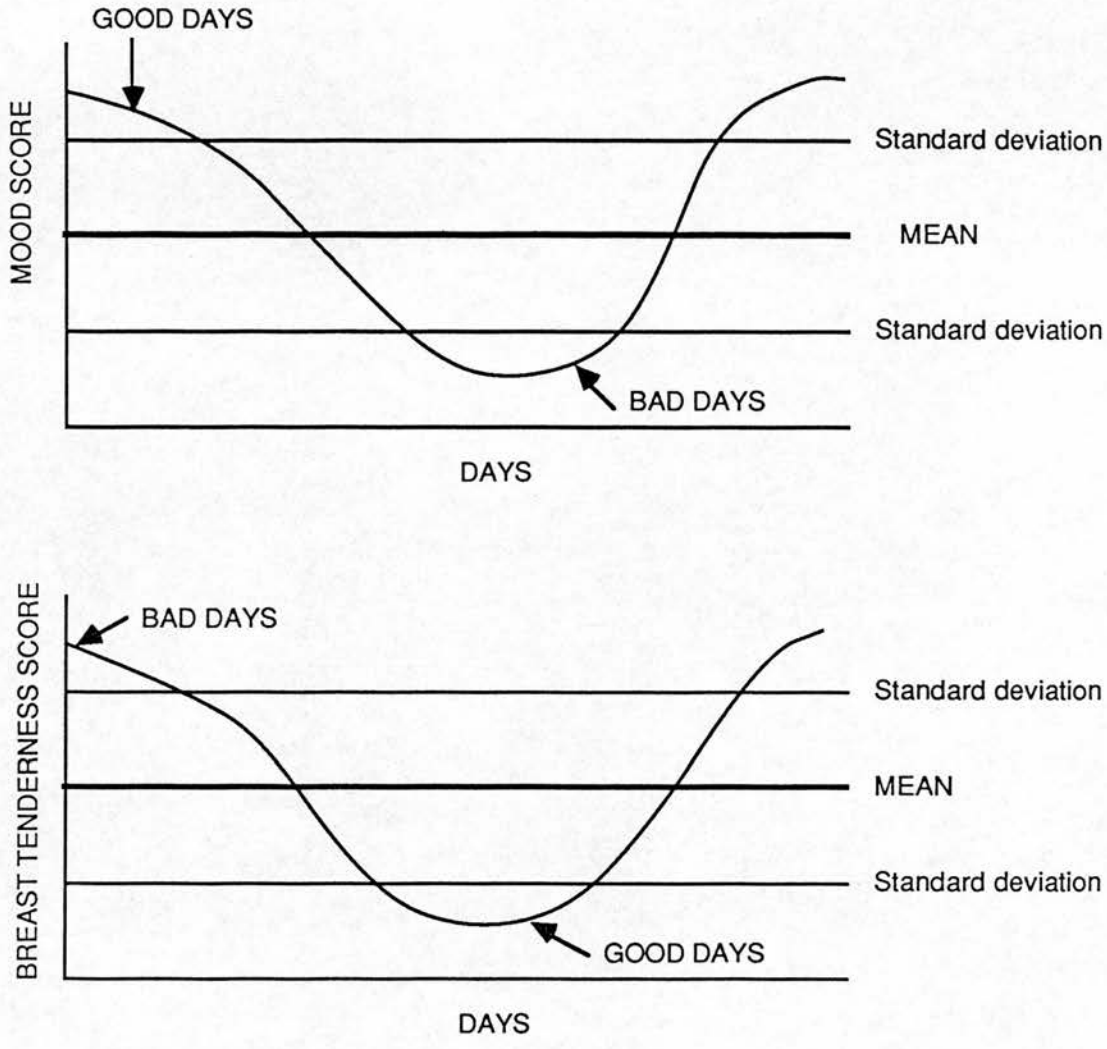


Figure 6.8. Diagrammatic representation of the definition of of " Good Days " and " Bad Days "

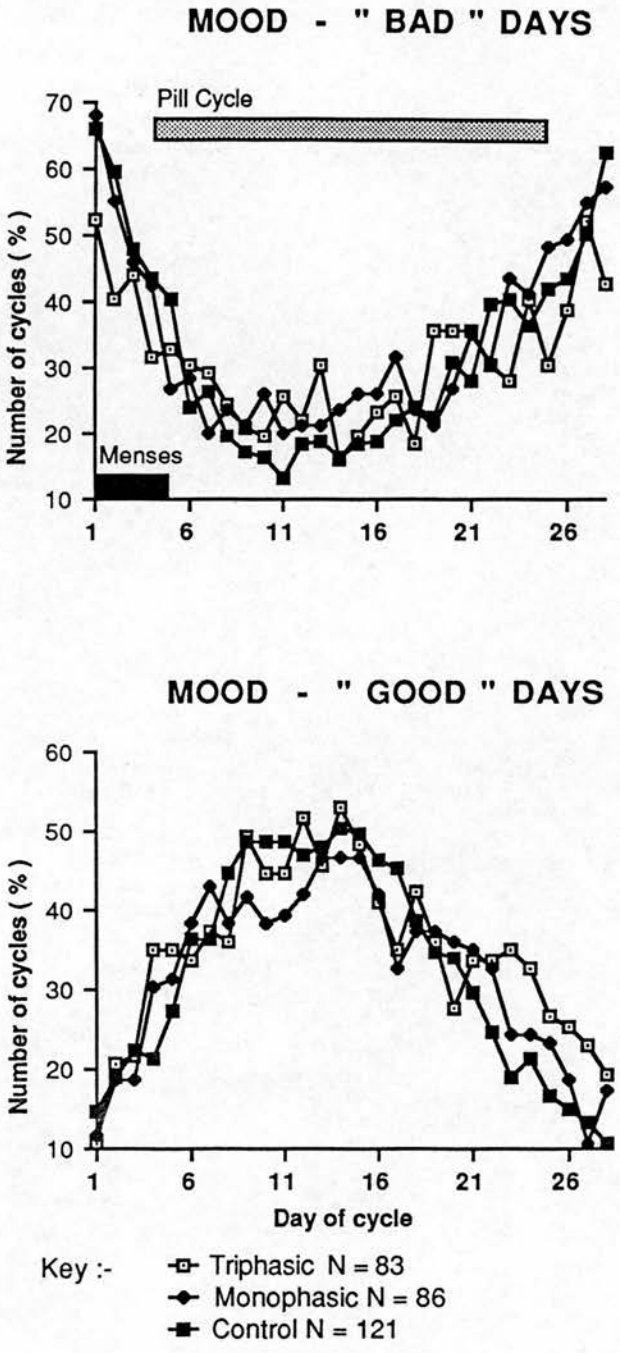


Figure 6.9 Frequency distribution of " good " days and " bad " days by cycle day on the measure of mood .
(Day 1 = first day of menstruation) .

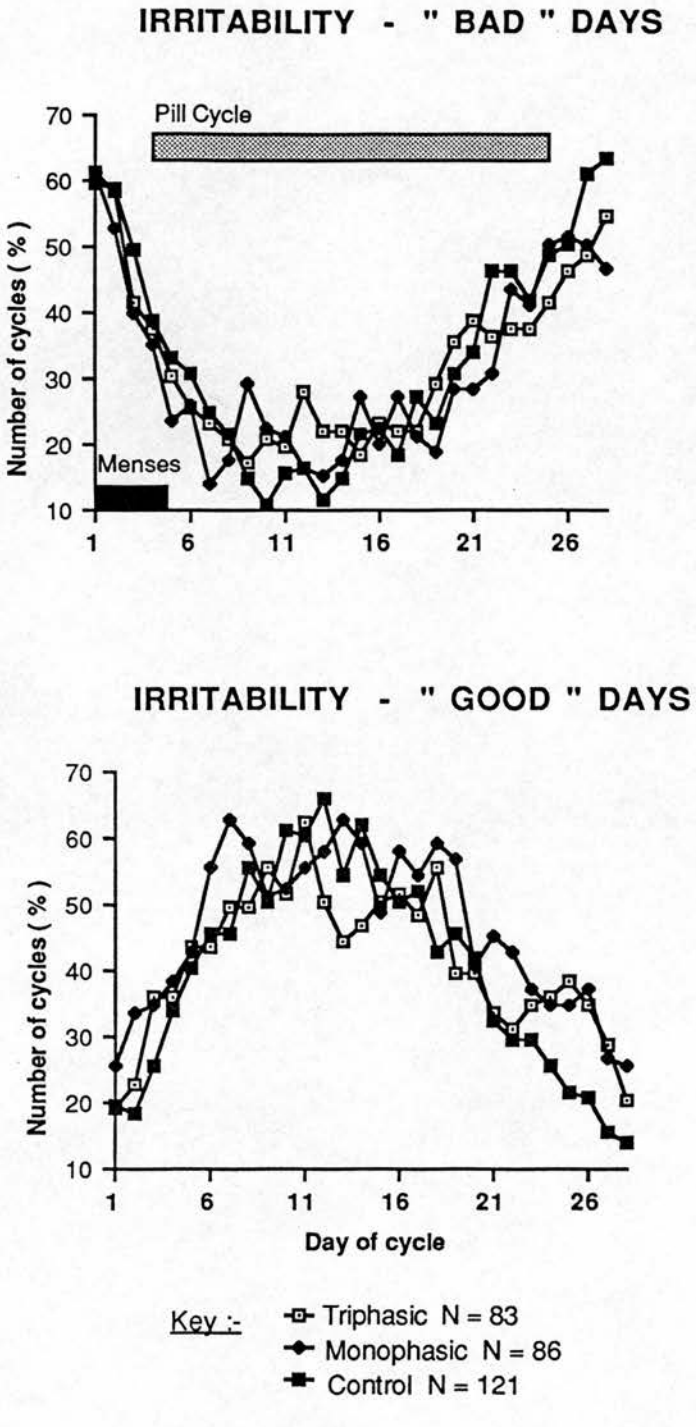


Figure 6.10 Frequency distribution of " good " days and " bad " days by cycle day on the measure of irritability
(Day 1 = first day of menstruation)

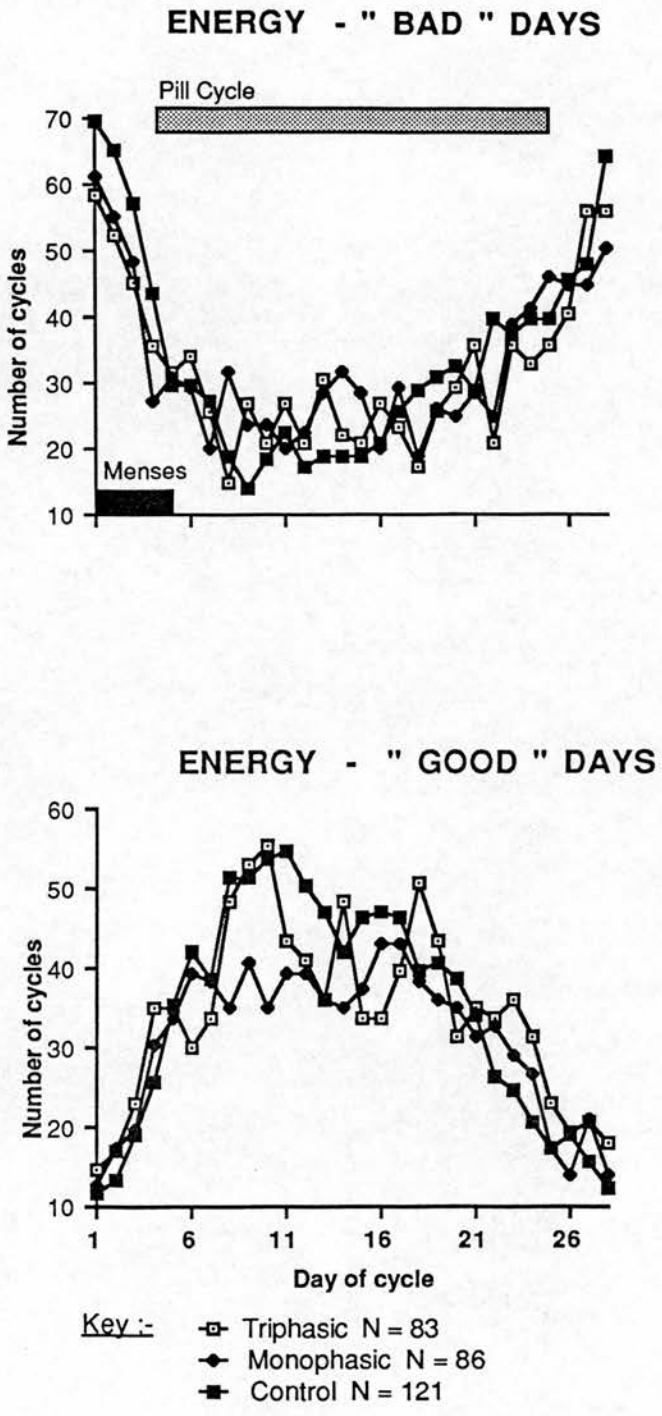


Figure 6.11 Frequency distribution of " bad " days and " good " days by cycle day on the measure of energy

(Day 1 = first day of menstruation)

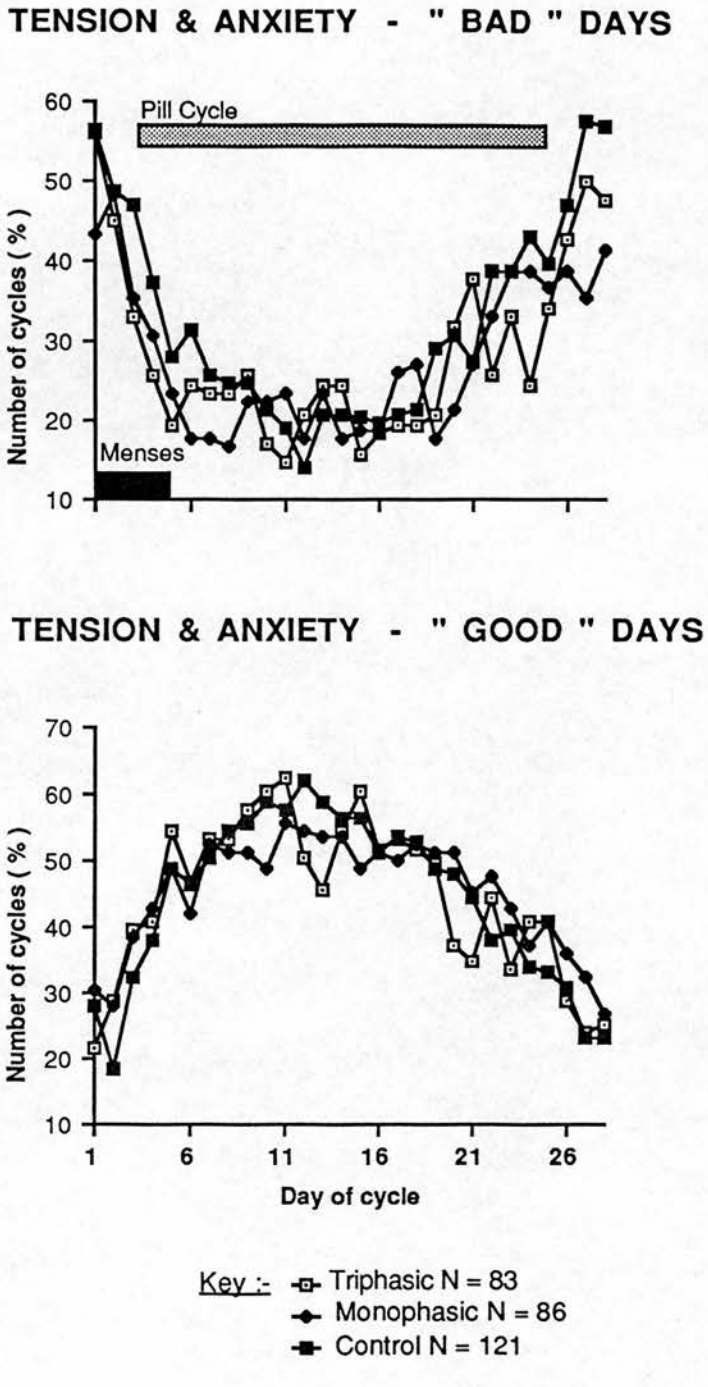


Figure 6.12 Frequency of distribution of " bad " days and " good " days by cycle day on the measure of tension & anxiety (Day 1 = first day of menstruation)

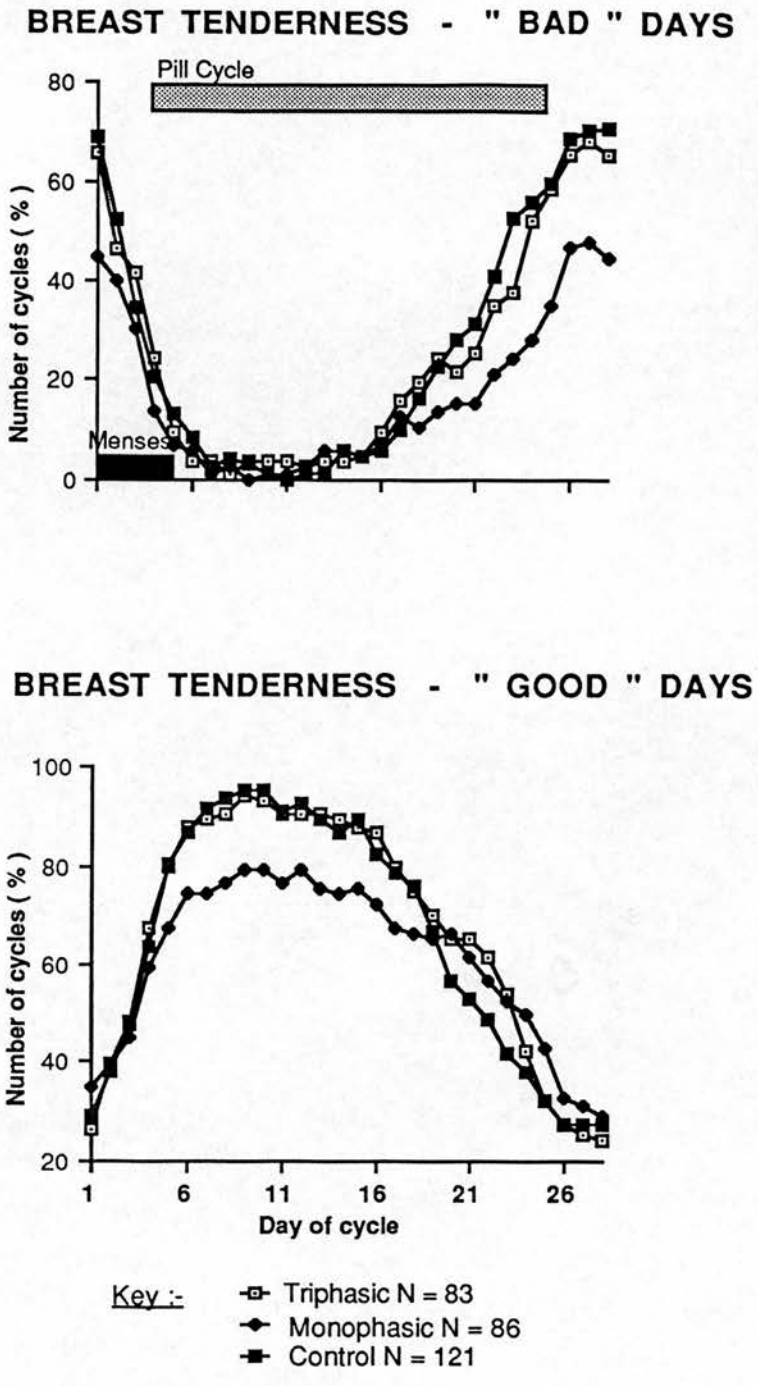


Figure 6.13 Frequency distribution of " bad " days and " good " days by cycle day on the measure of breast tendernes (Day 1 = first day of menstruation)

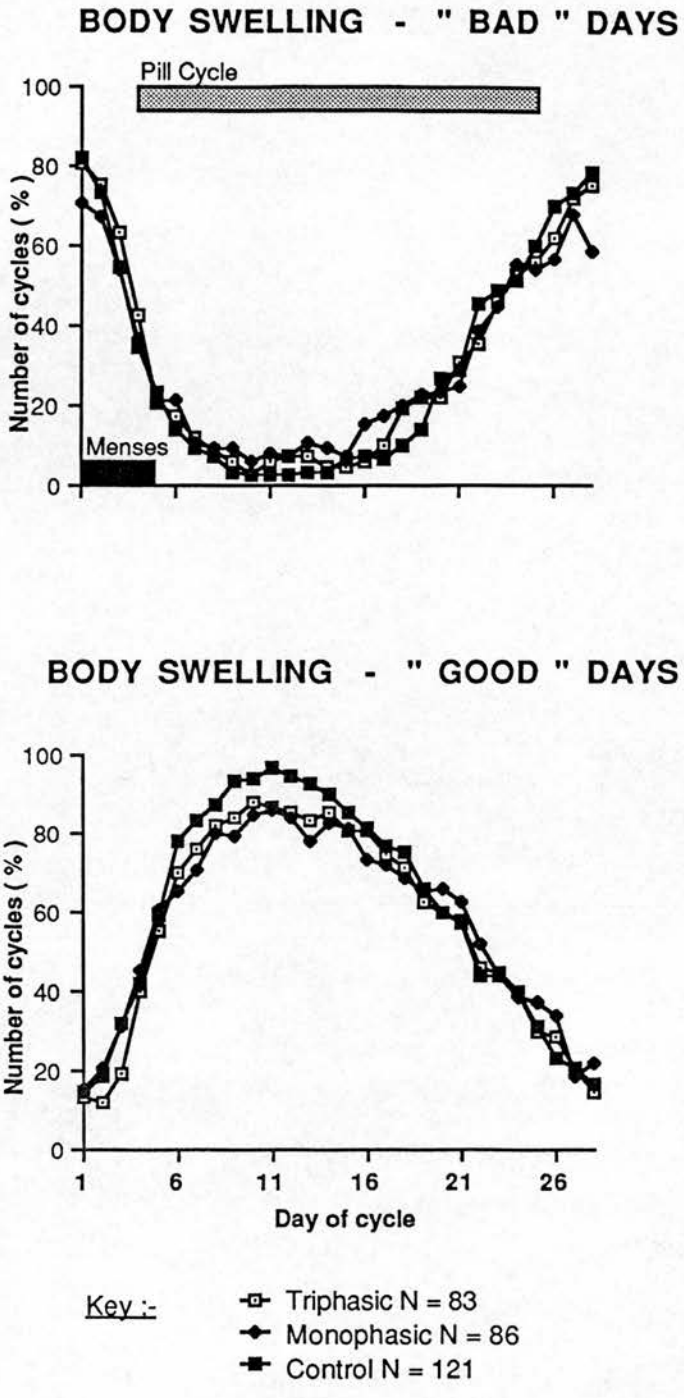


Figure 6.14 Frequency distribution of " bad " days and " good " days by cycle day on the measure of body swelling (Day 1 = first day of menstruation)

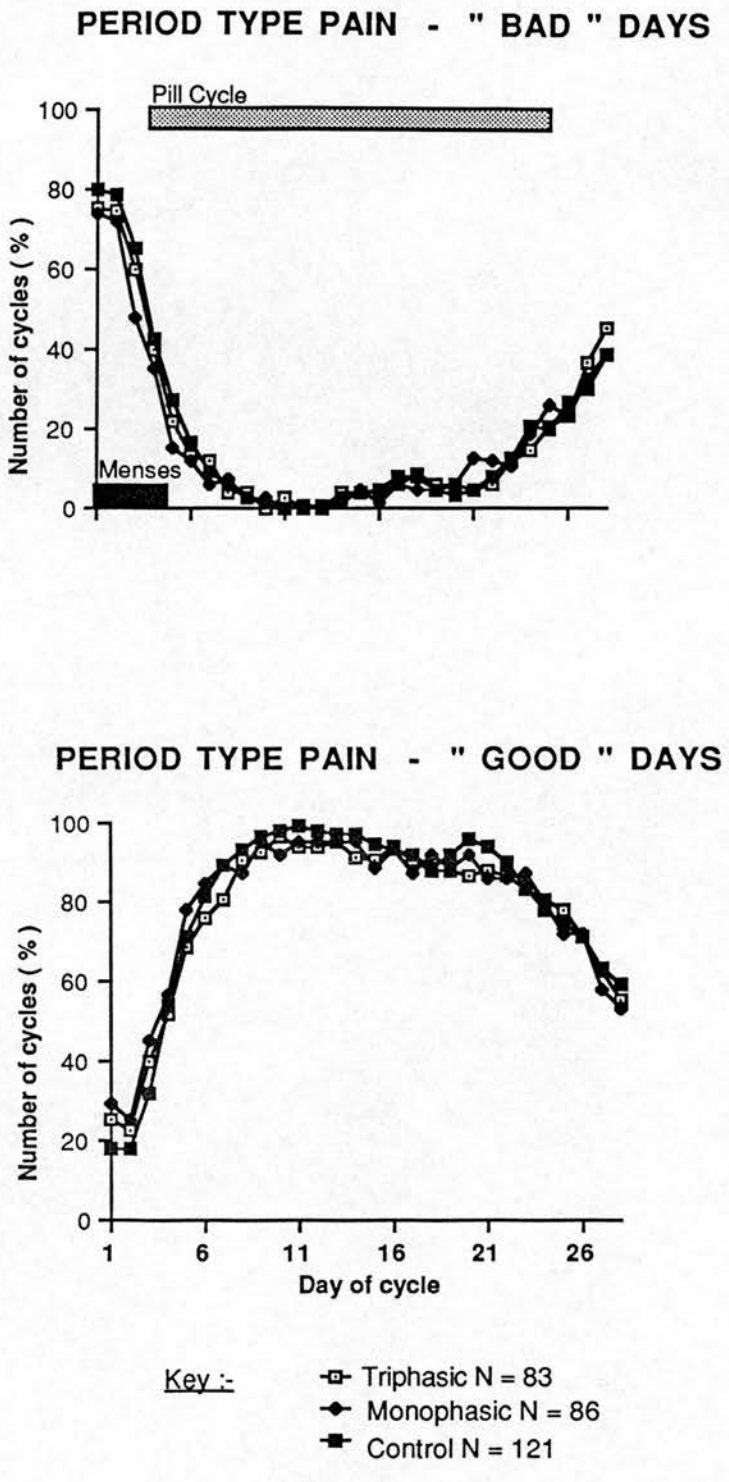


Figure 6.15 Frequency distribution of " good " days and " bad " days by cycle day on the measure of period type pain (Day 1 = first day of menstruation)

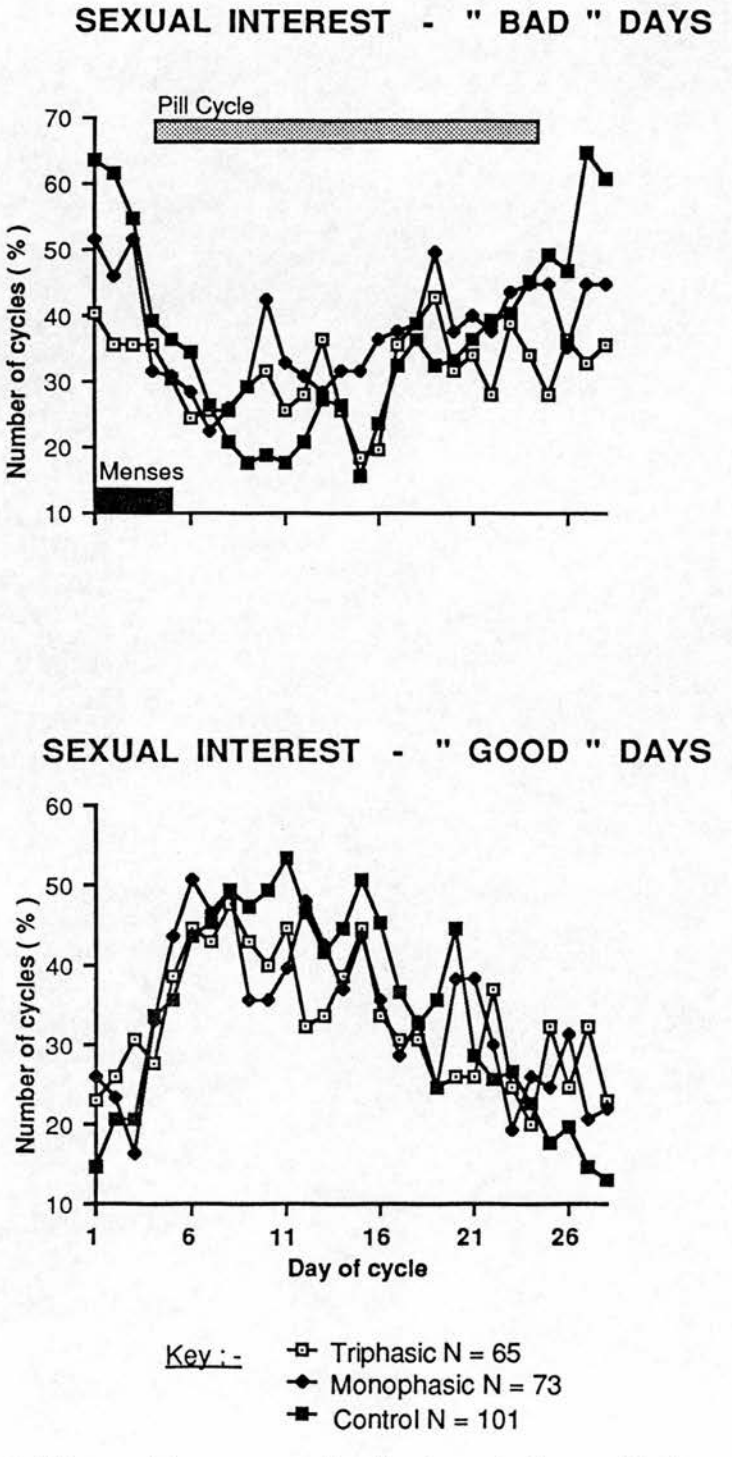


Figure 6.16 Frequency distribution of " good " days and " bad " days by cycle day on the measure of sexual interest . (Day 1 = first day of menstruation)

linked with menstruation showing a steep increase from about day 17 or 18 of the menstrual cycle and a precipitous decline during menstruation . The psychological variables on the other hand show a clear but less dramatic cyclical pattern with good days tending to peak at about day 11 or 12 with a gradual decline to a peak of bad days at the beginning of menstruation.

3) As mentioned above , the variables examined here describe a cyclical pattern . None except possibly period type pain , could be said to be absent for most of the menstrual cycle and present only for the week before or during menstruation , rather they are truly cyclical . Individual case studies may reveal many different cycles which when considered collectively produce the patterns seen here .

Statistical testing of non-parametric data of this kind is difficult . Each cycle can potentially contribute a different amount of data to the final total e.g. one cycle may
contain 5 bad days , wheras another contains 10 , due to the manner in which the raw data were assessed . In order to reduce the error due to this variability , scores were weighted to ensure that each cycle in fact contributed one data point to the overall total . For example , if a cycle contained 7 bad days , each of these was assigned a value of one-seventh , hence the total cycle score was one . If a cycle contained two bad days , each was assigned a score of one-half. These revised scores then replaced the " bad " days in the numerical representation of the symptom pattern . These weighted scores were collected for each cycle day, as the original frequencies had been , and a Chi-square test of association between the three groups was performed on the resultant frequencies . Three parameters were chosen for this treatment , two on the basis of possible group differences evident from the graphs , i.e. breast tenderness and sexual interest , and one other , i. e. mood . The Chi-square test showed no significant group differences on any of the parameters after the data had been collapsed to cope with small cells (Mood Chi-square = 2.23 , df = 6 ; Breast tenderness Chi-square = 3.72 , df = 6 ; Sexual interest Chi-square = 3.21, df = 6 - see Appendix).

6.3.5 ANALYSIS OF SYMPTOM PATTERNS

One of the sources of error in the description of data by means of averages is the possibility of obscuring extreme subgroups within the data . In this case , the discussion of overall average symptom scores or

frequencies revealing no major group differences may be obscuring subtle differences in the conformation of subgroups of symptom patterns within the data . In order to assess this possibility fully , detailed analyses of each individual would be required . However , a crude approximation can be achieved if symptom scores in specific time phases are compared to each other . In this case ratios were calculated between scores in the menstrual and premenstrual phases and scores in the postmenstrual phase (these phases are defined in section 6.3.2) . In this analysis the overall data for each woman was considered regardless of possible intrasubject variability between cycles . On this basis each variable was categorized for each woman according to the following schedule . A ratio of 1.26 to 1.49 (or 0.51 to 0.99 if either score were zero) was considered to be evidence of a mild change . A ratio of ≥ 1.5 (or ≥ 1.0 if either score were zero) was cosidered evidence of a severe change . If ratios of ≤ 1.25 (or ≤ 0.5) occurred then the variable was considered to be noncyclical , and if a ratio reaching the criteria occurred other than between the specified phases or in a different direction , the variable was described as atypical . This schedule led to 10 possible pattern combinations i.e. mild premenstrual (MP); severe premenstrual (SP) ; mild menstrual (MM) ; severe menstrual (SM) ; MP+MM ; MP+SM ; SP+MM ; SP+SM ; Noncyclical and Atypical .Each woman was categorised into one of these groups for each symptom . Frequencies of occurrence of these categories for each variable in the three groups were calculated (table 6.19). This frequency data was tested using the Chi-square test of association . In order to do this , it was necessary to collapse data thus avoiding small cell sizes . Hence the reduced categories are :- premenstrual only ; menstrual only ; premenstrual + menstrual ; and noncyclical + atypical . Graphical representations of the data can be seen in figures 6.17 and 6.18 and the numerical data in table 6.20. Each of the variables reveals a slightly different pattern . For instance in the case of mood , a high incidence of atypical and noncyclical patterns is seen in all three groups . However , body swelling shows a high premenstrual + menstrual incidence , and period pain a high menstrual only incidence . Three variables produced evidence suggestive of group differences on the basis of Chi-square :-

i) Energy - The difference here is a relative excess of women in the monophasic group experiencing menstrual only energy loss with consequently lower frequencies in the premenstrual and premenstrual +

TABLE 6.18

FREQUENCIES OF ALL SYMPTOM PATTERN CATEGORIES

TRIPHASIC GROUP

PARAMETER	MP	SP	MM	SM	MP/MM	MP/SM	SP/MM	SP/SM	Atypical	Non cyclical	N
Mood	4	1	1	1	2	0	0	1	7	12	30
Irritable	1	1	2	0	1	1	2	13	4	4	30
Energy	6	0	1	0	2	4	0	3	3	10	30
Tense & Anxious	2	4	1	0	0	1	2	9	4	6	30
Breast tenderness	0	5	0	0	0	0	2	17	1	4	30
Body Swelling	0	1	1	1	1	0	1	23	1	0	30
Period Pain	1	0	2	15	0	1	1	7	0	2	30
Sexual Interest	2	2	1	6	0	2	2	5	3	1	24

MONOPHASIC GROUP

PARAMETER	MP	SP	MM	SM	MP/MM	MP/SM	SP/MM	SP/SM	Atypical	Non cyclical	N
Mood	0	1	4	1	3	1	2	1	4	18	35
Irritable	0	1	1	8	0	2	1	15	7	0	35
Energy	2	1	8	4	0	1	2	0	2	15	35
Tense & Anxious	2	2	2	5	1	1	1	10	7	4	35
Breast tenderness	0	1	1	2	0	2	0	12	4	13	35
Body Swelling	0	2	1	1	1	1	1	23	0	4	35
Period Pain	0	0	4	14	0	2	0	9	0	6	35
Sexual Interest	0	1	2	4	2	3	3	8	3	4	30

CONTROL GROUP

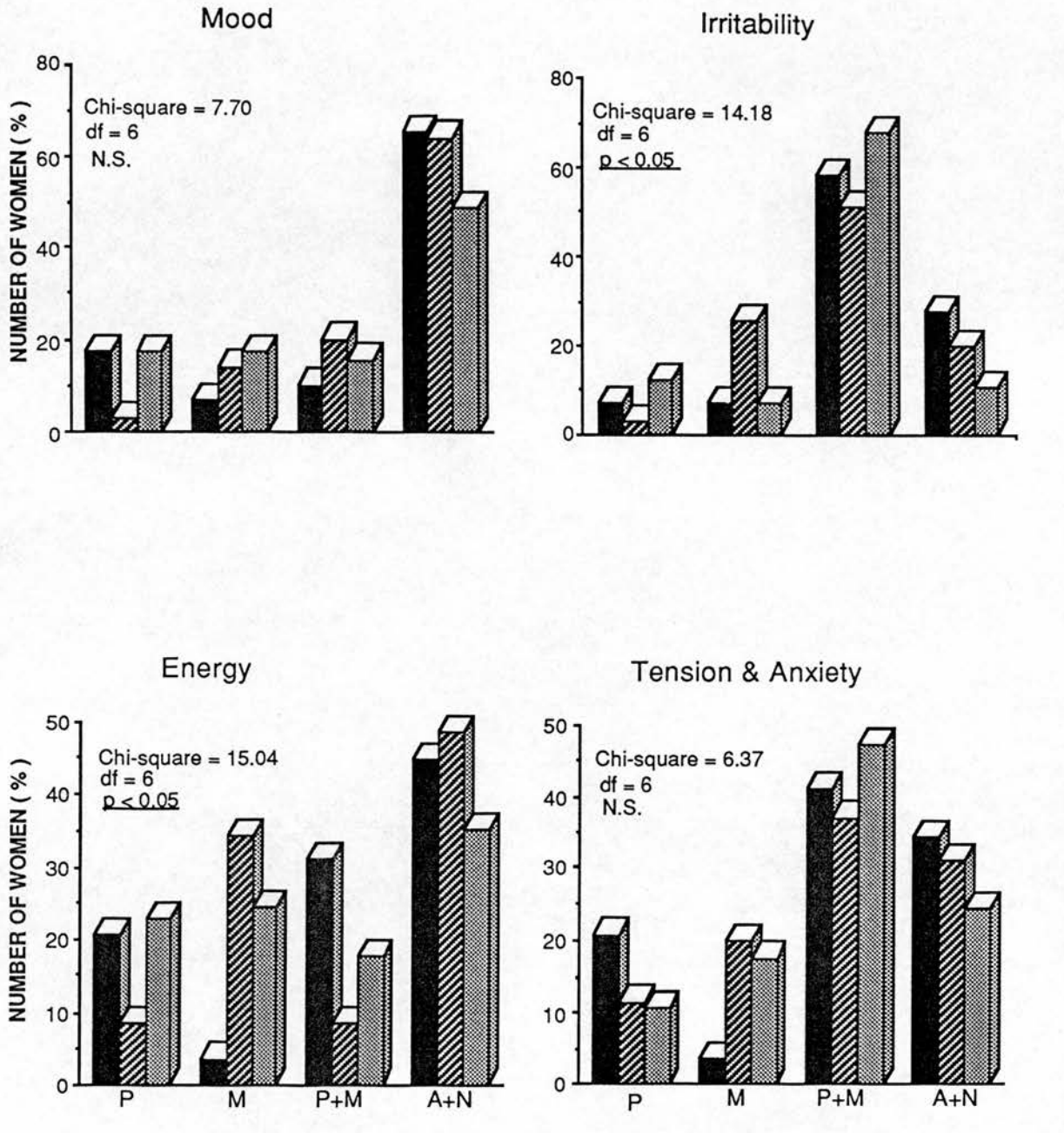
PARAMETER	MP	SP	MM	SM	MP/MM	MP/SM	SP/MM	SP/SM	Atypical	Non cyclical	N
Mood	8	2	6	4	3	4	1	1	7	21	57
Irritable	2	5	2	2	2	4	3	31	5	1	57
Energy	8	5	8	6	2	3	2	3	3	17	57
Tense & Anxious	3	3	4	6	0	2	3	22	6	8	57
Breast tenderness	4	9	0	5	0	0	6	27	1	5	57
Body Swelling	3	3	0	2	2	2	4	36	2	3	57
Period Pain	0	0	4	29	1	6	0	9	0	8	57
Sexual Interest	2	6	1	3	1	5	5	14	6	6	49

Key : MP - mild premenstrual ; SP - severe premenstrual
MM - mild menstrual ; SM - severe menstrual

TABLE 6.19
FREQUENCIES OF " COLLAPSED " SYMPTOM PATTERN CATEGORIES

PARAMETER	Group	Premenstrual only	Menstrual only	Premenstrual + menstrual	Atypical + noncyclical
MOOD	T	5 (17.2%)	2 (6.9%)	3 (10.3%)	19 (65.5%)
	M	1 (2.9%)	5 (14.3%)	7 (20.0%)	22 (62.8%)
	C	10 (17.5%)	10 (17.5%)	9 (15.8%)	28 (49.1%)
IRRITABLE	T	2 (6.9%)	2 (6.9%)	17 (58.6%)	8 (27.6%)
	M	1 (2.9%)	9 (25.7%)	18 (51.4%)	7 (20.0%)
	C	7 (12.3 %)	4 (7.0%)	40 (70.2%)	6 (10.5%)
ENERGY	T	6 (20.7%)	1 (3.4%)	9 (31.0%)	13 (44.8%)
	M	3 (8.6%)	12 (34.3%)	3 (8.6%)	18 (51.4%)
	C	13 (22.8%)	14 (24.6%)	10 (17.5%)	20 (35.1%)
TENSE & ANXIOUS	T	6 (20.7%)	1 (3.4%)	12 (41.4%)	10 (34.5%)
	M	4 (11.4%)	7 (20.0%)	13 (37.1%)	11 (31.4%)
	C	6 (10.5%)	10 (17.5%)	27 (47.4%)	14 (24.6%)
BREAST TENDERNESS	T	5 (17.2%)	0	19 (65.5%)	5 (17.2%)
	M	1 (2.8%)	3 (8.6%)	14 (40.0%)	17 (48.6%)
	C	13 (22.8%)	5 (8.8%)	33 (57.9%)	6 (10.5%)
BODY SWELLING	T	1 (3.4%)	2 (6.9%)	25 (86.1%)	1 (3.4%)
	M	2 (5.7%)	3 (8.6%)	26 (74.3%)	4 (11.4%)
	C	6 (10.5%)	2 (3.5%)	44 (77.2%)	5 (8.8%)
PERIOD PAIN	T	1 (3.4%)	17 (58.6%)	9 (31.0%)	2 (6.9%)
	M	0	18 (51.4%)	11 (31.4%)	6 (17.1%)
	C	0	33 (57.9%)	16 (28.1%)	8 (14.0%)
SEXUAL INTEREST	T	4 (16.7%)	7 (29.2%)	9 (37.5%)	4 (16.7%)
	M	1 (3.3%)	6 (20.0%)	16 (53.3%)	7 (23.3%)
	C	8 (16.3%)	4 (8.2%)	25 (51.0%)	12 (24.5%)

Key T - triphasic group; M - monophasic group; C - control group



Key :- P - Premenstrual only category ; M - Menstrual only category ;
P+M - Premenstrual + Menstrual category ; A+N - Atypical and noncyclical categ

■ Triphasic N = 30
▨ Monophasic N = 35
▩ Control N = 57

Figure 6.17 Distribution of the four pattern categories for mood , irritability , energy and tension & anxiety , within the three hormonal group

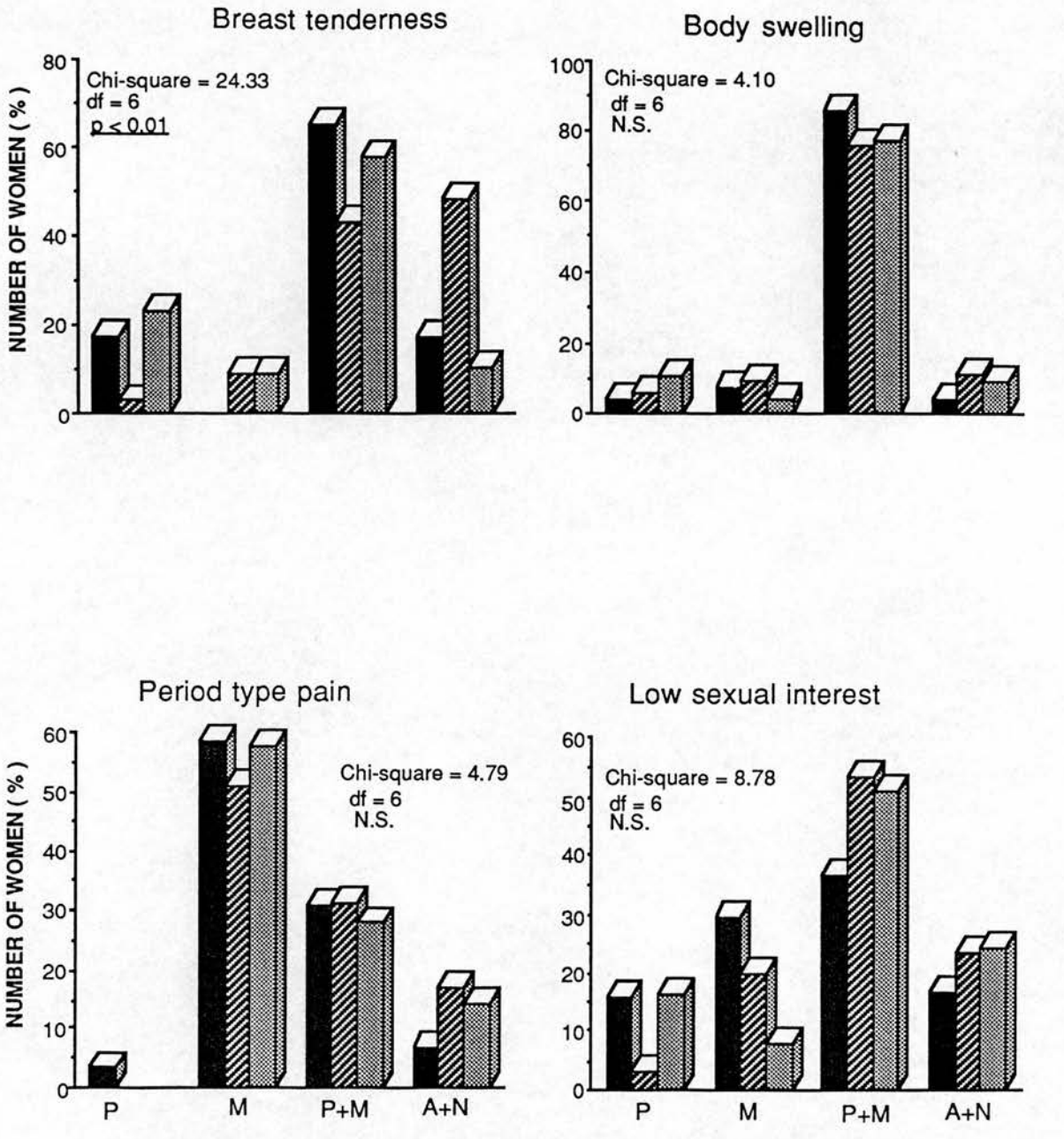


Figure 6.18 Distribution of pattern categories for breast tenderness , body swelling , period pain and low sexual interest within the three hormonal groups .

menstrual categories . This is in contrast to the triphasic group which shows a marked low frequency in the menstrual only category with concomitant increases in the premenstrual and premenstrual + menstrual categories . It should also be noted that the majority of women in each group are experiencing noncyclical or atypical changes in energy .

ii) Irritability - In this case the majority in each group fall into the premenstrual + menstrual category . A relative excess of monophasic group members fall into the menstrual only category .

iii) Breast Tenderness - In this case the majority of women in the triphasic and control groups fall into the premenstrual + menstrual category . However the majority of monophasic pill users are noncyclical , this frequency being greatly in excess of the noncyclical frequencies in the other two groups . There are concomitantly fewer monophasic women in the premenstrual only and premenstrual + menstrual categories . The triphasic and control groups being similar throughout .

The striking differences found between the groups by this analysis suggest that other differences found on measures of breast tenderness are due to the presence within the monophasic group of a large subgroup of women who are not experiencing cyclical breast tenderness i.e. they either have no breast symptoms or a chronic noncyclical level of breast pain .

6.4 DISCUSSION

In the introduction , three possible outcomes were suggested for this study , on the basis of a hormonal role in cyclical mood changes in women . They were :-

1) The two pill groups will produce similar data , but different from the control group suggesting a role for both ovulation as such and luteal hormones - or a non-hormonal side effect of oral contraceptive use .

2) The triphasic and control groups will produce similar data divergent from the monophasic group , suggesting a role for changing hormone levels , but not ovulation *per se* .

3)The three groups will all produce similar data suggesting a lack of importance of either ovulation or luteal hormones in the expression of cyclical mood change .

It would appear that the data presented here largely support the latter alternative .

Most of the symptoms showed a high level of cyclicity . Noncyclical subgroups were found in each of the experimental groups for those symptoms in which a less obvious cyclical pattern was expressed e.g. mood. Several factors emerged whichever method of analysis was employed , suggesting a lack of uniformity between symptoms . The three groups were found to be almost indistinguishable on measures of irritability , energy , tension & anxiety , body swelling and , surprisingly , period pain . However , measures of breast tenderness and mood were found to be more congruent in the triphasic and control groups compared to the monophasic group .

Analysis of the data by menstrual cycle phase suggested a tendency for monophasic users to experience some symptoms (namely irritability , tension & anxiety , energy , body swelling and low sexual interest) during menstruation rather than before . This effect can be attributed to menses itself rather than the pfw since it disappears when the data is analysed by pill cycle phase . The possibility arises that monophasic users experience menstruation in a different way either psychologically or physiologically from the other two groups . This effect is supported by the discovery of an excess of monophasic users falling into the menstrual only pattern category on measures of energy and irritability .

Measures of tension & anxiety and sexual interest tended to show some congruity between pill groups as opposed to the control group , although these effects were never present to a significant degree . This effect , especially in the case of sexual interest , could be explicable by non-specific effects of oc's on the length of menses or period pain . However the three groups were surprisingly indistinguishable on the basis of period pain . An alternative explanation is the psychological effect of oc's . Those women who use an oc are almost completely free from the fear of pregnancy , hence both they and their partners may feel more able to express their sexuality at all times of the menstrual cycle . Tension and anxiety about a possible pregnancy may also be removed from the premenstrual phase , suggesting that this symptom is more closely associated with reproductive function than PMS . The use of an oc may also result in very light menstrual bleeding , perhaps reducing the menstrual sex taboo for both partners . Arguably , the coincident reduction in premenstrual tension & anxiety may be due to the removal of the expectation of a period of sexual abstinence . The originally hypothesized explanation for this type of result i.e. that ovulation and luteal function are necessary for the expression of those symptoms which show

similarity between the pill groups but not the control group , is then not the only possible explanation for these results .

The parameters of breast tenderness and to a lesser extent mood , seem to fall into the second hypothetical category . That is - similarity is present between the triphasic and control groups and absent in the monophasic group . In both cases this appears to be due to a large subgroup of women who experience noncyclical mood and breast tenderness . In the former case , the subgroup is found in all experimental groups . However , in the case of breast tenderness , only the monophasic group showed the high incidence of noncyclicity . This divergence between the two pill groups makes alternative hypotheses on the basis of oc use unlikely . It would appear to be the case that breast tenderness is more dependent for its expression on luteal activity than are symptoms such as body swelling or irritability .

These results add further weight to the idea of subtypes of PMS with differing aetiologies , perhaps the assumption that cyclicity is the key to PMS and that the individual symptoms are unimportant is wrong . These data suggest that pill use is having an effect on the expression of cyclical symptoms at two levels . Firstly all types of oc would seem to have similar psychological effects on the perception of reproductive capacity with " knock on " effects on the expression of sexual interest and premenstrual anxiety , coupled with physiological effects on menstrual function which may also cause an alteration in the expression of sexual interest and anxiety . Secondly the monophasic type of oc would appear to have an endocrinological effect , flattening the expression of those symptoms which are sensitive to luteal hormones i.e. breast tenderness .

Another aspect of importance in these results is the appearance of subgroups within different pill taking samples . In the case of breast tenderness , not all of the monophasic users demonstrated the same response . Whilst the majority of them did not show any cyclical changes on this measure , some of them still did . The causes of this diversity of response are unknown . Possibly endocrinological studies of the subgroups of oc users would reveal different levels of endogeneous hormone activity .

Potentially the most important effect shown in this study is the lack of effect of long term oc use on symptoms of PMS such as irritability and body swelling . The possibility exists that sufficient residual ovarian activity is present in low-dose pill users to allow these symptoms to occur . This type of

hypothesis shifts the emphasis from progesterone and the luteal phase hormonal milieu to oestrogen and its fluctuating effects . At present there is insufficient knowledge of the residual ovarian activity in low dose oc users to allow a definite conclusion from the above data that ovarian activity is not a prerequisite for the occurrence of those symptoms which do not differ between experimental groups . However , this would appear to be a distinct possibility .

6.5 SUMMARY

Cyclical symptoms do occur in all three experimental groups . The expression of this cyclicity is however variable both between symptoms and on occasion between groups . The most striking between group difference occurs on measures of breast tenderness . In this case , the triphasic users and the control group are virtually indistinguishable throughout the analysis . However , the monophasic group , with their steady hormonal milieu , exhibit a large and highly significant subgroup of women who are noncyclical in this respect . Thus a role for cyclical ovarian hormones is implied in the expression of breast tenderness although not for ovulation itself .

All other variables show consistent similarity across groups , reducing the likeliehood of a dominant hormonal aetiology . There is a suggestion , however , that cyclical changes in sexual interest and tension & anxiety may be suppressed by the use of either type of oral contraceptive . This may indicate that ovulation is a prerequisite for these changes to occur , however other non-specific psychological and physiological effects of oc's may predominate .

CHAPTER SEVEN
GENERAL DISCUSSION , SUMMARY , CONCLUSIONS AND SUGGESTIONS FOR FURTHER RESEARCH

7.1 INTRODUCTION

The primary aim of this research was to investigate the often cited relationship between premenstrual symptoms and the ovarian cycle . It cannot be said , from a review of the literature , that either of these two areas of research are adequately delineated in their own right . Many unanswered questions remain , both about the nature , and very existence of premenstrual symptoms and about the controlling mechanisms behind the ovarian cycle . In such a state of affairs , an attempt to elucidate the link between them is arguably an attempt to run before we are able to walk. However , the controversy which reigns about the role of the ovarian cycle in the expression of female behaviour , and the widespread prescription of hormonal remedies for PMS , makes just such an investigation imperative from both theoretical and clinical viewpoints .

In Chapter Three , the major approaches to this area were discussed, and it was seen that the investigation of symptom patterns in normal and abnormal menstrual cycles had been neglected . If some factor inherent in the normal ovarian cycle is responsible for the occurrence of premenstrual symptoms , then arguably , disruption of the cycle may cause disruption of the symptom pattern . In this thesis , the potential factors under investigation were the endocrine event of ovulation and the concomitant changing levels of oestrogen and progesterone . In order to simplify and rationalise the investigations , six questions were formulated , dealing with specific effects of various hormonal patterns on premenstrual symptoms .

1) Can premenstrual symptoms occur in the natural absence of ovulation?

2) Can premenstrual symptoms occur in naturally ovulatory and anovulatory cycles in the same woman ?

3) Are premenstrual symptoms similar or different in totally ovulatory and totally anovulatory women of the same age group ?

4) Can premenstrual symptoms occur in artificially anovulatory cycles ?

5) If premenstrual symptoms can occur in artificial menstrual cycles , are they related to levels of exogenous steroids ?

6) Is symptom timing or severity related to the adequacy of corpus luteum activity?

These questions can be divided into two categories ; those which can be answered by an investigation of naturally occuring abnormal menstrual

cycles , and those which can be addressed by the artificial manipulation of the menstrual cycle . Hence , two complementary studies were instigated , whose design and results are described in Chapters Five and Six . In this chapter an attempt will be made to answer the posed questions from the results obtained , to relate these findings to previous research and to discuss the aetiological implications with regard to premenstrual symptoms.

7.2 PREMENSTRUAL SYMPTOMS AND NATURALLY OCCURING ABNORMAL MENSTRUAL CYCLES

In this study , the original intention was to compare symptomatically normal and abnormal menstrual cycles in the same woman . Despite the attempte made at recruitment in the appropriate age groups and categories , the number of abnormal cycles was disappointingly small . This may be due in part to inappropriate selection criteria . For instance , more abnormal cycles may have occurred in the perimenopausal group if subjects had been selected on the basis of peripheral FSH levels rather than age alone ; or if the recruitment poster had been directed more closely at women who had recently experienced a change in their menstrual pattern . In this way it might have been possible to identify truly perimenopausal , rather than middle-aged women . Similarly in the post-partum group , it appeared that those women who breast fed for a long time were more likely to ovulate and have fairly normal luteal phases even before the first post-partum menstruation . Hence , a higher frequency of abnormal cycles might have been seen if the study had concentrated on women who intended to bottle feed or to stop breast feeding fairly abruptly , at three months for instance. However , motivation for the study was fairly low in the post-partum group as a whole , and particularly among the bottle and short-term breast feeders . This may be in part because the latter group were more likely to have other small children at home or to be going back to full or part-time work , hence there were other demands on their time . Another major interfering factor in this group was the choice of contraceptive method . Although the women were encouraged to use barrier methods for the course of the study , it was felt to be neither ethical nor desirable to forbid the use of steroidal contraception if the women felt this to be their only option . Hence , several of the datasets are abbreviated or interrrupted by the use of oral contraceptives . In total

then , it would seem that the post-partum period may not be a particularly appropriate focus for this type of research , although the relative "unexpectedness" of the first post-partum menstruation may be useful from a theoretical point of view[1].

It should also be borne in mind that the women studied had not been diagnosed as PMS sufferers , by anyone other than themselves . The majority of them , as seen from the profiles in Chapter Five , cannot be said to show a typical debilitating premenstrual pattern , suggestive of the classic premenstrual syndrome . In this approach , the degree of symptomatology experienced is relatively unimportant . However, any conclusions from the study should be applied with caution to the aetiology or manifestation of PMS . Such an extension is endorsing the assumption that mild , or arguably normal , premenstrual symptoms are aetiologically similar to the PMS .

Three of the original six questions can however be approached from these data, and they will be considered in turn .

i) Can premenstrual symptoms occur in the natural absence of ovulation?

The small number of anovulatory cycles seen in this group makes data interpretation difficult . Premenstrual symptoms did appear to occur in the absence of ovulation in some cases , and no evidence emerged to suggest that anovulatory cycles are necessarily symptomatically different from ovulatory ones , except possibly in the case of breast tenderness . This finding agrees with several previous research studies which have suggested that ovulation itself makes no difference to the appearance of symptoms

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[1] A subjective impression was gained from talking to the women that the first post-partum menstruation was possibly not as unexpected as theory might suggest . The majority of them were reasonably well informed about pregnancy and lactation and / or had had previous children . Hence , they realised that they would start to menstruate after stopping breast feeding . Although the actual date of menstruation was unknown , they were aware at the appropriate time that they would bleed within the next week or so . This factor was of course enhanced by the presence of a researcher attempting to guess the time of return of ovarian activity . The unexpectedness of the first bleed might have been increased by studying all the women from delivery - although in some cases this would have meant 9 months to a year of data collection before the study proper began , and would only really be feasible in combination with another research project , e.g. a study of mood changes during lactation .

(Adamopoulos , Loraine , Lunn , Coppen & Daly 1972 ; Andersen, Larsen , Steenstrup , Svendstrup & Nielsen 1977; Backstrom et al 1983) . hence , the evidence would appear to be at odds with the assertion made by Magyar , Boyers , Marshall & Abraham (1979) , amongst others, that premenstrual symptoms are indicative of ovulation .

ii) Can premenstrual symptoms occur in naturally ovulatory and anovulatory cycles in the same woman : and if so - are they similar in type , intensity or duration?

As indicated above , the small number of anovulatory cycles seen makes this question difficult to answer . However , it would appear that for all symptoms except breast tenderness , the presence or absence of ovulation in a particular individual has little or no effect on the occurrence , intensity or duration of symptom experience . In the case of breast tenderness , levels would appear to be less pronounced in anovulatory cycles and to be associated with menstruation rather than the premenstrual phase . This finding , however is not universal , with some degree of variability being seen between consecutive ovulatory and consecutive anovulatory cycles .

iii) Is symptom timing or severity related to the adequacy of corpus luteum activity ?

Two assessments were made of luteal phase adequacy in this study - short luteal phase and inadequate luteal phase . The presence of either one of these appeared to have little effect on the occurrence , timing or duration of premenstrual symptoms , except in the case of breast tenderness . Measures on this symptom were found to be either lower , and of a lesser duration , than normal , or higher and more prolonged than usual in cycles characterized by an inadequate luteal phase . However , cross-correlational analyses of the relationship between symptoms and the absolute hormone levels measured showed no significant correlations for any of the subjects studied , suggesting that some other component of the ILP is involved .

Several features can be extracted from a consideration of this section of data and the answers to the three questions above . Firstly : there would appear to be considerable variability in terms of symptoms between consecutive cycles , whether normal or abnormal , in the same subject . Secondly : the symptoms observed cannot be assumed to follow parallel paterns of occurrence in the same individual . In this study , breast tenderness appeared to be at odds with all the other symptoms in both group

and individual analyses; however, since only eight variables were measured, the possibility must be considered that other symptoms may also be different . Thirdly : there does not appear to be any systematic relationship between symptom occurrence or otherwise and the physiological event of ovulation in any of the women studied . Although differences did occur between ovulatory and anovulatory cycles , they were no larger than differences between consecutive normal cycles . This statement would not appear to hol.d true for the measure of breast tenderness , which did show a consistent diminution in anovulatory cycles . Fourthly : the presence of a short luteal phase made no demonstrable difference to symptom experience on any of the variables assessed either in terms of timing of onset , intensity or duration of symptoms . Hence , luteal phase length , and therefore the timing of ovulation , would not appear to be related to symptom duration . Fifthly : The presence of an inadequate luteal phase did appear to have a bearing on the experience of breast symptoms , although not on any of the others . Breast tenderness was either reduced and confined to menstruation , or markedly increased in ILP cycles . Sixthly : correlational analyses of all the individual subjects showed no relationship between absolute hormone levels or ratios and symptom occurrence .

The potential reasons behind these observations range from the methodological to the endocrinological . The possibility exists that the results seen are misleading because none of the women showed classical PMS type symptomatology . Hence , it could be argued that breast tenderness is the only variable measured which can be considered to be part of the syndrome . Therefore , the observation of lower levels of breast tenderness in ILP and anovulatory cycles would have been parallelled by changes in any other variable if these women had shown clear cyclical patterns on that variable . Similarly , the results found may be an artefact of the type of statistical analysis employed . The use of cycle division and ANOVA in such a situation is fraught with the dual problems of serial dependency and small , differential group sizes (see Chapter Four) . It would have been possible to remove the serial dependency in the data , either partially , by detrending the series , or completely by developing an ARIMA model from each dataset , performing the analysis on the " whitened " values . However , it is difficult to conceptualise the relationship such values would have with time , or how they could be divided into phases suitable for ANOVA . As indicated in

Chapter Four , the probability is that ANOVA is not a suitable statistical approach to this type of data , however , little alternative exists . Attempts have been made throughout to draw conclusions on the basis of graphical evidence , using inferential statistics only as a judgemental aid , in order to reduce the influence of Type I errors , however they cannot be said to have been entirely ruled out .

Another methodological explanation for these results arises from the fact that anovulatory and deficient luteal phase cycles are abnormal , and as such women who experience them , or are likely to experience them , could be described as untypical . The possibility arises that the very abnormality , or transitional state , causing the deficient menstrual cycle may also be associated with the disruption of mood and symptom patterns generally . Hence , the demonstration of similarities or differences between apparently normal and abnormal hormonal cycles in women during transitional phases of their reproductive lives may have more to do with the state of the women than the aetiology of premenstrual symptoms.

In summary , then , it would seem that this approach to PMS research is not particularly cost effective in terms of producing a reasonable quantity of abnormal menstrual cycles in an otherwise emotionally stable situation. The applicability of findings from this study to women in situations other than the perimenopause or the post partum period must be in doubt . Despite these reservations, the effects seen would appear to be fairly clear . The variables of mood , irritability , energy , tension, body swelling , period pain and sexual interest are apparently unaffected by either ovulation or the absolute levels of luteal phase steroids . Breast tenderness can be reduced in inadequate (or absent) luteal phase cycles , although this effect is not due to a direct or lagged relationship with ovarian steroids . Hence , some other explanation is required for the appearance of premenstrual symptoms , vested either in follicular phase endocrinology or some other unmeasured variable . In the case of breast tenderness , there would appear to be a relationship with some substance , other than the ovarian steroids , which is associated with luteal phase adequacy . This factor may be present in the follicular phase, or it may be some luteal factor not measured in this study .

7.3 PREMENSTRUAL SYMPTOMS AND ARTIFICIALLY ABNORMAL MENSTRUAL CYCLES

In this study , a cross sectional approach was employed to compare women using two different types of oral contraceptive, with a control group , matched for age , parity and occupation , on their daily ratings of eight variables .

Recruitment was accomplished by selecting potential subjects from a pool of respondents to a national magazine survey . Hence , one major criticism which could be levelled at the study is the potentially biassed nature of the original sample . There may be some characteristic of a woman who is motivated to complete and return a magazine questionnaire which makes her untypical of the average " woman on the Clapham Omnibus " . The postal nature of both the original survey and this study , made any assessment of personality characteristics an impossibility . The fairly low response rate to the first approach also indicates that some caution should be applied before the results are generalized to cover most women .

The artificial manipulator assessed in this study was the oral contraceptive pill (oc) . As pointed out by Cullberg (1972) and discussed in Chapter Six , the psychological effects of oc's due to the prevention of pregnancy may to some extent confound the pharmacological effects . From an endocrinological point of view too , although the global action of oc's is understood (see Chapter Two) , their precise effects , especially in the case of the newer low-dose brands , on the ovarian cycle are not well characterised . It would appear that some follicular development can occur in some women - especially during the early pill-taking cycles . Attempts were made in the study to control for these factors by studying only women who had already been using the particular oc for some time (≥6 months) , and were therefore likely to be adjusted to it . This rationale can be criticized for the exclusion of all those women who cannot tolerate oc's . Since , arguably, these women are more sensitive to hormones , potentially we are excluding the very women we should be studying . Further to this , by age-matching the control group to the pill-users , we may well be including those women who are more sensitive to exogeneous steroids , and potentially more likely to be symptomatic . Hence , the theoretical possibility exists that the sampling procedure used artificially distorted the rates of symptomatology seen . In

practice , despite the low response rate , the number of women in the study was probably sufficient to outweigh this effect . Although most of the women in the control group had used an oral contraceptive in the past , they were more likely to have given it up as a result of media fears about long-term side effects than because they were unable to tolerate it.

No hormonal measures were assessed at any point during the study . The initial assumptions were made that all women in the control group were experiencing regular , normal , ovulatory cycles and all the women in the pill taking groups were exclusively influenced by the exogeneous steroid . Since the women were all in the 18 - 35 age group , this assumption is probably reasonable in the case of the control group - although Metcalf & Mackenzie (1980) have shown a higher than expected incidence of anovulatory cycles in the early twenties age group , especially amongst students . The assumption may not be so true in the pill taking groups however . Studies of endogeneous hormone activity during long term low dose oc use are still rare . Those studies which do exist suggest that some degree of subjective variability is present after three months of pill use (Kuhl , Gahn , Romberg , Marz & Taubert 1985) . The proportion of cycles in which follicular development occurred being higher in the triphasic group ,36 % compared to 18 % in the monophasic group . The question of whether this is a transient effect - that some women take longer to adjust to the pill regime , but by , for instance , six months , follicular activity is absent in both groups remains unanswered . However, studies of " missed pill conceptions " , e.g. Guillebaud 1986 , suggest that considerable follicular activity can occur in the pill free week (pfw) , and that this may lead to ovulation if pills are missed , or not absorbed at either end of the pfw . So the assumption in this case is probably wrong - the pill taking women , or at least a proportion of them are not exclusively influenced by the exogeneous steroids , there may be some endogeneous ovarian activity , especially during the pfw .

The statistical methods used to analyse this data are subject to the same criticisms as those in Chapter Five - namely , the question of serial dependency and the loss of information in the use of ANOVA . Although the larger subject numbers in this study tend to reduce the error effects , concern over the statistical methodology remains a pertinent consideration .

Two of the original six questions can be addressed by this study :-

i) Can premenstrual symptoms occur in artificially anovulatory cycles ? - and if so , are they similar in type , severity , timing of onset or duration to matched ovulatory cycles ?

The answer to this would appear to be yes , on all counts . All the variables studied showed a premenstrual increase in the pill taking cycles , and for all of them except breast tenderness , the intensity , timing of onset and duration was virtually indistinguishable from the control cycles . A tendency was noted for symptoms to occur menstrually rather than premenstrually in the monophasic group, particularly on measures of energy and irritability . Having said this , however , subgroups of women were found in all three categories who experienced noncyclical or atypical changes . These groups were especially pronounced for measures of mood and breast tenderness . Large noncyclical subgroups were found for mood in all three experimental groups . However , in the case of breast tenderness only the monophasic group showed a high incidence of noncyclicity . This factor explained the observation of lower overall levels of breast tenderness seen in the monophasic group (see Chapter Six) . Hence , there would appear to be some divergence between symptoms and between individuals in response to artificially anovulatory cycles ; although it can be said that all the measured variables can occur in pill cycles and be expressed in the same way as in control cycles , some symptoms , and specifically breast tenderness , may be more likely to be reduced or absent in women using monophasic pills .

ii) If premenstrual symptoms can occur in artificial menstrual cycles ; are they related to the levels of exogenous steroid ?

The answer to this question would appear to be no , on the basis of the evidence seen here . Five phase analysis of all three groups showed no differences in terms of timing or severity of any of the symptoms except breast tenderness . Hence , it would not appear to be the case that symptoms occur in association with , or in response to , exogenous or endogenous steroid levels . As before , breast tenderness is slightly different in this regard . In this case , the monophasic group - with constant exogenous hormone levels experienced lower overall levels of breast tenderness as described above .

The major findings of this study echo to a certain extent those of the study of symptoms in naturally occuring abnormal cycles . Primarily - neither

ovulation itself nor the " normal " luteal phase hormone pattern seem to be prerequisites for symptom occurence on most of the variables measured . Secondly - some divergence was seen in this study between symptoms , with breast tenderness being apparently more sensitive to differing steroid patterns than other symptoms . Measures of sexual interest and tension & anxiety tended to be more congruous in the pill groups as opposed to the control group . As discussed in Chapter Six , this effect may be due in part to the removal of the fear of pregnancy - reducing tension and allowing a freer expression of sexuality . Lighter menstrual flow may also be implicated in this observation . Thirdly - variability could also be discerned between individuals , indicated by the presence of subgroups of women on all the variables who show different symptom patterns .

Few research studies have been undertaken in this field, hence comparisons are difficult to draw . Those which have been conducted on long term oc users in a cross sectional manner , have tended to concentrate on depression and negative affect , rather than the full range of premenstrual symptoms . Forrest (1979) studied twelve women over one pill cycle , from the point of view of oc related depression . He found essentially the same mood pattern as described in this study, in users of low dose pills (he does not indicate which brands were used) . The gradually increasing levels of depression seen as the cycle progressed are related by Forrest to a cumulative effect of exogenous steroid . However , since the same pattern was seen in the present study control group , this hypothesis would appear to lose validity .

A classic study was conducted by Paige (1973) , in an attempt to differentiate the effects of different oc formulations on affective fluctuations . In her study , the affective measures assessed were anxiety , hostility and total negative affect derived from a content analysis of speech samples obtained at four stages of the cycle . Hence , this study is not truly comparable to the present research in which daily subjective ratings were used . It should also be borne in mind that the subjects in this study were using pills which would now be described as " high dose " in terms of oestrogen content , and that the sequential pills followed a 15:5 day ratio rather than the 6:5:10 day ratio more common today . Her results indicated that fluctuations in negative affect do not occur in users of combination oral contraceptives , The sequential group , although their numbers were small ,

did show mild changes in total negative affect which mimicked those in normal cycles . She cites this as evidence in support of the Grant & Pryse-Davis (1968) hypothesis that the magnitude of premenstrual anger , depression and irritability is directly related to endometrial MAO activity , this biochemical activity being suppressed in oc users . These results were not replicated in the present study - although the reasons are difficult to pinpoint. Arguably , the methods used by Paige to detect affective fluctuations are more sensitive than subjective daily ratings - however , the infrequency of collection clouds the issue . Since the speech samples were only collected at four time points during the cycle , the possibility of slightly different symptom timing or duration between the groups is neglected . The dosages of pill used - most of them containing twice as much oestrogen per tablet as modern pills , may also have had an effect , reducing the likeliehood of endogenous follicular development . Hence , the effects seen in the present study may be a reflection of some follicular or " luteal " phase factor which was suppressed in previous research .

7.4 THE RELATIONSHIP BETWEEN PREMENSTRUAL SYMPTOMS AND THE OVARIAN CYCLE

The two research studies described in this thesis are complementary both to each other and to previous studies which have investigated the occurence of premenstrual symptoms in normal menstrual cycles (e.g. Backstrom *et al* 1983) . The message from all these varied approaches would seem to be that the relationship between premenstrual symptoms in general and the ovarian cycle is temporal rather than absolute in nature . That is - neither the physiological event of ovulation nor specific levels of luteal phase hormones appear to be related to symptom timing or severity . Secondary to this observation are the findings of wide individual differences and symptomatic differences both in terms of the patterns seen and in response to the hormonal environment . The observation that breast tenderness tended to be responsive to situations of relative hormonal abnormality in both of the studies described is the clearest example of this . In the first study, the lack of relationship between breast tenderness and absolute hormone levels was clearly shown , despite the apparent effect of the presence of an inadequate luteal phase . In the second study , the picture is rather less

clear, largely because of the current state of ignorance about the level of endogeneous ovarian activity experienced during low dose oral contraceptive administration . Although this discussion has been geared towards likening the triphasic regime to the normal cycle , hormonally , identifying the monophasic pill as being different - this may be an over simplification . The triphasic regime , with its " pill free week " and abrupt hormonal changes bears only a crude resemblance to the events of a normal cycle. The point of similarity between the two , and divergence from the monophasic group , is the presence of relatively elevated levels of progestagen in the " luteal " phase in the former pair , with constant levels being maintained in the latter case . Hence , the evidence from this study would appear to suggest that some women respond to the absence of a change in progesterone levels , or some associated factor , by a reduction , or by a loss of cyclicity , in breast symptoms .

It is perhaps useful to consider the results of this research in terms of the "systems model " of PMS described by Backstrom & Bancroft (1985) and reproduced in figure 1.4 . The hypotheses outlined in this model are well supported by the results of these studies . The majority of symptoms in this research appeared to be related to the ovarian cycle temporally , presumably by the "zeitgeber " influence of the regular menstrual cycle on the central regulatory system . Hence , the absence of an absolute influence of cyclical steroids on mood variables etc. is supported . In this study " body swelling " - the only measure of bloating available , appeared to fit with measures of mood change rather than breast tenderness . Arguably , this may be an artefact of subjective assessment - producing a changing measure of body image rather than bloatedness or water retention *per se* . An objective assessment of this variable might find some concordance with breast tenderness .

It would appear that breast tenderness is related more closely to changes in ovarian steroid levels than the other variables measured . However , it would be fair to say that the visualization of such a relationship as a direct one is over simplistic . The evidence from the first study suggested that some other factor associated with luteal phase activity might be involved . The second study suggested that in some individuals breast symptoms may be under the same control as mood symptoms , whilst in others , the key aetiological factor may be associated with changing levels of luteal phase

progesterone . In order to reconcile these two observations , it may be useful to suggest that two seperate " syndromes " are being seen here . In one of these , described as " PMS " for convenience , all of the symptoms , including mood and breast tenderness are caused by , or related to , some central regulatory system , with the ovarian cycle being involved only at the level of symptom timing . In the second " syndrome " , breast changes are directly related to some aspect of the ovarian cycle , either changes in cyclical steroids themselves or some other factor which is associated with luteal function , the disruption of this factor leading to the reduction or exacerbation of symptoms . This latter description sounds remarkably like a phenomenon known as " cyclical mastalgia " , a syndrome whose aetiology remains obscure but which is thought to be associated with altered breast sensitivity to prolactin in response to ovarian steroids (Mansel, Preece & Hughes 1980 ; Kumar , Mansel , Hughes , Woodhead , Edwards , Scanlon & Newcombe 1984) .

So , in terms of the systems model , perhaps the term " peripheral effects " should be removed and be replaced by " cyclical mastalgia " , whilst the term "mood change " should be extended to cover all PMS symptoms . Hence , the possibility arises that one of the characteristics of PMS , the variability in symptom type seen between different women , may be due in part at least to the inclusion under one umbrella of several different cyclical syndromes with different aetiologies. The possibility that two or more of these syndromes may co-exist in the same woman further complicates the issue . This model would explain the large individual differences seen and the differential response of symptoms to various treatments .

7.5 SUMMARY , CONCLUSIONS AND SUGGESTIONS FOR FURTHER RESEARCH

The major findings derived from this thesis are as follows :-

i) There was no evidence , either from naturally occuring or artificially manipulated abnormal menstrual cycles , to suggest that the appearance of any of the premenstrual symptoms measured was related to the physiological event of ovulation .

ii) There was evidence from both of the studies to suggest that premenstrual breast tenderness is related in some way to luteal phase changes in some women .

iii)There was no evidence to suggest that any of the other symptoms assessed were related , directly or indirectly , to absolute ovarian steroid levels .

iv) Some considerable evidence arose to support the idea of symptom variability both between individuals and between consecutive cycles in the same individual .

v) The use of naturally occurring abnormal menstrual cycles in this type of study would seem to be contraindicated in terms of its cost effectiveness and applicability to women experiencing consistently normal cycles .

The main conclusion derived from these findings is that the term PMS as it is currently used may possibly include several different "syndromes" under its umbrella , some of which are directly related to ovarian steroid levels , or concomitants of ovarian function , and some of which are linked to the menstrual cycle in a purely temporal fashion .The case in point here is the possibility that a subgroup of women who report PMS actually have a condition known as " cyclical mastalgia " , either alone , with potentially associated mood changes , or in combination with PMS .

Several suggestions for further research can be made , arising both from this hypothesis and from the assumptions and inadequacies of this project .

i) One of the major stumbling blocks in the interpretation of this data has been the lack of any robust and suitable statistical technique for the analysis of long term serial data in a physiologically meaningful context . The observation of individual variability also argues for a small N approach to the PMS field in the future , rather than an attempt to derive information from the superficial analysis of large groups of data, which have been inappropriately aggregated . If this type of approach is to be useful , then some time should be spent on developing an appropriate statistical approach - both in terms of the clinical diagnosis of PMS and in terms of the broader investigation of cyclical mood change .

ii) The first approach used in this thesis , i.e. the investigation of symptoms in naturally abnormal cycles , would appear with hindsight not to be particularly appropriate for this type of study . Abnormal cycles tend to be a reflection of physiological transition or abnormality , and hence do not

occur independently ; other physiological and psychological systems may also be disrupted . Therefore , it was probably naive to expect that results obtained from this study would be applicable to all women . If the aim of further research is to investigate the relationship between symptoms and the ovarian cycle , then a means of inducing consistent anovulatory cycles, e.g. the oral contraceptive pill , in women who are not in any kind of transitional state might be more profitable.

iii) The lack of knowledge about endogenous ovarian activity during low-dose oc administration , particularly on a long term basis , makes the interpretation of effects due to hormonal changes difficult . Basic research is needed to assess precisely what is happening endocrinologically in these women - research which would also be useful in determining the dose responsiveness , or otherwise , of long term side effects in years to come .

iv) The studies outlined above largely substantiate the Bancroft & Backstrom (1985) model . Hence , further studies are indicated to test other aspects of the model , for instance , the role of steroid feedback on the timing of cyclical symptoms, and the precise role of ovarian steroids in breast symptoms . The first of these could be investigated in women who use oral contraceptive pills continuously, i.e. without a pill free week. In this study , either cyclical steroids could be removed altogether in users of monophasic pills , or the cycle could be shortened to 21 days in users of triphasic pills . If cyclical steroids are responsible for the timing of premenstrual symptoms , then the monophasic group would be expected to show random symptom occurrence , whilst the triphasic group would have three weekly cycles .

In conclusion : most premenstrual symptoms would appear to be related to the ovarian cycle temporally , although breast tenderness shows some relationship to ovarian steroids themselves . Hence , the proposed model of PMS is supported . Further studies are needed to investigate the precise nature of the temporal relationship and the aetiology of breast symptoms .

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APPENDIX ONE
THE NATURE OF DEFINITION

THE NATURE OF DEFINITION

Firstly - a definition is a purely linguistic phenomenon . It is not possible to define concepts such as " Premenstrual Syndrome " or " work of art " , only linguistic objects (e.g. words , phrases , stetements etc.) can be defined . Hence , it is necessary to rephrase the question into - " how should we define the phrase premenstrual syndrome ? " or " how should we define the term work of art ? " .

Secondly - definitions are conventions . That is - the meaning of a word or phrase is not a natural attribute of that word which man discovers , rather , meaning is given to a word by people who agree to let it have that meaning (Salmon 1973 p. 122) . Usually conventions have grown up gradually and informally over a length of time , however , they are not necessarily static - as the language grows and changes , so the convention about the meaning of a particular word may also grow and change . Conventions can also occur formally when a new word is assigned a definition or an existing word is given a more precise definition to establish it within a particular context . Although defionitions are conventions , it does not follow to say that one definition is as good as any other . The purpose of the definition is important and some conventions achieve their purpose better than others .

These two general points are important in establishing the limitations of a definitional system . It is now possible to discuss the four different types of definition .

i) The " Real " definition

The Real definition of a word is its objective meaning and can be demonstrated with reference to the world around it . For instance , the meaning of the word " dog " can be given by pointing at a variety of dogs or by naming various dogs . This type of definition is limited by the fact that words vcan only have the meanings that their users give them . A real definition is only possible when there is no ambiguity in the object , or lack of unanimity in the users convention . For instance , it would be possible to give a real definition of the term " work of art " by saying that Van Gogh's " Sunflowers " and Constable's " Haywain " are both works of art . This definition is not very useful however when the question " Is Jackson Pollock's " No. 32 " a work of art ? " arises . This limitation applies also to the application of a real definition to PMS . To say that x and y have PMS is not very useful when we want to know whether z has it .

ii) The " Pure Stipulative " definition

In this case , a user endows a word or phrase with a particular meaning by declaring the conditions under which s/he intends to use it irrespective of how anyone else uses it . The concept is rather like that of a floating joker in a card game , during which the " owner " of the joker can play it as any card s/he chooses regardless of its actual face value or how other players may wish to define it . This is the type of definition which is usually used in PMS research . That is - each research group stipulates its own meaning of PMS for the purpose of that particular study , to a large extent irrespective of its use in other studies . Although this type of definition is a beginning - and at least better than no definition at all - the initial assignments can set restrictions on the further use of the word and become meaningless if each user stipulates a slightly different definition . The pure stipulative definition does not allow for growth or change in the concepts behind the definition . For instance , the original definition of Premenstrual Tension (Frank 1931) was purely stipulative and its limitations soon became apparent when symptoms other than tension were identified , leading to the coining of the term Premenstrual Syndrome .

iii) The " Pure Reportive " definition

This type of definition is more or less a reportive account of how existing users of the word already use it . However , although this seems the logical basis for definition , it falls down when there is any lack of unanimity between users , and it necessitates defining a word in terms of other words . In this type of definition , circular arguments can very quickly develop . For example :-

a) " Parent " has the same meaning as " Father or Mother "

b) " Father " has the same meaning as " Male Parent "

c) " Mother " has the same meaning as " Parent , but not Father "

To determine the meaning of the word " Father " we would replace " parent " in (b) by its definition in (a) which gives : " Father " has the same meaning as " Male (father or mother) " . Thus buy using a pure reportive definition a circular argument can develop in which words are defined in terms of themselves . This occurs when the pure reportive definition of PMS as "symptoms which regularly occur in the premenstrual phase of the menstrual cycle " is used .

iv) The " Reformatory " definition

This is a hybrid between the purely stipulative and purely reportive definitions . It occurs when someone stipulates that they will use a word with a partial alteration to the ordinary usage . For instance , words such as " work " and " energy " are given precise definitions in physics derived from their ordinary usage . This type of definition occurs in PMS studies when a researcher stipulates symptoms occurring in " the week before menses " rather than the " premenstrual phase " . If a reportive definition is possible , then a reformatory derivation from it is also feasible , and logical in certain circumstances . However, the limitations applying to reportive definitions also apply here .

APPENDIX TWO
THE PREGNANEDIOL GLUCURONIDE ELISA ASSAY

THE PREGNANEDIOL-3 - GLUCURONIDE ELISA

The concept behind ELISA is essentially similar to that behind RIA (see Section 4.3.1) , however the former system is rather more flexible . In the ELISA system , an enzyme label is used which can be attached to either the antibody or antigen . The enzyme acts by converting a substrate to a coloured product , the intensity of which can be measured . Hence , the assay proceeds in a similar fashion up to the point of seperation of bound and free , a procedure performed by a second antibody technique , at this stage the substrate is added . The amount of substrate which becomes coloured depends directly upon the amount of enzyme present . This , however , is not the only difference between RIA and ELISA . the second major difference is the immobilisation of either the antidody or antigen onto a solid phase , where it can act as an immunosorbent - " capturing " the corresponding antibody or antigen , and allowing rapid seperation of bound from free reagents by simple washing procedures .

The procedure used in this study utilized an immobilised second antibody technique , in which the second antibody (in this case DARS) is immobilized on the surface of plastic mictrotitre plate wells in order to " capture " the first antibody. The first antibody , enzyme-labelled antigen and samples are then added .

PROCEDURE

The microtitre plates used were Costar Serocluster EIA plates supplied by Northumbrian Biologicals . These plates were coated with a 1:200 dilution of second antibody (DARS) in coating buffer (0.1M Carbonate buffer , pH 9.6) , added at the rate of 200 µl per well . The plates were then sealed to prevent evaporation and stored at 4 degrees centigrade overnight , to allow adsorption of second antibody to the well surfaces . After adsorption , the DARS solution was " flicked " out of the wells , and the plates washed three times in 0.1 % Tween 20 detergent . This allowed all the remaining plate binding sites to be filled . The plates were then rinsed repeatedly in distilled water , to remove any excess Tween 20 , and blotted dry .

The reagents - samples , standards , first antibody and label were all made up in assay buffer (0.1 M Phosphate gelatin saline , pH 7.4 , with a few drops of non-reactive dye , e.g. carmosine , to aid visibility on the plates). The label was Pregnanediol-3-glucuronide-Horseradish

peroxidase, prepared by Mr. I Swanston , and added at a dilution of 1 : 10,000 . All other reagents were as per RIA . The plates were then sealed as before and incubated for a minimum of 3 hours at room temperature , or overnight at 4 degrees centigrade .

In order to seperate bound from free , the assay incubate was " flicked " out of the wells , the plates washed x5 with distilled water and blotted dry . The substrate solution was then added . This solution is light sensitive and therefore was added immediately after preparation . The substrate udes was 5mM o-phenylenediamine / 0.03% Hydrogen peroxide made up in 0.1 M Citrate phosphate buffer (pH 5.0) . The speed of the enzyme reaction is temperature dependent , therefore all reagents (including the substrate buffer) were at room temperature before use . The solution was added at a rate of 200µl per well , and the plates were immediately rendered in darkness by covering with aluminium foil . They were allowed to incubate @ RT for 15 - 30 minutes . After incubation 50µl of 2N Sulphuric acid was added per well to stop the reaction and develop the final colour . The plates were then read on an optical density platereader at OD 492 nm . Standard curves are plotted , and sample values calculated as in the RIA system .

Thanks are due to Mr. I Swanston , for his help in the preparation of this appendix , the purification of the DARS used and the preparation of the PdG-Horseradish peroxidase .

APPENDIX THREE
INTERVIEWS AND QUESTIONNAIRES USED IN THE STUDY

MENSTRUAL HEALTH QUESTIONNAIRE

PART TWO

A) PERSONAL HISTORY

1) NAME _____

2) ADDRESS _____

_____

TELEPHONE _____

3) DATE-OF-BIRTH _____

4) OCCUPATION (or previous occupation) _____

4a) HUSBAND/PARTNER'S OCCUPATION _____

B) GYNAECOLOGICAL HISTORY

5) HOW OLD WERE YOU WHEN YOUR PERIODS STARTED? _____

6) WHAT WERE YOUR PERIODS LIKE DURING THE NEXT FIVE YEARS?

i (a) REGULAR ☐
(b) IRREGULAR ☐
(c) VERY IRREGULAR ☐

ii (a) PAINLESS ☐
(b) SLIGHTLY PAINFUL ☐
(c) MODERATELY PAINFUL ☐
(d) VERY PAINFUL ☐

7) HOW MANY DAYS DID YOUR PERIOD LAST DURING THOSE YEARS? _____

8) HOW LONG WAS YOUR CYCLE (from one period to the next) IN THOSE YEARS? _____

WHAT ARE YOUR PERIODS LIKE NOW?

i (a) REGULAR ☐
(b) IRREGULAR ☐
(c) VERY IRREGULAR ☐

ii (a) PAINLESS ☐
(b) SLIGHTLY PAINFUL ☐
(c) MODERATELY PAINFUL ☐
(d) VERY PAINFUL ☐

10) HOW MANY DAYS DOES YOUR PERIOD LAST NOW? _____

11) HOW LONG IS YOUR CYCLE (from one period to the next) NOW? _____

12) HOW MANY PREGNANCIES HAVE YOU HAD? _____

13) HOW MANY CHILDREN HAVE YOU HAD? _____

14) HOW OLD ARE THEY? _____

15) DID YOU HAVE ANY PROBLEMS DURING PREGNANCY OR CHILDBIRTH?

(a) NOT APPLICABLE ☐

	PREGNANCIES					
	1st	2nd	3rd	4th	5th	6th
(b) None	☐	☐	☐	☐	☐	☐
(c) High Blood Pressure	☐	☐	☐	☐	☐	☐
(d) Depression	☐	☐	☐	☐	☐	☐
(e) Morning Sickness	☐	☐	☐	☐	☐	☐
(f) Threatened Miscarriage	☐	☐	☐	☐	☐	☐
(g) Normal Childbirth	☐	☐	☐	☐	☐	☐
(h) Breach delivery	☐	☐	☐	☐	☐	☐
(i) Forceps delivery	☐	☐	☐	☐	☐	☐
(j) Caesarian delivery	☐	☐	☐	☐	☐	☐
(k) Induced birth	☐	☐	☐	☐	☐	☐
(l) Epidural Anaesthesia	☐	☐	☐	☐	☐	☐
(m) Episiotomy	☐	☐	☐	☐	☐	☐
(n) Other (please specify)	☐	☐	☐	☐	☐	☐

16) DID YOU BREASTFEED? _____

17) IF YES; HOW LONG FOR _____

18) DID YOU GET DEPRESSED DURING THE FIRST SIX MONTHS AFTER CHILDBIRTH?

(a) NOT APPLICABLE ☐

	PREGNANCIES					
	1st	2nd	3rd	4th	5th	6th
(b) NOT DEPRESSED	☐	☐	☐	☐	☐	☐
(c) DEPRESSED FOR SHORT TIME DURING 1st WEEK	☐	☐	☐	☐	☐	☐
(d) DEPRESSED FOR MORE THAN A WEEK BUT NOT SEVERE	☐	☐	☐	☐	☐	☐
(e) SEVERELY DEPRESSED BUT DID NOT SEEK MEDICAL HELP	☐	☐	☐	☐	☐	☐
(f) SEVERELY DEPRESSED AND SAW DOCTOR ABOUT IT	☐	☐	☐	☐	☐	☐

19) HAVE YOU EVER BEEN TOLD BY A DOCTOR THAT YOU HAVE ANY OF THE FOLLOWING?

(a) NOT APPLICABLE ☐

(b) MENORRHAGIA (heavy periods) ☐

(c) AMENORRHEA (no periods for more than 6 months) ☐

(d) FIBROIDS ☐

(e) DYSFUNCTIONAL UTERINE BLEEDING ☐

(f) ENDOMETRIOSIS ☐

(g) OLIGOMENORRHEA (few or scanty periods) ☐

(h) DYSMENORRHEA (painful periods) ☐

(i) POLYMENORRHEA (too many periods) ☐

(j) PID (pelvic inflammatory disease) ☐

(k) THRUSH, TRICHOMANIASIS etc. ☐

(l) VENEREAL DISEASE ☐

(m) OTHER (please specify) ☐

C) CONTRACEPTIVE HISTORY

20) HAVE YOU EVER USED AN ORAL CONTRACEPTIVE? _____

(If NO please go to question 30)

(a) CURRENTLY USING ☐

(b) LESS THAN 6 MONTHS AGO ☐

(c) 6 MONTHS - 2 YEARS AGO ☐

(d) 2 - 5 YEARS AGO ☐

(e) MORE THAN 5 YEARS AGO ☐

(f) CAN'T REMEMBER / DON'T KNOW ☐

21) HOW OLD WERE YOU WHEN YOU FIRST STARTED USING THE PILL? _____

22) WHY DID YOU START USING THE PILL?

(a) FOR CONTRACEPTION ONLY ☐

(b) FOR PAINFUL PERIODS ☐

(c) FOR HEAVY PERIODS ☐

(d) FOR IRREGULAR PERIODS ☐

(e) FOR PMS ☐

(f) OTHER (please specify) ☐

23) HAVE YOU EVER HAD ANY SIDE FROM THE PILL? (please describe)

_____

_____

24) HAVE YOU ALWAYS USED THE SAME PILL? _____

25) IF NOT: WHY DID YOU CHANGE? _____

_____

26) IF YOU ARE TAKING THE PILL A THE MOMENT, HOW LONG HAVE YOU BEEN USING IT FOR? _____

27) IF YOU HAVE USED THE PILL IN THE PAST; WHY DID YOU STOP? _____

_____

29) DID THE PILL HAVE ANY EFFECT ON YOUR PREMENSTRUAL SYMPTOMS?

(a) IMPROVED PREMENSTRUAL SYMPTOMS ☐

(b) HAD NO EFFECT ON PREMENSTRUAL SYMPTOMS ☐

(c) MADE PREMENSTRUAL SYMPTOMS WORSE ☐

(d) NOT SURE OR CAN'T REMEMBER ☐

(e) DID NOT HAVE PMS AT THE TIME ☐

(f) OTHER (please specify) ☐

30) IF YOU HAVE NEVER USED AN ORAL CONTRACEPTIVE, IS IT FOR ANY PARTICULAR REASON?

(a) NO ☐

(b) FAMILY HISTORY OF THROMBOSIS etc. ☐

(c) FEAR OF LONG TERM SIDE EFFECTS ☐

(d) PREFERRED OTHER FORMS OF CONTRACEPTION ☐

(e) NEVER HAD ANY NEED FOR CONTRACEPTION ☐

(f) PERSONAL MEDICAL HISTORY ☐

(g) OTHER (please specify) ☐

D) LIFE HISTORY

31) HAVE THERE BEEN ANY TIMES DURING YOUR LIFE WHEN YOU HAVE FELT PARTICULARLY UNHAPPY OR DEPRESSED? _____

_____

32) IF SO; WAS IT IN RELATION TO SOMETHING WHICH HAPPENED TO YOU (e.g. bereavement, loss of job, house move etc)? _____

_____

33) HOW LONG AGO WAS THAT EPISODE? _____

34) DID YOU FEEL BAD ENOUGH TO SEE YOUR DOCTOR ABOUT IT? _____

35) IF SO, DID HE/SHE GIVE YOU ANY TREATMENT? _____

_____

36) HOW WOULD YOU RATE YOUR GENERAL HEALTH?

(a) GOOD ☐

(b) MODERATE ☐

(c) POOR ☐

37) DO YOU HAVE ANY PERSISTENT MEDICAL CONDITIONS (e.g. Diabetes)?

---

38) IF SO; HOW MUCH DOES THIS INTERFERE WITH YOUR LIFE?

(a) NOT AT ALL ☐

(b) VERY LITTLE ☐

(c) QUITE A LOT ☐

(d) VERY DISABLING ☐

39) HOW HAPPY IS THE RELATIONSHIP BETWEEN YOU AND YOUR PARTNER AT THE MOMENT?

(a) NOT APPLICABLE: NO RELATIONSHIP ☐

(b) VERY HAPPY ☐

(c) FAIRLY HAPPY ☐

(d) NOT VERY HAPPY ☐

(e) NOT AT ALL HAPPY ☐

40) ARE YOU PERSONALLY UNDERGOING ANY UNUSUAL STRESS AT THE MOMENT?

(a) YES, A GREAT DEAL OF STRESS ☐

(b) YES, SOME STRESS ☐

(c) NO ☐

E) TREATMENT HISTORY

41) HAVE YOU TRIED ANY FORM OF TREATMENT FOR YOUR PMS?

(a) YES ☐

(b) NO ☐

IF YES , PLEASE TICK APPROPRIATE BOX ON NEXT PAGE.

	Not tried	No help	Made symptoms worse	Slight help	Good effect first 2 or 3 months only	Good effect more than 3 months
a) Vit. B6 or Pyridoxine	☐	☐	☐	☐	☐	☐
b) Oil of evening Primrose or Efamol	☐	☐	☐	☐	☐	☐
c) Diuretics (water tablets)	☐	☐	☐	☐	☐	☐
d) Duphaston	☐	☐	☐	☐	☐	☐
e) Aspirin or Panadol	☐	☐	☐	☐	☐	☐
f) Cyclogest suppositories	☐	☐	☐	☐	☐	☐
g) Progesterone injection	☐	☐	☐	☐	☐	☐
h) Primolut N	☐	☐	☐	☐	☐	☐
i) Provera tablets	☐	☐	☐	☐	☐	☐
j) Provera injections	☐	☐	☐	☐	☐	☐
k) Bromocriptine (Parlodel)	☐	☐	☐	☐	☐	☐
l) Danazol (Danol)	☐	☐	☐	☐	☐	☐
m) Oral contraceptive (state which one)	☐	☐	☐	☐	☐	☐
n) Oestrogen implant	☐	☐	☐	☐	☐	☐

Would you be prepared to fill in a form describing how you feel each day for one or two months? An example is enclosed together with an instruction sheet.

Yes ☐ No ☐

If YES, please fill in the attached diary form describing how you felt yesterday, so that we can check that the instructions have been sufficiently clear, and return it to us together with the questionnaire.

Thank you very much for your help. I look forward to further contact with you.

MRS ANN WALKER

INFORMAL DEMOGRAPHIC QUESTIONNAIRE / INTERVIEW

Subject Number :_____

Date of Birth : _____ Age :_____

Marital Status : _____

Any other marriages ? _____

Date of marriage (in order of marriage)_____

Date of divorce / seperation / widowhood _____

Age at leaving school _____

Any further education or training ? _____

Work outside the home ? _____

Job? _____

Full-time , Part-time , self employed ? _____

Is husband working ? _____

Who is the main breadwinner ? _____

Do you have any children ? _____

How old are they ? _____

Type of delivery _____

How many children did you want ? _____

Do all of your children live at home ? _____

Did you have any other pregnancies ? _____

Outcome ? _____

Did you have any problems in pregnancy ? _____

How did you feel in the first few days after each birth ? _____

And how were you in the first few months after each birth ? _____

Did you breastfeed ?_____

How long did you breastfeed fully ? _____

Did you enjoy breastfeeding ? _____

What method of contraception are you using now ? _____

How long have you been using this method ? _____

Are you satisfied with it ? _____

If not , why not ? _____

Have you ever used the pill ? _____

If not , why not ? _____

Which pill(s) were you on ? _____

When were you on it ? _____

How long did you take it ? _____

Why did you stop ? _____

Do you smoke now ?_____ How many a day ? ____

Did you have any side effects from the pill ? _____

What other methods have you used ? _____

Why did you stop using these methods ? _____

Do you have a regular menstrual cycle now ? _____

What is the normal number of days from the start of one period to the start of the next ? _____

Does this vary ? _____ From _____to_____days .

Has this ever been different ? _____

How many days was it then ? _____

Did this vary ? _____

When was this ? _____How long ago ? _____

What is your usual number of days of bleeding ? _____

Has this ever been different ? _____ When ? _____

Does the number of days of bleeding vary from cycle to cycle ? _____

Do you have midcycle bleeding ? _____

How would you describe your bleeding ? Light / Medium / Heavy

Has this changed recently ? _____

Is there any known reason for this ? _____

Have you ever had flooding / passed clots ? _____

Do your periods interfere with your normal life ? _____

Have you ever been anaemic ? _____

Have you ever had a D & C ? _____

Do you have pain with your periods ? _____

How severe is this pain ? _____

How many of your periods are painful ? _____

Do you need to take medication for it ? _____

What do you take ? _____

How would you rate your physical health over the last 5 years ? ____

Any persistent conditions ? _____

How much does this interfere with ordinary life ? _____

Any major illnesses ? _____

Any operations ? _____

In the past five years , have there been any times when you have felt particularly unhappy or not yourself ? _____

Were external factors relevant ? _____

How severe was the episode ? _____
Was anyone a particular help to you at that time ? _____
Did you see your G.P.?_____How often ? _____
Any treatment ? _____
Did you see a psychiatrist ? _____ How often ? _____
Any treatment ? _____
Were you admitted as an inpatient ? _____How long for ? _____
Any treatment ? _____
Have there been any times in the past 5 years when you have been particularly happy or unusually cheerful ? _____
Have you or your partner had any change in your job in the last year ?
Have you or your husband had any financial difficulties in the last year ?
Have you or any close relatives had any serious illnesses in the last year ?
Have you had any problems with your marriage in the last year ? Have you moved , or had someone new living in your home in the last year ?
Have you or your family been involved with the law in the last year ?
Are there any other events not covered ?
Have you had anyone who has tried to help you with these or any other difficulties you may have had ?

APPENDIX FOUR
FIGURES AND TABLES NOT ELSEWHERE DISPLAYED

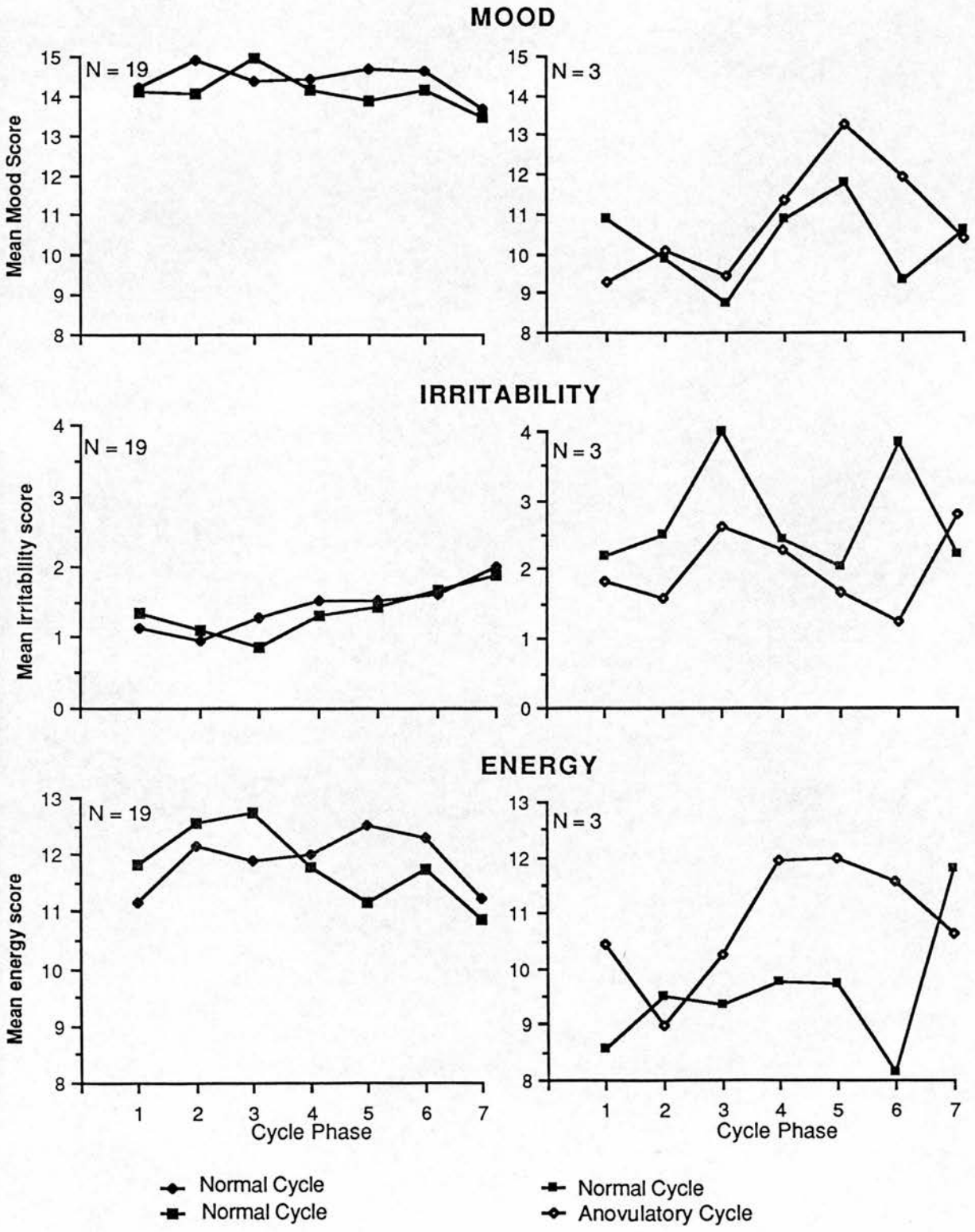

Figure A-1 Comparison of mood , irritability and energy levels across 7 standardized cycle phases in normal / normal cycle pairs and normal / anovulatory cycle pairs

(From Chapter Five)

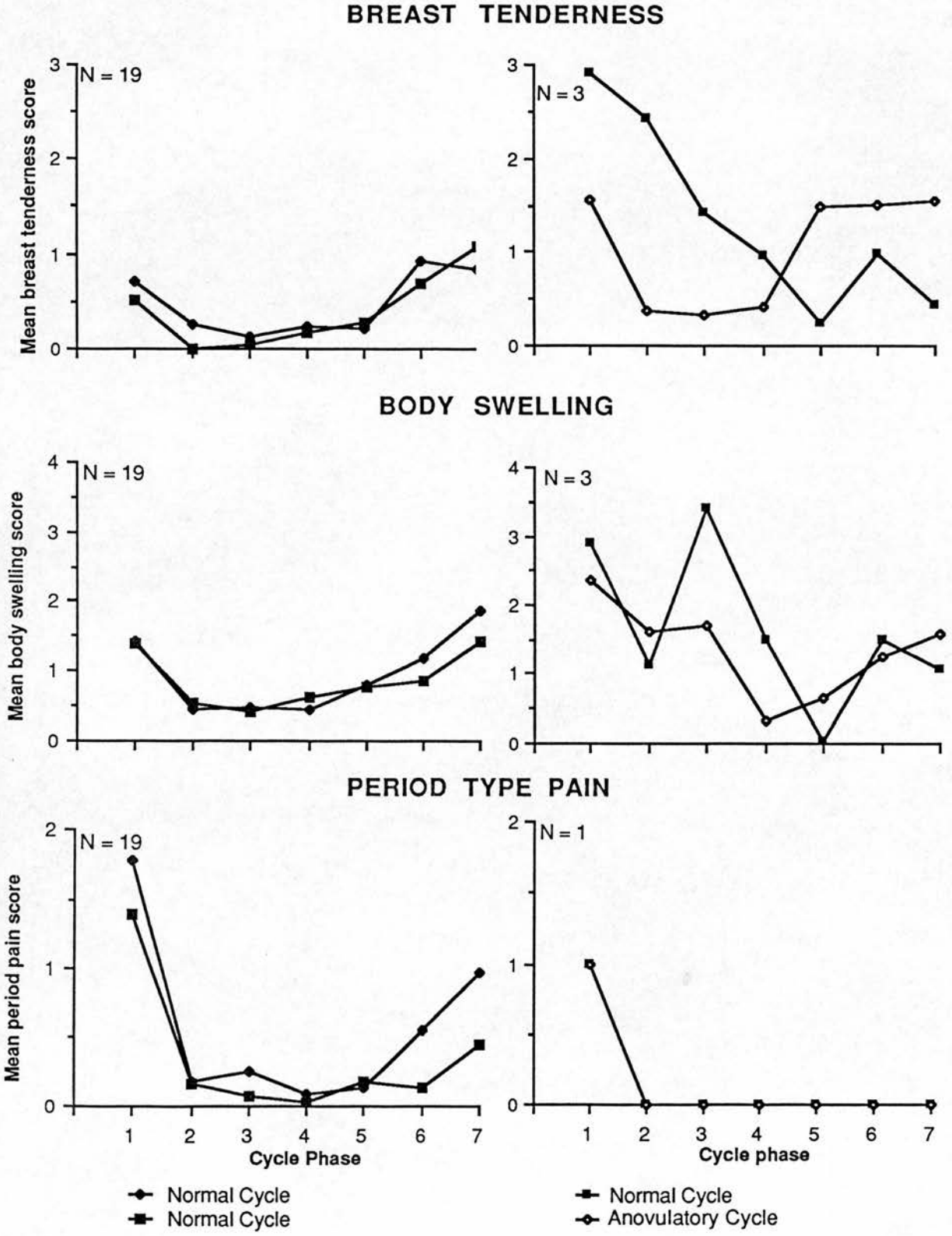

Figure A-2 Comparison of breast tenderness , body swelling and period pain levels across 7 standardized cycle phases in normal / normal cycle pairs and normal / anovulatory cycle pairs
(From Chapter Five)

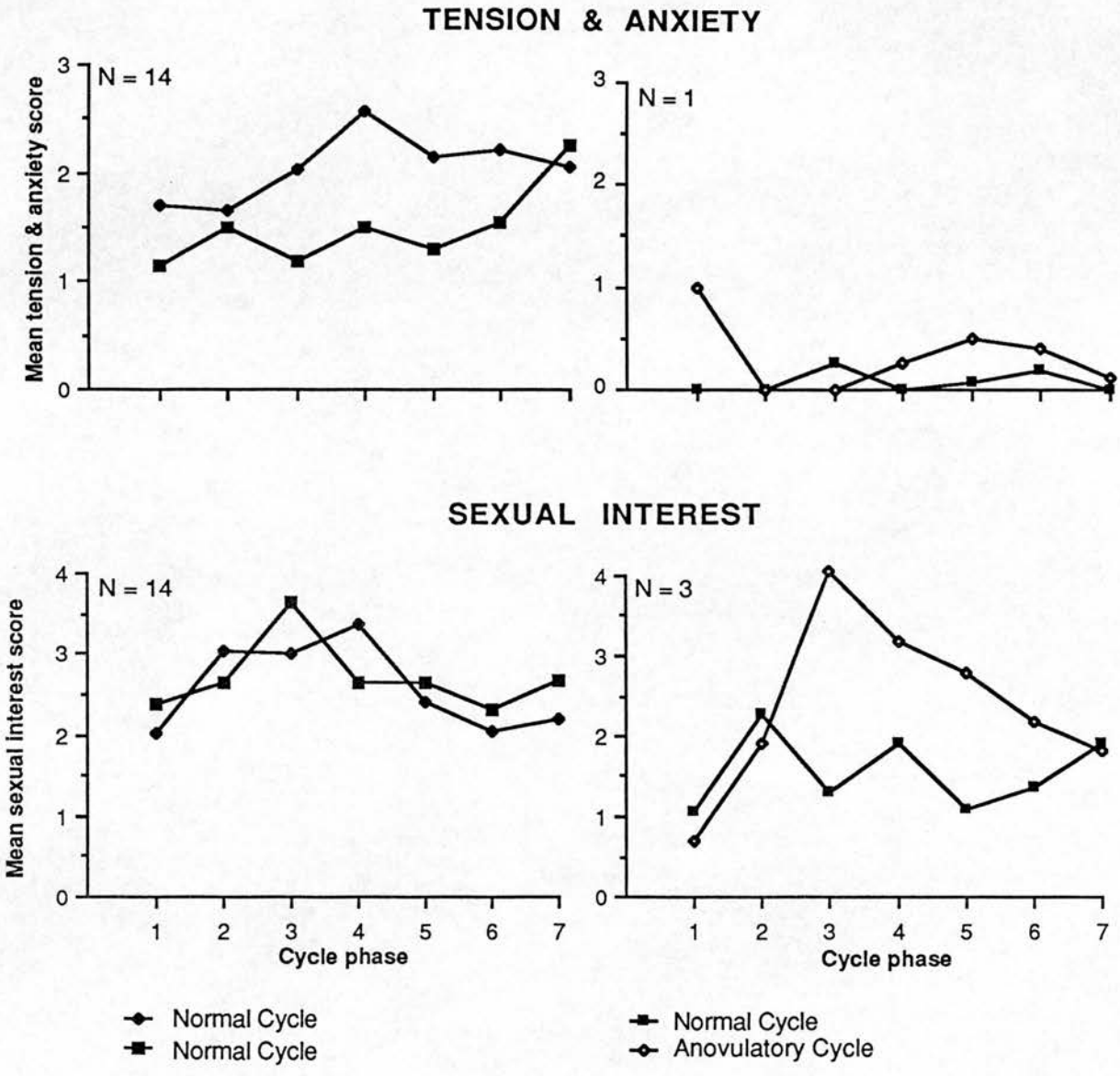

Figure A -3 Comparison of tension & anxiety and sexual interest levels across 7 standardized cycle phases in normal / normal cycle pairs and normal / anovulatory cycle pairs .
(From Chapter Five)

TABLE A - 1

THREE-WAY AND TWO-WAY ANOVA RESULTS FOR NORMAL AND ANOVULATORY CYCLES BY STANDARDIZED CYCLE PHASE

i) Three-way ANOVA.

	G	C	G x C	P	G x P	C x P	G x C x P
Mood	ns	ns	ns	ns	ns	ns	ns
Irritable	ns	ns	ns	ns	ns	ns	ns
Energy	ns	ns	ns	ns	ns	ns	ns
Tense & anxious	Insufficient data						
Breast tenderness	*	ns	ns	**	T	**	*
Body swelling	ns	ns	ns	**	*	ns	T
Period pain	Insufficient data						
Sexual interest	ns	ns	ns	**	ns	ns	ns

ii) Two-way ANOVA between normal cycles .

	C	P	C x P	P@C1	P@C2
Mood	ns	ns	ns	ns	ns
Irritable	ns	T	ns	ns	ns
Energy	ns	ns	T	ns	*
Tense & anxious					
Breast tenderness	ns	**	ns	**	**
Body swelling	ns	**	ns	**	**
Period pain					
Sexual interest	ns	**	ns	*	ns

iii) Two-way ANOVA between normal and anovulatory cycles .

	C	P	C x P	P@C1	P@C2
Mood	ns	ns	ns	ns	ns
Irritable	ns	ns	ns	ns	ns
Energy	ns	ns	ns	ns	ns
Tense & anxious	Insufficient data				
Breast tenderness	ns	ns	ns	ns	ns
Body swelling	ns	ns	ns	ns	ns
Period pain	Insufficient data				
Sexual interest	ns	ns	ns	ns	ns

Key :- ns - not significant ; T - trend ($p < 0.10$) ; * - $p < 0.05$;
** - $p < 0.01$; G - Group ; C - Cycle ; P - Phase

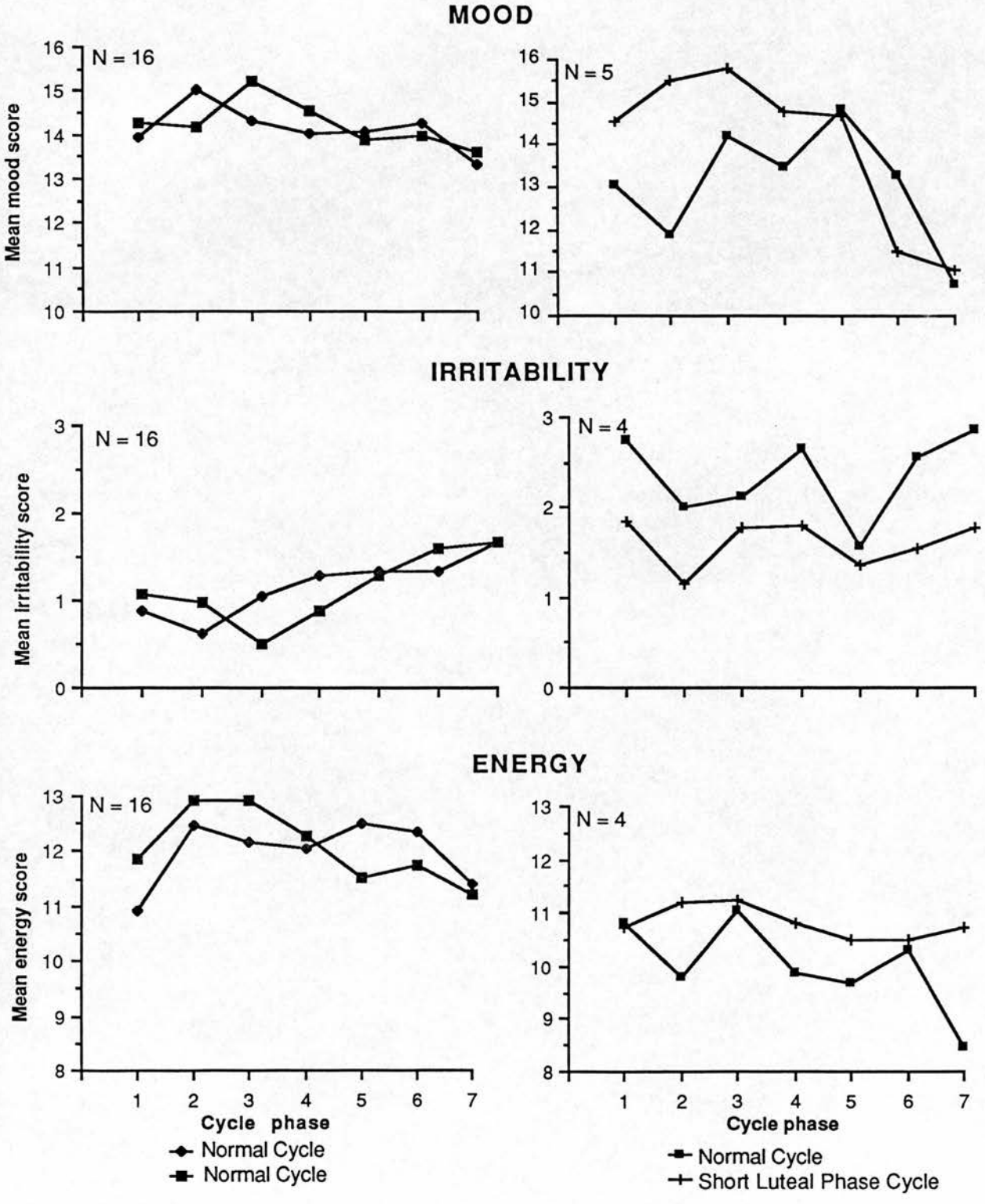

Figure A -4 Comparison of mood , irritability and energy levels across 7 standardized cycle phases in normal / normal cycle pairs and normal / short luteal phase cycle pairs
(From Chapter Five)

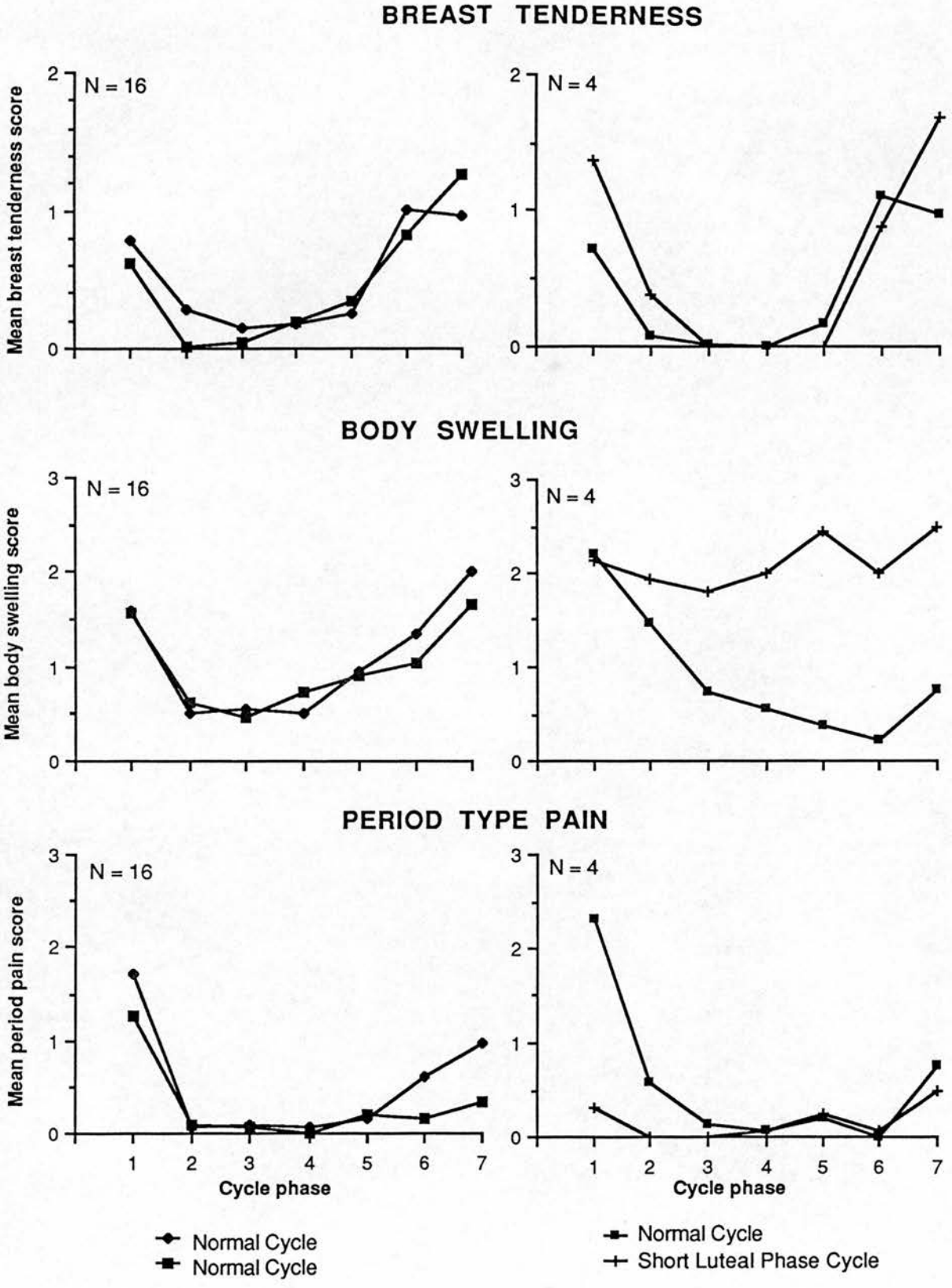

Figure A - 5 Comparison of breast tenderness , body swelling and period pain scores across 7 standardized cycle phases in normal / normal cycle pairs and normal / short luteal phase cycle pairs .
(From Chapter Five)

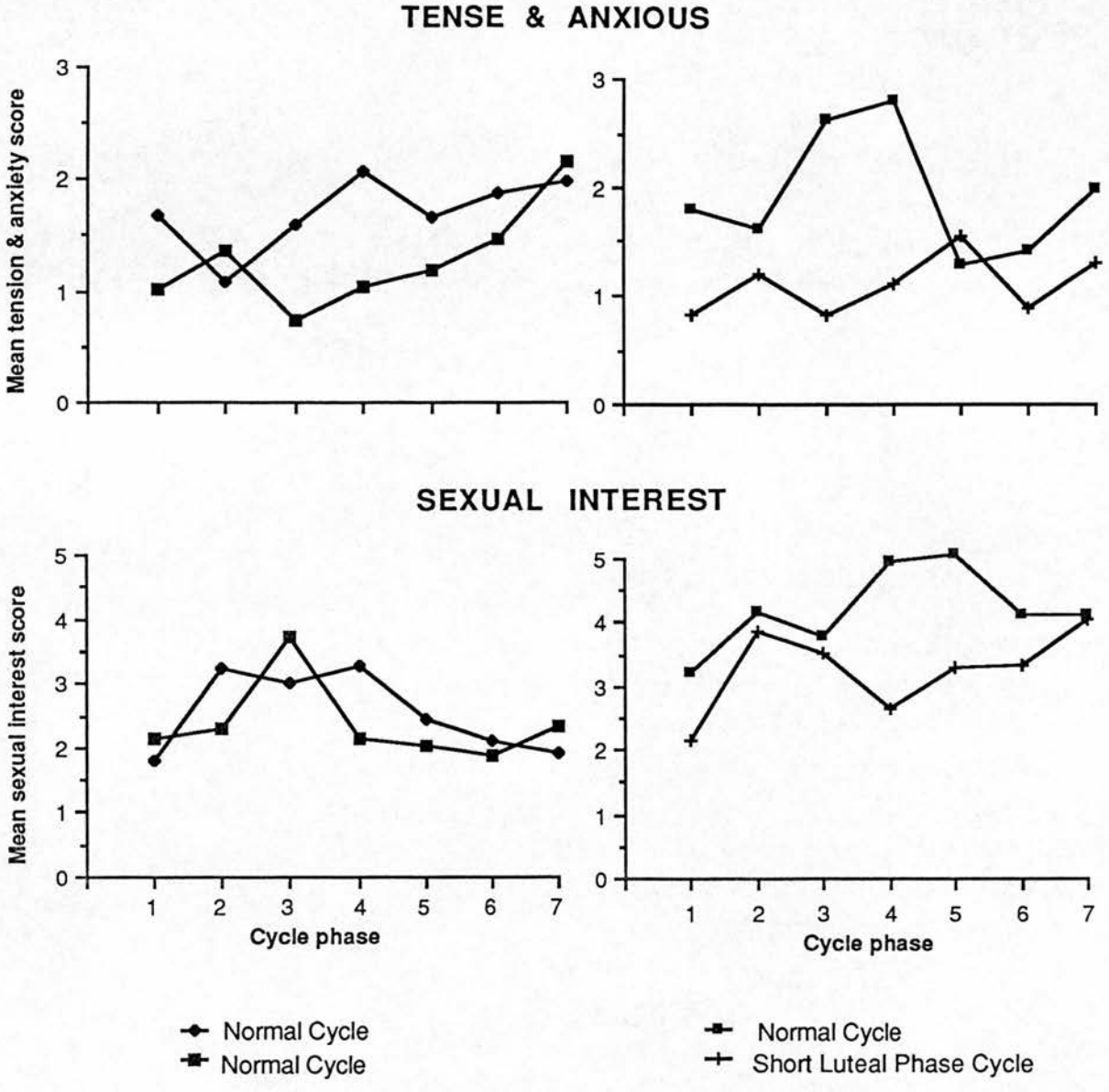

Figure A - 6 Comparison of tension & anxiety and sexual interest scores across 7 standardized cycle phases in normal / normal cycle pairs and normal / short luteal phase cycle pairs .
(From Chapter Five)

TABLE A-2

THREE-WAY AND TWO-WAY ANOVA RESULTS FOR NORMAL AND SLP CYCLES BY STANDARDIZED CYCLE PHASE

i) Three-way ANOVA .

	G	C	G x C	P	G x P	C x P	GxCxP
Mood	ns	ns	ns	*	ns	ns	ns
Irritable	ns	ns	ns	ns	ns	ns	ns
Energy	ns	ns	ns	ns	ns	ns	ns
Tense & anxious	ns	T	ns	ns	ns	ns	ns
Breast tenderness	ns	ns	ns	**	ns	ns	ns
Body swelling	ns	ns	ns	T	ns	ns	ns
Period pain	ns	ns	ns	**	ns	ns	ns
Sexual interest	ns	ns	ns	T	ns	ns	ns

ii) Two-way ANOVA between normal cycles .

	C	P	CxP	P@C1	P@C2
Mood	ns	ns	ns	ns	ns
Irritable	ns	ns	ns	ns	T
Energy	ns	ns	ns	ns	ns
Tense & anxious	ns	ns	ns	ns	ns
Breast tenderness	ns	**	ns	**	**
Body swelling	ns	**	ns	**	**
Period pain	ns	**	ns	**	**
Sexual interest	ns	**	ns	**	T

iii) Two-way ANOVA between normal and SLP cycles .

	C	P	CxP	P@C1	P@C2
Mood	ns	ns	ns	ns	ns
Irritable	ns	ns	ns	ns	ns
Energy	ns	ns	ns	ns	ns
Tense & anxious	ns	ns	ns	ns	ns
Breast tenderness	ns	ns	ns	ns	ns
Body swelling	ns	ns	ns	ns	ns
Period pain	ns	*	*	*	ns
Sexual interest	ns	ns	ns	ns	ns

Key :- ns - not significant ; T - trend ($p < 0.10$) ; * - $p < 0.05$

** - $p < 0.01$; G - Group ; C - Cycle ; P - Phase .

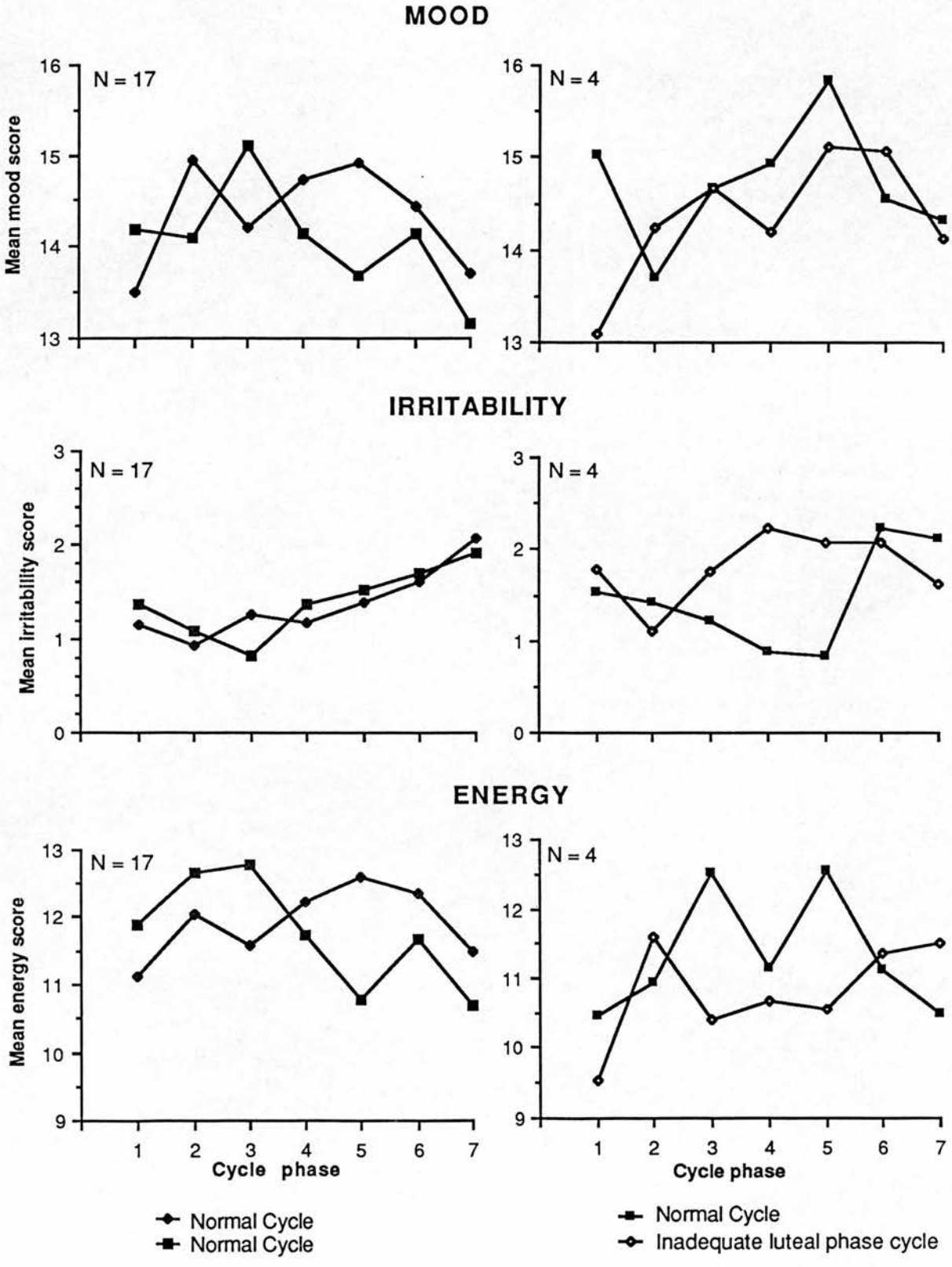

Figure A-7 Comparison of mood , irritability and energy levels across 7 standardized cycle phases in normal / normal cycle pairs and normal / inadequate luteal phase cycle pairs
(From Chapter Five)

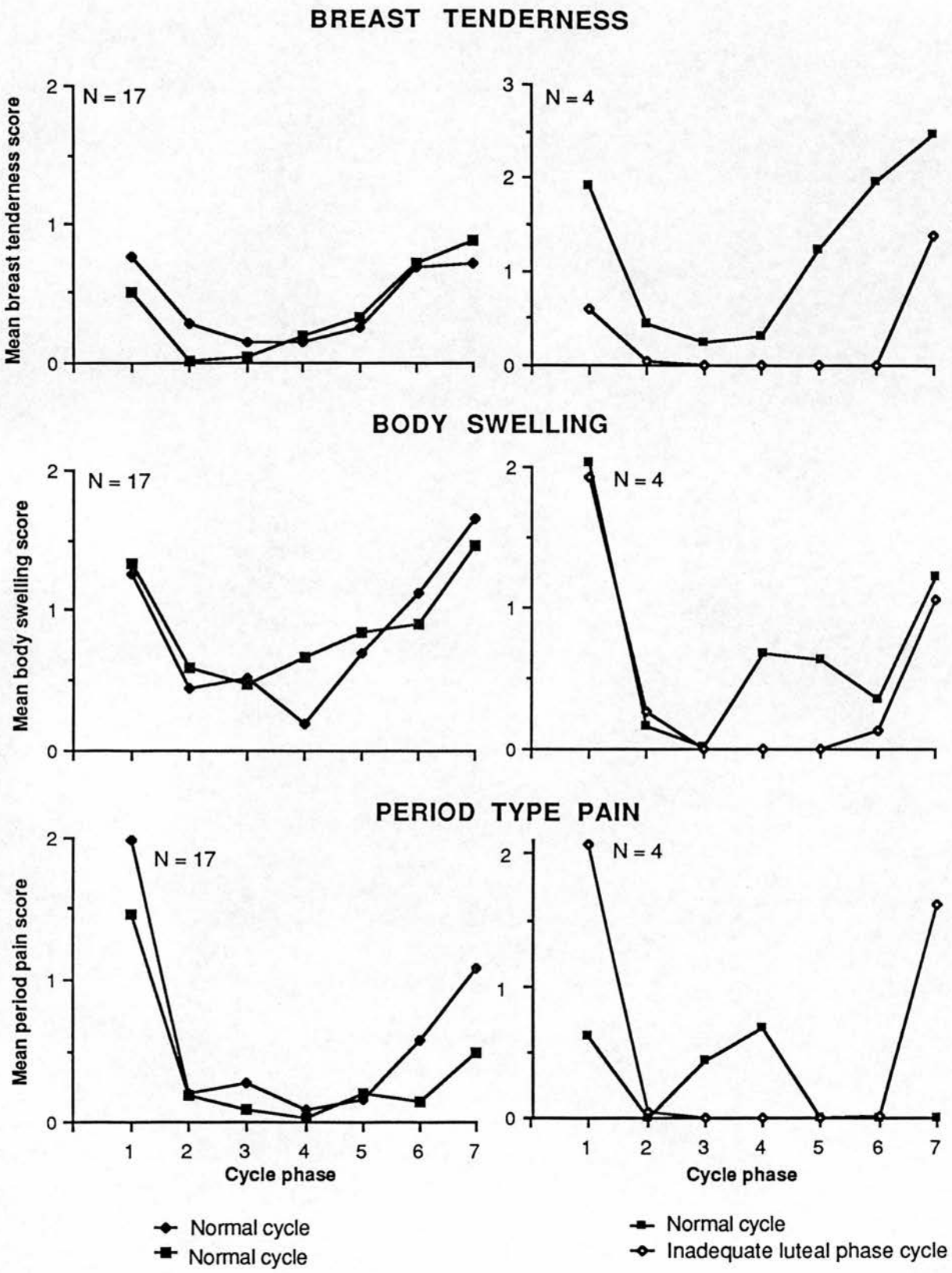

Figure A-8 Comparison of breast tenderness , body swelling and period pain scores across 7 standardized cycle phases in normal / normal cycle pairs and normal / inadequate luteal phase cycle pairs (From Chapter Five) .

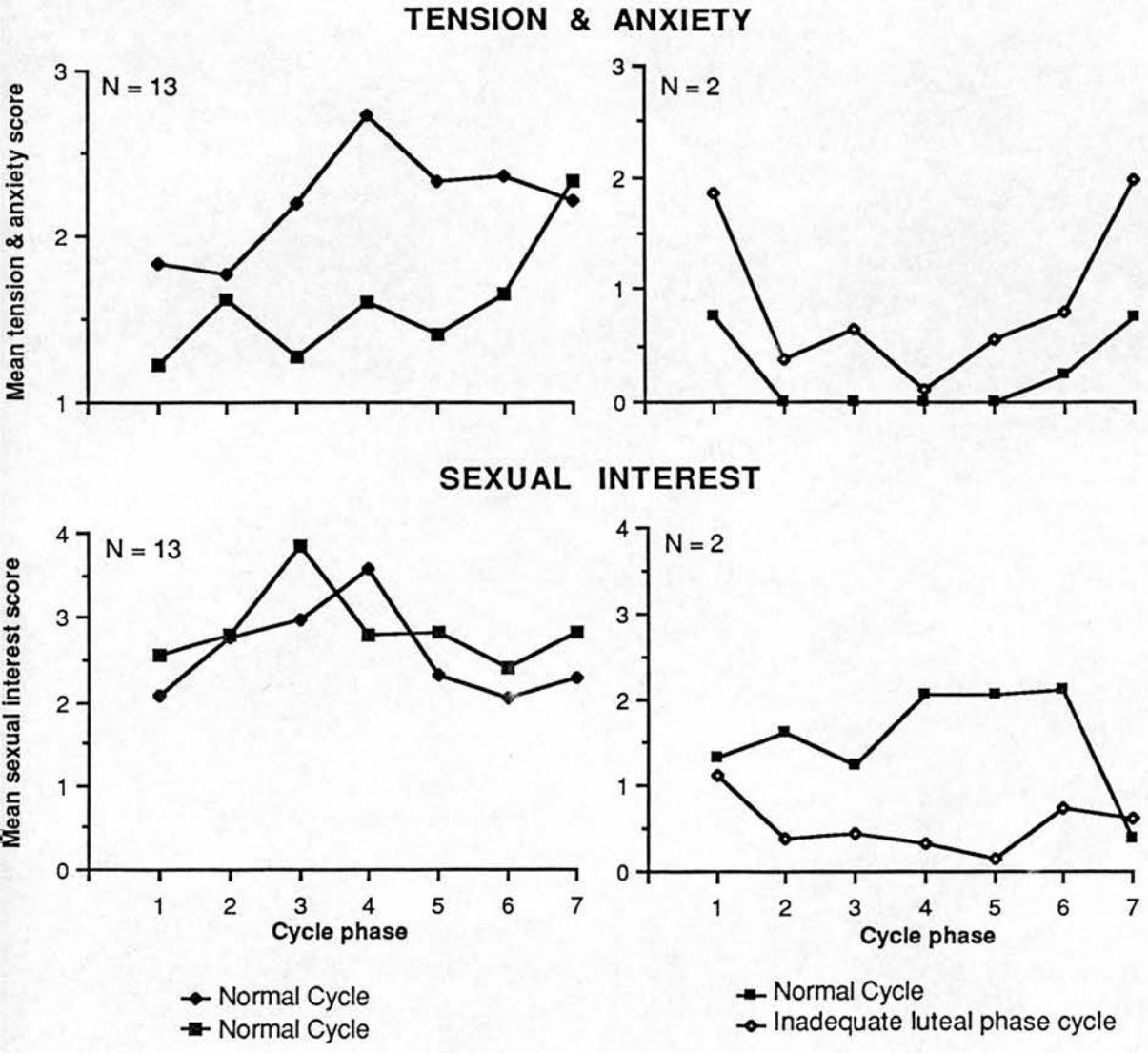

Figure A-9 Comparison of tension & anxiety and sexual interest scores across 7 standardized cycle phases in normal / normal cycle pairs and normal / inadequate luteal phase cycle pairs (From Chapter Five) .

TABLE A-3

THREE-WAY AND TWO-WAY ANOVA RESULTS FOR NORMAL AND ILP CYCLES BY STANDARDIZED CYCLE PHASE

i) Three-way ANOVA .

	G	C	G x C	P	G x P	C x P	GxCxP
Mood	ns	ns	ns	ns	ns	ns	ns
Irritable	ns	ns	ns	ns	ns	ns	ns
Energy	ns	ns	ns	ns	ns	ns	ns
Tense & anxious	ns	ns	ns	ns	ns	ns	ns
Breast tenderness	ns	**	**	**	ns	ns	ns
Body swelling	ns	ns	ns	**	ns	ns	ns
Period pain	ns	ns	ns	**	ns	ns	T
Sexual interest	ns	ns	ns	ns	ns	ns	ns

ii) Two-way ANOVA between normal cycles .

	C	P	CxP	P@C1	P@C2
Mood	ns	ns	ns	ns	ns
Irritable	ns	*	ns	T	ns
Energy	ns	ns	**	ns	**
Tense & anxious	*	ns	ns	ns	ns
Breast tenderness	ns	**	ns	*	**
Body swelling	ns	**	ns	*	**
Period pain	ns	**	ns	**	**
Sexual interest	ns	**	ns	**	ns

iii) Two-way ANOVA between normal and ILP cycles .

	C	P	CxP	P@C1	P@C2
Mood	ns	ns	ns	ns	ns
Irritable	ns	ns	ns	ns	ns
Energy	ns	ns	ns	ns	ns
Tense & anxious	ns	ns	ns	ns	ns
Breast tenderness	ns	*	ns	ns	T
Body swelling	ns	**	ns	**	T
Period pain	ns	ns	ns	ns	ns
Sexual interest	ns	ns	ns	ns	ns

Key : - ns - not significant ; T trend ($p<0.10$) ; * - $p < 0.05$;

** - $p < 0.01$; G - Group ; C - Cycle ; P - Phase .

TABLE A-4

PERCENTAGE OF CYCLES WITHIN EACH GROUP SHOWING WORSE THAN NORMAL SCORES

	MOOD			IRRITABLE			ENERGY			TENSION		
Day	T	M	C	T	M	C	T	M	C	T	M	C
1	52.4	68.2	66.1	61.0	61.2	59.5	58.5	61.2	69.4	56.1	43.5	56.2
2	40.2	55.3	59.5	58.5	52.9	58.7	52.4	55.3	65.3	45.1	48.2	48.8
3	43.9	45.9	47.9	41.5	40.0	49.6	45.1	48.2	57.0	32.9	35.3	47.1
4	31.7	42.4	43.8	37.8	35.3	38.8	35.4	27.1	43.8	25.6	30.6	37.2
5	32.9	27.0	40.5	30.5	23.5	33.1	31.7	30.6	29.7	19.5	23.5	28.1
6	30.5	28.2	23.9	25.6	25.9	30.6	34.1	29.4	29.7	24.4	17.6	31.4
7	29.3	20.0	26.4	23.2	14.1	24.8	25.6	20.0	27.3	23.2	17.6	25.6
8	24.4	23.5	19.8	20.7	17.6	21.5	14.6	31.7	19.0	23.2	16.5	24.8
9	20.7	21.2	17.4	17.1	29.4	14.9	26.8	23.5	14.1	25.6	22.4	24.8
10	19.5	25.9	16.5	20.7	22.4	10.7	20.7	23.5	18.2	17.1	22.4	21.5
11	25.6	20.0	13.2	19.5	21.2	15.7	26.8	20.0	22.3	14.6	23.5	19.0
12	21.9	21.2	18.2	28.1	16.5	16.5	20.7	22.4	17.4	20.7	17.6	14.0
13	30.5	21.2	19.0	21.9	15.3	11.6	30.5	28.2	19.0	24.4	23.5	20.7
14	15.8	23.5	16.5	21.9	17.6	14.8	21.9	31.8	19.0	24.4	17.6	20.7
15	19.5	25.9	18.2	18.3	27.1	21.5	20.7	28.2	19.0	15.8	18.8	22.3
16	23.2	25.9	19.0	23.2	20.0	22.3	26.8	20.0	20.7	18.3	18.8	19.8
17	25.6	31.8	22.1	21.9	27.1	18.2	23.2	29.4	25.6	19.5	25.9	20.7
18	18.3	23.5	23.9	21.9	21.2	27.3	17.1	18.8	28.9	19.5	27.1	21.5
19	35.4	21.2	22.3	29.3	18.8	23.1	25.6	25.9	30.6	20.7	17.6	28.9
20	35.4	27.0	30.6	35.4	28.2	30.6	29.3	24.7	32.2	31.7	21.2	30.6
21	35.4	35.3	28.1	39.0	28.2	33.9	35.4	28.2	28.9	37.8	27.1	27.3
22	30.5	30.6	39.7	36.6	30.6	46.3	20.7	24.7	39.7	25.6	32.9	38.8
23	28.0	43.5	40.5	37.8	43.5	46.3	35.4	38.8	37.2	32.9	38.8	38.8
24	40.2	41.2	36.4	37.8	41.2	42.1	32.9	41.2	39.7	24.4	38.8	42.9
25	30.5	48.2	42.1	41.5	50.6	48.8	35.4	45.9	39.7	34.1	36.5	39.7
26	39.0	49.4	43.8	46.3	51.7	50.4	40.2	44.7	45.5	42.7	38.8	47.1
27	52.4	55.3	50.4	48.8	50.6	61.2	56.1	44.7	47.9	50.0	35.3	57.8
28	42.7	57.6	62.8	54.9	47.0	63.6	56.1	50.6	65.4	47.6	41.2	57.0

Table A-4 Continued

	BREAST TENDERNESS			BODY SWELLING			PERIOD PAIN			SEXUAL INTEREST		
Day	T	M	C	T	M	C	T	M	C	T	M	C
1	65.8	44.7	68.6	80.5	70.6	81.8	75.6	74.1	80.2	40.2	51.7	63.7
2	46.3	40.0	52.1	75.6	67.1	73.6	74.4	71.7	78.5	35.4	45.9	61.7
3	41.5	30.6	34.7	63.4	54.1	54.5	59.7	48.2	65.3	35.4	51.7	54.9
4	24.4	14.1	20.7	42.7	36.5	34.7	40.2	35.3	42.9	35.4	31.7	39.2
5	9.7	7.1	13.2	20.7	21.2	23.1	21.9	15.3	27.3	30.5	30.6	36.3
6	3.7	5.9	8.3	17.1	21.2	14.0	13.4	11.7	16.5	24.4	28.2	34.3
7	3.7	1.2	2.5	12.2	10.6	9.1	12.2	5.9	9.1	25.6	22.4	26.5
8	1.2	2.4	4.1	8.5	9.4	7.4	3.7	7.1	5.8	25.6	25.9	20.6
9	3.7	0	3.3	6.1	9.4	3.3	3.7	2.4	2.5	29.3	29.4	17.6
10	3.7	1.2	0.8	2.4	5.9	2.5	0	2.4	1.6	31.7	42.4	18.6
11	3.7	1.2	0	6.1	8.2	2.5	2.4	0	0	25.6	32.9	17.6
12	2.4	2.4	0.8	7.3	7.1	2.5	0	0	0.8	28.1	30.6	20.6
13	3.7	5.9	1.6	7.3	10.6	3.3	0	0	0.8	36.6	28.2	27.4
14	3.7	5.9	5.8	4.9	9.4	3.3	3.7	1.2	2.5	25.6	31.7	26.5
15	4.9	4.7	4.9	4.9	7.1	6.6	3.7	4.7	4.1	18.3	31.7	15.7
16	9.8	7.1	5.8	6.1	15.3	7.4	3.7	1.2	4.9	19.5	36.5	23.5
17	15.8	12.9	9.9	9.8	17.6	6.6	6.1	5.9	8.3	35.4	37.6	32.4
18	19.5	10.6	16.5	19.5	20.0	9.9	8.5	4.7	8.3	39.0	38.8	36.3
19	24.4	14.1	23.1	21.9	22.4	14.1	6.1	4.7	4.9	42.7	49.4	32.3
20	21.9	15.3	28.1	21.9	23.5	26.4	6.1	5.9	3.3	31.7	37.6	33.3
21	25.6	15.3	31.4	30.5	24.7	28.9	4.9	12.9	4.9	34.1	40.0	36.3
22	35.4	21.2	41.3	35.4	38.8	45.5	6.1	11.8	8.3	28.0	37.6	39.2
23	37.8	24.7	52.9	46.3	44.7	48.7	12.2	10.6	12.4	39.0	43.5	40.2
24	52.4	28.2	56.2	52.4	55.3	51.2	14.6	18.8	20.7	34.1	44.7	45.1
25	58.5	35.3	59.5	56.1	54.1	60.3	20.7	25.9	19.8	28.0	44.7	49.0
26	65.8	47.1	68.6	62.2	56.5	70.2	23.2	23.5	26.4	36.6	35.3	47.0
27	68.3	48.2	70.2	71.9	68.2	73.6	36.6	32.9	29.7	32.9	44.7	64.7
28	65.8	44.7	71.1	75.6	58.8	78.5	45.1	38.8	38.8	35.4	44.7	60.8

Number of cycles in each group :- Triphasic = 83 (65)
Monophasic = 86 (73)
Control = 121 (102)

(Figures in brackets indicate numbers for sexual interest)

TABLE A-5

PERCENTAGE OF CYCLES WITHIN EACH GROUP SHOWING BETTER THAN NORMAL SCORES

	MOOD			IRRITABLE			ENERGY			TENSION		
Day	T	M	C	T	M	C	T	M	C	T	M	C
1	10.8	11.6	14.8	19.3	25.6	19.8	14.5	12.8	11.6	21.7	30.2	28.1
2	20.5	18.6	19.0	22.9	33.7	18.2	16.9	17.4	13.2	28.9	27.9	18.2
3	21.7	18.6	22.3	36.1	34.9	25.6	22.9	19.8	19.0	39.7	38.4	32.2
4	35.0	30.2	21.5	36.1	38.4	33.9	34.9	30.2	25.6	40.9	43.0	38.0
5	35.0	31.4	27.3	43.4	43.0	40.5	34.9	33.7	35.5	54.2	48.8	48.8
6	33.7	38.4	36.4	43.4	55.8	45.5	30.1	39.5	42.1	46.9	41.9	46.3
7	37.3	43.0	36.4	49.4	62.8	45.5	33.7	38.4	38.8	53.0	52.3	50.4
8	36.1	38.4	44.6	49.4	59.3	55.4	48.2	34.9	51.2	53.0	51.1	54.5
9	49.4	41.7	48.8	55.4	51.2	50.4	53.0	40.7	51.2	57.8	51.1	55.4
10	44.6	38.4	48.8	51.8	52.3	61.1	55.4	34.9	53.7	60.2	48.8	58.7
11	44.6	39.5	48.8	62.6	55.8	60.3	43.4	39.5	54.5	62.6	55.8	57.8
12	51.8	41.9	47.1	50.6	58.1	66.1	40.9	39.5	50.4	50.6	54.6	62.0
13	45.8	46.5	47.9	44.6	62.8	54.5	36.1	36.0	47.1	45.8	53.5	58.7
14	53.0	46.5	50.4	46.9	59.3	61.9	48.2	34.9	42.1	54.2	53.5	56.2
15	48.2	46.5	49.6	50.6	48.8	54.5	33.7	37.2	46.3	60.2	48.8	56.2
16	40.9	41.9	46.3	51.8	58.1	50.4	33.7	43.0	47.1	51.8	51.2	51.2
17	34.9	32.6	45.5	48.2	54.6	52.1	39.7	43.0	46.3	53.0	50.0	53.7
18	42.2	37.2	38.8	55.4	59.3	42.9	50.6	38.4	39.7	51.8	52.3	52.9
19	36.1	37.2	34.7	39.7	56.9	45.5	43.4	36.0	40.5	49.4	51.2	48.8
20	27.7	36.0	33.9	39.7	40.7	42.1	31.3	34.9	38.8	37.3	51.2	47.9
21	33.7	34.9	29.7	33.7	45.3	32.2	34.9	31.4	33.9	34.9	45.3	44.6
22	33.7	32.6	24.8	31.3	43.0	29.7	33.7	32.6	26.4	44.6	47.7	38.0
23	35.0	24.4	19.0	34.9	37.2	29.7	36.1	29.1	24.8	33.7	43.0	39.7
24	32.5	24.4	21.5	36.1	34.9	25.6	31.3	26.7	20.7	40.9	37.2	33.9
25	26.5	23.2	16.5	38.6	34.9	21.5	22.9	17.4	17.4	40.9	40.7	33.1
26	25.3	18.6	14.9	34.9	37.2	20.7	19.3	13.9	19.0	28.9	36.0	30.6
27	22.9	10.5	13.2	28.9	26.7	15.7	20.5	20.9	15.7	24.1	32.6	23.1
28	19.3	17.4	10.7	20.5	25.6	14.0	18.1	13.9	12.4	25.3	26.7	23.1

Table A-5 Continued :

Day	BREAST TENDERNESS			BODY SWELLING			PERIOD PAIN			SEXUAL INTEREST		
	T	M	C	T	M	C	T	M	C	T	M	C
1	26.5	34.9	28.9	13.3	15.1	14.9	25.3	29.1	18.2	23.1	26.0	14.8
2	39.7	39.5	38.0	12.1	20.9	19.0	22.9	25.6	18.2	26.1	23.3	20.8
3	48.2	45.3	47.9	19.3	31.4	32.2	39.7	45.3	32.2	30.7	16.4	20.8
4	67.5	59.3	63.6	39.7	45.3	42.1	51.8	56.9	53.7	27.7	32.9	33.7
5	79.5	67.4	80.2	55.4	60.5	59.5	68.7	77.9	71.1	38.5	43.8	35.6
6	87.9	74.4	86.8	69.9	65.1	77.7	75.9	84.9	81.0	44.6	50.7	43.6
7	89.1	74.4	91.7	75.9	70.9	83.5	80.7	89.5	89.3	43.1	46.6	45.5
8	90.4	76.7	93.4	81.9	80.2	87.6	90.4	87.2	93.4	47.7	49.3	49.5
9	93.9	79.1	95.0	84.3	79.1	93.4	92.8	95.3	96.7	43.1	35.6	47.5
10	92.8	79.1	95.0	87.9	84.9	94.2	96.4	91.8	98.3	40.0	35.6	49.5
11	90.4	76.7	90.9	86.7	86.0	96.7	94.0	95.3	99.2	44.6	39.7	53.5
12	90.4	79.1	92.6	85.5	83.7	95.0	94.0	95.3	98.3	32.3	47.9	46.5
13	90.4	75.6	89.3	83.1	77.9	92.6	95.2	95.3	97.5	33.8	42.5	41.6
14	89.2	74.4	86.8	85.5	82.6	90.1	91.6	95.3	97.5	38.5	37.0	44.6
15	87.9	75.6	89.3	80.7	81.4	85.1	90.4	88.4	95.0	44.6	43.8	50.5
16	86.7	72.1	82.6	80.7	73.2	81.0	94.0	93.0	93.4	33.8	35.6	45.5
17	79.5	67.4	78.5	74.7	72.1	76.8	90.4	87.2	91.7	30.8	28.8	36.6
18	74.7	66.3	76.0	71.1	68.6	75.2	87.9	91.8	88.4	30.8	32.9	32.7
19	69.9	65.1	66.9	62.6	65.1	66.1	87.9	88.4	91.7	24.6	24.6	35.6
20	65.1	66.3	57.0	60.2	66.3	60.3	86.7	91.8	95.9	26.1	38.4	44.5
21	65.1	61.6	52.9	57.8	62.8	57.0	87.9	86.0	94.2	26.1	38.4	28.7
22	61.4	56.9	48.8	45.8	52.3	43.8	86.7	86.0	90.1	36.9	30.1	25.7
23	54.2	52.3	42.1	44.6	44.2	43.8	83.1	87.2	84.3	24.6	19.2	26.7
24	42.2	50.0	38.0	39.7	38.4	39.7	80.7	80.2	77.7	20.0	26.0	22.8
25	32.5	43.0	32.2	30.1	37.2	31.4	78.3	72.1	74.4	32.3	24.6	17.8
26	27.7	32.6	27.3	28.9	33.7	23.1	71.1	72.1	71.1	24.6	31.5	19.8
27	25.3	31.4	27.3	20.5	18.6	20.7	62.6	58.1	63.6	32.3	20.5	14.8
28	24.1	29.1	27.3	14.5	22.1	16.5	55.4	53.5	59.5	23.1	21.9	12.9

Number of cycles : Triphasic = 83 (65)
Monophasic = 86 (73)
Control = 121 (102)
(Figures in brackets indicate numbers for sexual interest)

Table A-6 Chi-square results for section 6.3.4

Frequencies of " bad days " within each group

Mood

	Triphasic	Monophasic	Control	Total
Menses	20 (22.6)	22 (23.2)	37 (33.2)	79
Postmenstrual	25 (21.8)	23 (22.3)	28 (31.9)	76
Intermenstrual	16 (14.6)	14 (15.0)	21 (21.4)	51
Premenstrual	23 (24.9)	27 (25.5)	37 (36.5)	87
Total	84	86	123	293

Chi-square = 2.23 , df = 6 , ns

Breast tenderness

	Triphasic	Monophasic	Control	Total
Menses	24 (22.6)	20 (19.2)	31 (33.2)	75
Postmenstrual	1 (3.6)	5 (3.1)	6 (5.3)	12
Intermenstrual	12 (11.7)	9 (10.0)	18 (17.3)	39
Premenstrual	37 (36.1)	29 (30.7)	54 (53.2)	120
Total	74	63	109	246

Chi-square = 3.72 , df = 6 , ns

Sexual interest

	Triphasic	Monophasic	Control	Total
Menses	13 (14.2)	14 (15.6)	25 (22.2)	52
Postmenstrual	20 (17.5)	21 (19.2)	23 (27.3)	64
Intermenstrual	15 (13.7)	16 (15.0)	19 (21.3)	50
Premenstrual	15 (17.5)	18 (19.2)	31 (27.3)	64
Total	63	69	98	230

Chi-square = 3.21 , df = 6 , ns

Key :- The menstrual , postmenstrual , intermenstrual and premenstrual phases represent blocks of 5 , 11 , 6 and 6 days respectively , collapsed in this way because of small cell sizes

df - degrees of freedom

ns - not significant (i.e. $p > 0.05$)

Table A-7 Chi-square results from section 6.3.5

Mood

	Triph	Monoph	Cont	TOTAL
P	5 (3.8)	1 (4.6)	10 (7.5)	16
M	2 (4.1)	5 (4.9)	10 (8.0)	17
P+M	3 (4.6)	7 (5.5)	9 (9.0)	19
A+N	19 (16.5)	22 (20.0)	28 (32.5)	69
TOTAL	29	35	57	121

Chi-square = 7.70
df = 6
ns

Irritability

	Triph	Monoph	Cont	TOTAL
P	2 (2.4)	1 (2.9)	7 (4.7)	10
M	2 (3.6)	9 (4.3)	4 (7.1)	15
P+M	17 (18.0)	18 (21.7)	40 (35.3)	75
A+N	8 (5.0)	7 (6.1)	6 (9.9)	21
TOTAL	29	35	57	121

Chi-square = 14.18
df = 6
$p < 0.05$

Energy

	Triph	Monoph	Cont	TOTAL
P	6 (5.3)	3 (6.4)	13 (10.4)	22
M	1 (6.5)	12 (7.8)	14 (12.7)	27
P+M	9 (5.3)	3 (6.4)	10 (10.4)	22
A+N	13 (12.0)	17 (14.5)	20 (23.6)	50
TOTAL	29	35	57	121

Chi-square = 15.04
df = 6
$p < 0.025$

Tension & Anxiety

	Triph	Monoph	Cont	TOTAL
P	6 (3.8)	4 (4.6)	6 (7.5)	16
M	1 (4.3)	7 (5.2)	10 (8.5)	18
P+M	12 (12.5)	13 (15.0)	27 (24.5)	52
A+N	10 (8.4)	11 (10.1)	14 (16.5)	35
TOTAL	29	35	57	121

Chi-square = 6.37
df = 6
ns

Table A-7 contd .

Breast tenderness

	Triph	Monoph	Cont	TOTAL
P	5 (4.6)	1 (5.5)	13 (9.0)	19
M	0 (1.9)	3 (2.3)	5 (3.8)	8
P + M	19 (15.8)	14 (19.1)	33 (31.1)	66
A + N	5 (6.7)	17 (8.1)	6 (13.2)	28
TOTAL	29	35	57	121

Chi-square = 24.33

df = 6

p < 0.001

Body Swelling

	Triph	Monoph	Cont	TOTAL
P	1 (2.2)	2 (2.6)	6 (4.2)	9
M	2 (1.7)	3 (2.0)	2 (3.3)	7
P + M	25 (22.8)	26 (27.5)	44 (44.8)	95
A + N	1 (2.4)	4 (2.9)	5 (4.7)	10
TOTAL	29	35	57	121

Chi-square = 4.10

df = 6

ns

Period type pain

	Triph	Monoph	Cont	TOTAL
P	1 (0.2)	0 (0.3)	0 (0.5)	1
M	17 (16.3)	18 (19.7)	33 (32.0)	68
P + M	9 (8.6)	11 (10.4)	16 (17.0)	36
A + N	2 (3.8)	6 (4.6)	8 (7.5)	16
TOTAL	29	35	57	121

Chi-square = 4.79

df = 6

ns

Sexual interest

	Triph	Monoph	Cont	TOTAL
P	4 (3.0)	1 (3.8)	8 (6.2)	13
M	7 (4.0)	6 (5.0)	4 (8.1)	17
P + M	9 (11.7)	16 (14.6)	25 (23.8)	50
A + N	4 (5.4)	7 (6.7)	12 (10.9)	23
TOTAL	24	30	49	103

Chi-square = 8.78

df = 6

ns

Key :- Triph - Triphasic group , Monoph - Monophasic Group , Cont - Control Group

P - Premenstrual only symptom category
M - Menstrual only symptom category
P + M - Symptoms premenstrually and menstrually
A + N - Noncyclical and Atypical categories
Expected frequencies appear in brackets