A REAPPRAISAL OF THE SYNDROME OF PREMENSTRUAL TENSION AND THE ROLE OF HORMONAL MANIPULATION IN ITS MANAGEMENT

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CONTENTS

ABSTRACT

The cyclical disorder of mental and physical state known as premenstrual tension or the premenstrual syndrome poses a considerable management problem. Clinical trials involving various approaches to therapy have yielded conflicting and largely negative results. There is confusion in the literature about the exact definition and nature of the problem. In the initial chapter of this thesis, the current state of our knowledge of menstrual cycle symptomatology is reviewed, examining the extent to which cyclical variations in mental and physical symptoms should be regarded as normal and the factors influencing their presence and severity. The different methods used for measurement of mood and physical symptoms are described, together with the methods selected for use in this thesis.

The initial study was a prospective assessment of 100 women who presented with problems attributed to premenstrual tension. It revealed that the physical symptoms of breast discomfort and swelling were closely related to menstrual cycle phase in the majority of the women. However the psychological symptoms were confined to the premenstrual phase in only only one third of the group, being present to a variable degree throughout the cycle in the remainder. In almost half the women, they were maximal during menstruation. Those women whose mental symptoms were incompletely relieved following menstruation were significantly more likely to have a history of past psychiatric problems or marital breakdown than those with substantial postmenstrual relief. A classification of menstrual cycle related mood disorders is proposed as a basis for clinical management and further research.

In the next section, the relationship between endogenous and exogenous ovarian steroids, mood and physical symptoms is reviewed. There is no convincing evidence to support an underlying disorder of ovarian function in women with premenstrual tension. Studies with oral contraceptive steroids have shown these to have no adverse effect on mood, except in women with a past history of such problems. Overall, they show a damping down effect on cyclical symptoms, suggesting that ovulation suppression may be an appropriate therapy for premenstrual tension. The second study tests this theory using two synthetic progestogens, norethisterone (NET) and medroxyprogesterone acetate (MPA), each compared with placebo, to suppress ovulation. MPA was more effective than placebo in the relief of breast discomfort but neither progestogen significantly improved the psychological symptoms.

The third study explores the effect of a new synthetic agonist analogue of LHRH, goserelin (Zoladex). Inhibition of pituitary-ovarian activity and menstruation was associated with relief of physical symptoms and significant but not complete, suppression of mental symptoms. However return of ovulatory menstruation after completion of therapy was associated with a prompt recurrence of symptoms, supporting a link between these endocrine changes and mood. In a final pilot study, a new oral opiate antagonist, nalmefene, modified cyclical symptoms without altering plasma ovarian steroid concentrations. The role of endogenous opioids and other central neurotransmittors in the aetiology of the mental symptoms of premenstrual tension is discussed.

DECLARATION

I declare that the work presented in this thesis is entirely my own. The studies described in Chapters 2, 4, 6 and 7 were performed entirely by myself, with the exception of the hormone assays. Any help I received with methodology and planning is referred to in the Acknowledgements section. The study described in chapter 5 was performed in collaboration with others, named in the Acknowledgements section and the protocol was drawn up jointly by Professor Baird and myself. However the responsibility for the administration of the study was my own, as was the recruitment of the subjects and the analysis and presentation of the data.

Signed:

CHAPTER 1

MOOD, PHYSICAL CHANGES AND THE MENSTRUAL CYCLE - LITERATURE REVIEW

1.1 - Introduction

From adolescence to middle age, women experience a regularly recurring monthly sequence of hormonal and physical changes which comprise the menstrual cycle. Menstruation is associated with the potential of fertility as well as the reassurance or disappointment that conception has not occurred. It is also a cause of physical discomfort and inconvenience and, in some women, of morbidity which significantly disrupts their social and professional lives. Negative aspects of the menstrual cycle are not confined to menstruation itself. Physical discomforts such as headaches and pelvic pain are frequently present premenstrually and feelings of anticipation may be associated with the lead up to menstruation with relief once the 'bad time' is over. Mental and physical well-being may also be directly influenced by the hormonal changes which underlie menstrual cyclicity.

It is unclear to what extent these various factors normally influence mood and emotions and the way in which women cope with their day to day lives. Women commonly seek medical help with problems related to the menstrual cycle and in addition to menstrual disorders such as excessive bleeding and pain, the premenstrual phase of the cycle has become specifically associated with a group of adverse mental and physical symptoms known as premenstrual tension or the premenstrual tension syndrome.

It is the problem of premenstrual tension which is the central theme of this thesis. In this introductory chapter, the state of our current knowledge will be reviewed, highlighting the deficiencies in our understanding of the definition of the syndrome, its prevalence, the extent to which cyclical fluctuation in mood and physical symptoms is a normal phenomenon and possible influencing factors. Methods currently used in the assessment and measurement of mood will be discussed. Firstly the endocrine changes underlying menstrual cyclicity will be described.

1.2 - The endocrine control of the menstrual cycle

The menstrual cycle is the consequence of a sequence of endocrine events involving complex interactions between the ovaries, anterior pituitary and hypothalamus. Cyclical production of ovarian steroid hormones is under 'feedback' control by the anterior pituitary and modulated by the hypothalamus. In turn, ovarian steroids exert effects on target organs, in particular the uterus. As a basic understanding of the mechanisms involved is fundamental to many of the topics covered in this thesis, they will be briefly described below. The literature on the subject is extensive and references will be confined to a few recent reviews.

1.2.1 - The ovary and its steroid production

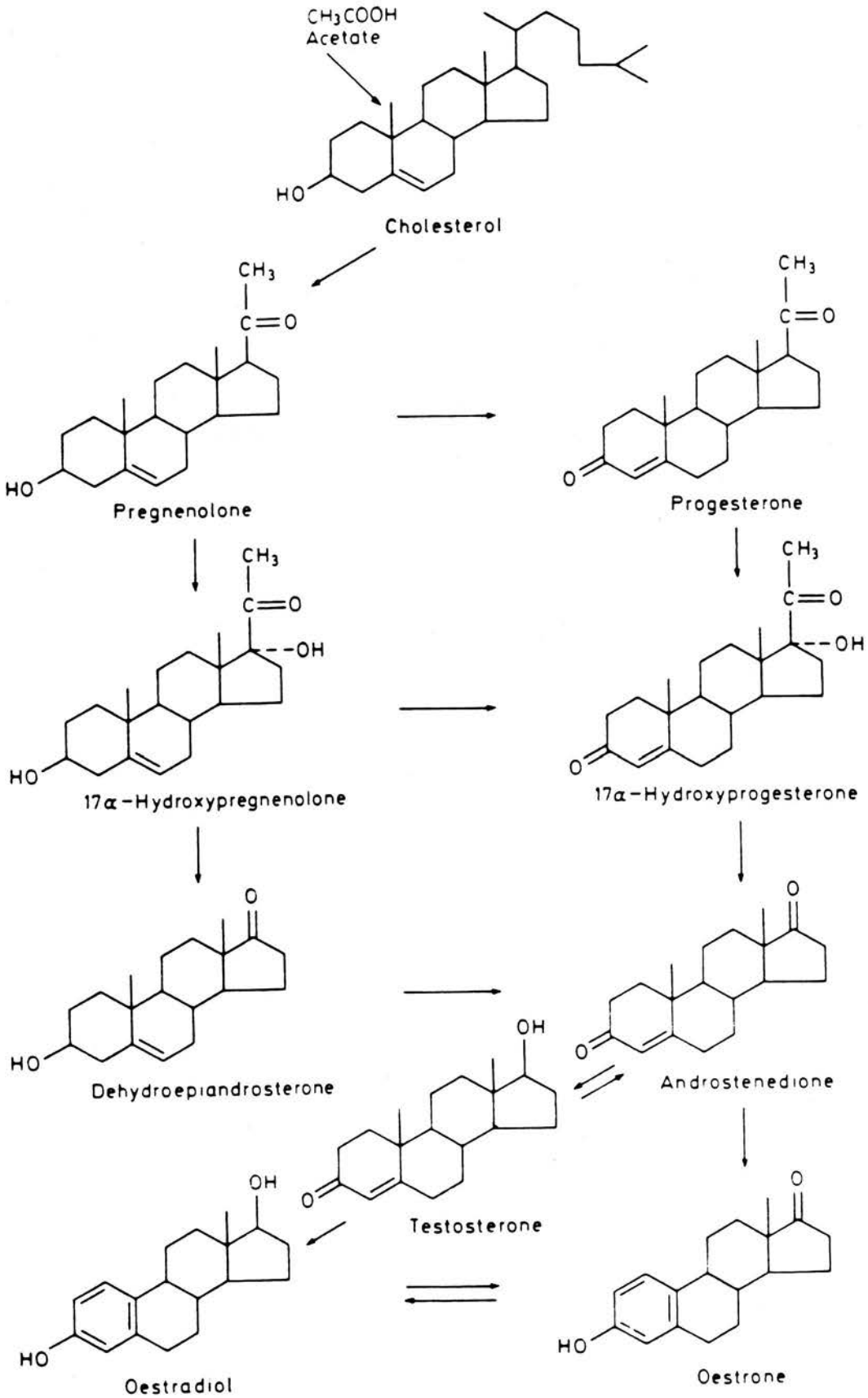
Reviews of ovarian follicular development and its regulation include those by Baird (1983) and Erickson (1986). The ovary contains a very large pool of follicles, several of which are able to respond to rising levels of circulating follicle stimulating hormone (FSH) at the onset of each menstrual cycle, resulting in their rapid growth and

development. Under normal circumstances the growth of a single follicle predominates from about day seven of the cycle, the remainder undergoing atresia (figure 1.2). The developing follicle comprises the oocyte surrounded by granulosa cells which secrete fluid into a central cavity, the antrum, and a compact layer of surrounding stromal cells, the theca interna which is separated from the granulosa cells by a basement membrane.

The principal ovarian steroid secreted by the developing follicle is oestradiol, produced by the granulosa cells from androgenic precursors, mainly androstenedione, synthesised in the thecal cells (figure 1.1). Aromatisation of androgens to oestrogen is stimulated by FSH but androgen production is dependent on the presence of luteinising hormone (LH). FSH stimulated growth of the dominant follicle is accompanied by the development of LH receptors on the granulosa cells in preparation for the preovulatory LH surge. Rapidly rising levels of circulating oestradiol initiates this LH surge by 'positive' feedback, following which the mature follicle ruptures, releasing the oocyte.

Ovulation with extrusion of the oocyte is followed by collapse of the follicle, loss of the basement membrane and invasion of the granulosa layer by blood vessels to produce the so-called corpus luteum. Cellular aspects of corpus luteum function have been reviewed by Hillier & Wickings (1985). Production of the other principal ovarian steroid, progesterone, increases rapidly after ovulation although levels rise slightly prior to this in parallel with the LH surge. Following ovulation, progesterone is secreted by the granulosa-lutein

Figure 1.1 - Structure and biosynthesis of ovarian steroids

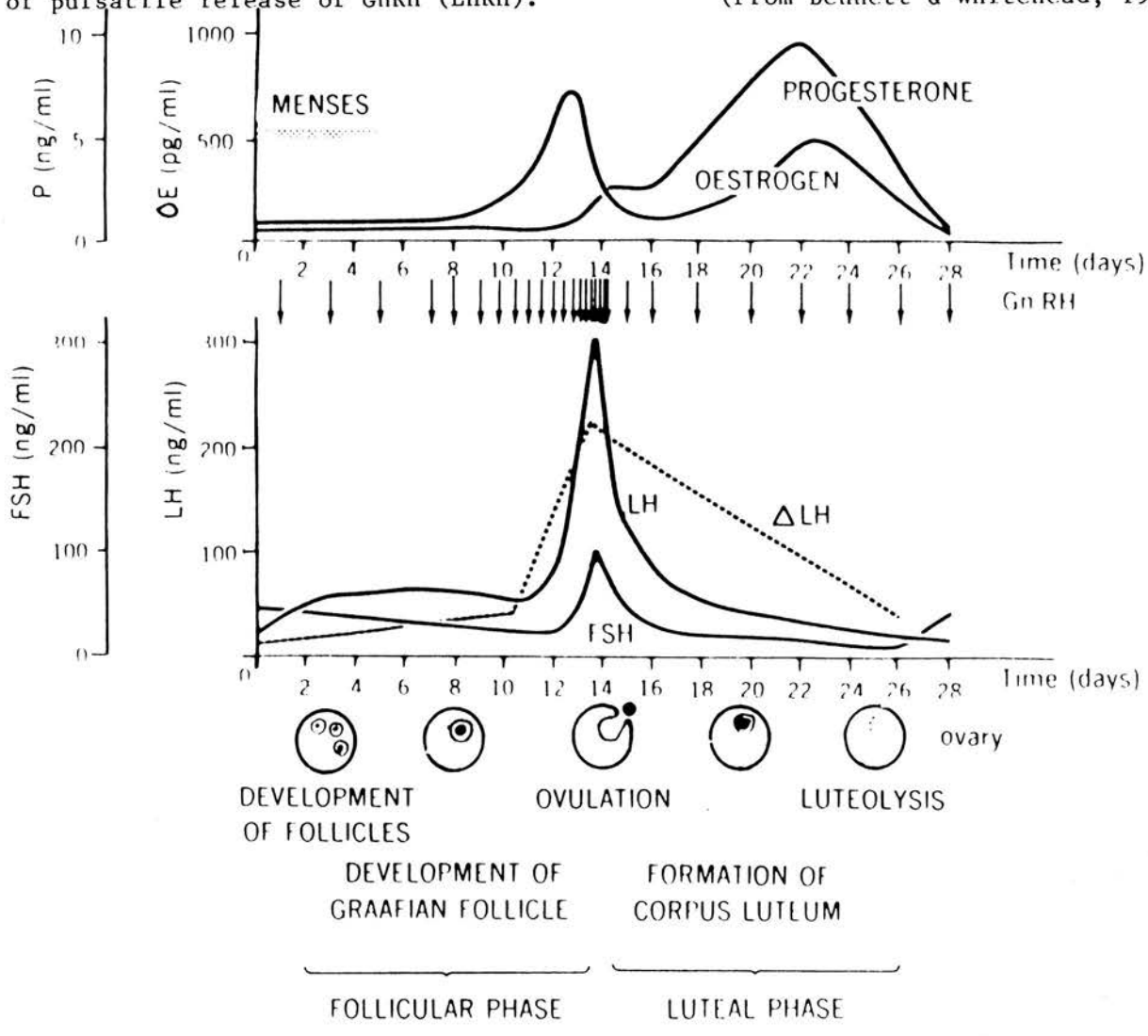


cells of the corpus luteum. This is accompanied by a parallel secondary rise in oestradiol secretion, again derived from androgens produced in theca-lutein cells. Steroid production from the corpus luteum is dependent on the presence of LH and to a lesser extent FSH. If conception does not occur, the corpus luteum regresses after 14 days, with a rapid fall in oestrogen and progesterone and this in turn triggers a rise in pituitary FSH, and to a lesser extent LH secretion by 'negative feedback' to initiate development of a fresh crop of ovarian follicles. The function of the corpus luteum is thought to be largely determined by the events preceding ovulation and various luteal phase 'defects' have been described (Jones, 1976) although their precise cause and significance remain to be determined.

1.2.2 - Hypothalamic control of the menstrual cycle

This subject has been reviewed by Bennett & Whitehead (1983) and Reichlin (1985). Gonadotrophin secretion and release is dependent on stimulation by a hypothalamic releasing factor, luteinising hormone releasing hormone (LHRH) also called gonadotrophin releasing hormone (GnRH) which is responsible for the initiation of pituitary-ovarian activity at puberty and exerts a modulating effect throughout reproductive life. This hypothalamic neurohormone is released into the hypophyseal portal vessels from neurosecretory cells which terminate in the median eminence (tuberoinfundibular system). Release of LHRH is characteristically pulsatile, the rate and amplitude of the pulses in part determining the pituitary response. Pituitary secretion of FSH and LH is also pulsatile, their relative proportions and pulsatile pattern varying throughout the menstrual cycle. Pulse frequency and amplitude is characteristically lowest during the luteal

Figure 1.2 - Hormonal and ovarian changes throughout the menstrual cycle. Arrows represent relative frequency of pulsatile release of GnRH (LHRH). (From Bennett & Whitehead, 1983).



phase, both progressively rising during the follicular phase to reach a maximum prior to ovulation.

The feedback effects of circulating ovarian steroids are exerted at the level of both the anterior pituitary and the hypothalamus, modulating the response of the anterior pituitary to LHRH as well as altering the frequency and amplitude of LHRH pulses. The rapidly rising oestrogen levels in the late follicular phase stimulate frequent high amplitude pulses of LHRH while increasing the sensitivity of the anterior pituitary to this stimulus, resulting in the initiation of the LH surge (figure 1.2). Falling levels in the late luteal phase result in low amplitude pulses which favour FSH secretion. Selective suppression of the latter in favour of LH as the follicular phase advances may be in part due to the effect of inhibin, a gonadal peptide secreted by the developing follicle although the exact mechanisms remain to be clarified.

Various hypothalamic neurotransmittors, in particular dopamine and noradrenaline may be involved as mediators in the control of LHRH secretion. In addition, direct neural regulation may play an important role via connections with the mid brain, forebrain and limbic system. This is important in various animal species where environmental factors, for example light, control patterns of oestrus. Stress is known to influence ovarian cyclicity in humans and may act via noradrenergic neurones arising from the locus coeruleus of the mid brain. The possible role of endogenous opioid peptides in the modulation of hypothalamic LHRH release is discussed in chapter 7.

1.2.3 - Menstruation and its control

The histological changes which take place in the endometrium in relation to changing steroid levels are well known although the mechanisms underlying menstrual bleeding and its disorders have yet to be fully clarified (Abel, 1985; Smith et al, 1985). Withdrawal of steroids in the late luteal phase of the cycle results in shrinkage of the endometrium with increased coiling of its spiral arterioles. Resulting vascular stasis is then followed by a period of intense vasoconstriction and finally by relaxation and active bleeding. It has been proposed that prostaglandins produced locally are responsible for the initiation and control of menstruation. Endometrium produces mainly PGF_{2a} and PGE_2 although the former predominates in secretory endometrium, being a powerful vasoconstrictor while the latter acts as a vasodilator. Release of arachadonic acid, the main precursor of prostaglandins occurs during the phase of vascular stasis and tissue ischaemia. Resulting synthesis and release of PGF_{2a} may be the factor responsible for the vasoconstriction mentioned above and also for the more intense myometrial contractions which characteristically occur at the onset of menstruation (spasmodic dysmenorrhoea). Prostacyclin (PGI_2) is synthesised only by myometrium but acts as a vasodilator and prevents platelet aggregation and it is possible that it is also involved in the control of menstrual blood loss, acting together with PGE_2 to counterbalance the vasoconstrictive effect of PGF_{2a}.

1.2.4 - Hormonal manipulation of the cycle

Understanding of the control of the menstrual cycle has led to the development of synthetic steroids for use in contraception and for management of menstrual and other gynaecological disorders.

Oestrogen-progestogen combinations or high doses of progestogen alone will inhibit follicular development and ovulation through negative feedback. More recently, synthetic analogues of LHRH have been used to suppress ovarian cyclicity by inhibition of gonadotrophin secretion (see chapter 5).

1.2.5 - Steroid hormones and the central nervous system

Oestrogens, like testosterone, are transported in the circulation bound to sex-hormone binding globulin (SHBG) (Anderson, 1974), while progesterone binds to cortisol-binding globulin. Only the unbound steroid is biologically active and an equilibrium exists between free and bound steroid. Steroid hormones are lipid soluble and readily cross the blood-brain barrier where they act via specific receptors in the central nervous system. In addition to their feedback control of gonadotrophin and LHRH secretion they influence sexual differentiation and play an important role in the control of sexual behaviour in animal species. Observations of mood change in relation to the menstrual cycle, childbirth, the menopause and oral contraceptive therapy in women suggest that ovarian steroids have direct behavioural effects although interpretation is made difficult because of the profound influence of learning and social conditioning. Possible endocrine mechanisms underlying disorders of mood related to the menstrual cycle and the response to hormonal manipulation will be considered in detail in later chapters of this thesis. Firstly the nature and prevalence of such problems will be reviewed, followed by a brief consideration of some of the physiological changes associated with the menstrual cycle and their relevance to symptomatology.

1.3 - The definition of premenstrual tension

The concept of psychological morbidity related to the menstrual cycle is not new but a distinct pathological condition described as 'premenstrual tension' was first described in the medical literature by Frank in 1931. He described fifteen women in whom 'grave systemic disorders manifest themselves predominantly during the premenstrual period'. Dramatic relief was seen within a few hours of the onset of the menstrual flow. Israel (1938) described a further 14 cases, also emphasising 'the sensation of indescribable tension, marked physical unrest and constant irritability'. Both these authors referred to the minor but unpleasant symptoms experienced by many women prior to menstruation but made a clear distinction between these and the much more extreme personality changes exhibited by those who suffered symptoms of premenstrual tension.

Since then, the concept of premenstrual tension has been widened to encompass a large cluster of adverse mental and physical symptoms covered by the term 'premenstrual syndrome'. Greene & Dalton (1953) published the first report based on British women. In an analysis of 84 cases, the commonest symptom was headache followed in decreasing frequency by skin and mucosal changes, arthralgia, exacerbations of asthma and epilepsy, nausea, irritability and depression, the latter present in only two percent of the women. This is a rather different picture from the descriptions of tension, depression, irritability, abdominal bloating, nausea, appetite changes and breast discomfort which have been characteristic of most of the later reports (e.g. Rees, 1953; Dalton, 1977; Sutherland & Stewart, 1965; Coppen & Kessel, 1963; Sampson & Jenner, 1977). Moos (1968) devised a list of 47

symptoms which he tested out on 839 healthy subjects, deriving eight separate intercorrelated symptom clusters by factor analysis. These symptom clusters, and the 'Menstrual Distress Questionnaire' which he devised on the basis of these results have been used extensively in subsequent research into the subject.

Most recent authors agree that it is the relationship of the symptoms to menstruation, rather than the symptoms themselves, which are critical to the diagnosis of the premenstrual syndrome. However, beyond this there is lack of consensus. Dalton (1977) who has written extensively on the subject, but performed no controlled studies, has described three symptom patterns. Symptoms may be present only premenstrually or may build up gradually from the time of ovulation. In a third pattern, symptoms may be present around the time of ovulation and then again premenstrually. In all three groups, symptom relief should occur during menstruation, with a symptom-free spell of at least a week thereafter. Reid & Yen (1981) agree with her definition but recognise a fourth pattern where symptoms extend into menstruation, gradually resolving towards its end. Kerr et al (1980) state that subjects should be symptom free within 48 hours of the onset of menstruation and O'Brien (1982) also maintains that symptoms around ovulation and continuing into the early part of menstruation are not indicative of the premenstrual syndrome. Dennerstein et al (1984) distinguish between women with a discrete premenstrual syndrome, relieved during menstruation and followed by a completely symptom-free week and those with symptoms present throughout the cycle, associated with diagnosable psychiatric problems. She

identifies the latter group as suffering from 'menstrual distress'; a term also used by Dalton (1977).

Sampson & Prescott (1981) favour a looser definition of "changes in mood, behaviour and physical symptoms in relation to the menstrual cycle, usually with an increase in intensity premenstrually and diminution in intensity with the onset of menstruation". Magos & Studd (1984) also believe that a distinction cannot be made between symptoms confined to the premenstrual phase and those which are an exacerbation of chronic problems present throughout the cycle, as there is no evidence that the two have a different aetiology. However, "a distinction should be made from premenstrual symptoms that are not considered abnormal or distressing and are experienced by most women".

Halbreich et al (1985) also prefer the concept of 'premenstrual change' and define this as cyclic recurrent change in intensity of symptoms from the second week of the menstrual cycle compared with the peak intensity during the luteal phase. However they define a minimal level of symptomatology which should exist postmenstrually. Rubinow & Roy Byrne (1984) use the term 'menstrually-related mood disorder' and are critical of past approaches to the problem, in particular of the methods used for their evaluation.

1.4 - The prevalence of premenstrual complaints

Against this background of confusion about the basic definition of the problem, a few workers have attempted to quantify its extent by surveys of the prevalence of premenstrual problems in various

populations of women of reproductive age. One of the earliest was reported by Pennington (1957). Her sample of 1000 American women was largely composed of high school and college graduates. 95% had at some time experienced menstrually-related symptoms, most commonly dysmenorrhoea, although 72% had experienced mixed psychological and somatic symptoms with 'nervousness' and irritability in around 40%. In her paper, Pennington made no distinction between symptoms which were largely premenstrual and those related to the menstrual phase of the cycle while Sutherland & Stewart (1965) asking specifically about premenstrual symptoms, surveyed 150 students and student nurses in Glasgow. They found that 59% reported premenstrual irritability, 53% premenstrual depression and 63% a sensation of 'swelling', with a triad of all three in 39%.

Both the latter studies were based on biased population groups and make no attempt to distinguish between mild and severe symptoms. Coppen & Kessel (1963) overcame both these problems in their study of a random sample of 500 women from 10 English general practices. The women were asked to rate each symptom retrospectively on a simple four-point scale. Moderately severe symptoms of irritability, tension and/or depression were reported by 20% of the women with severe symptoms in around 9%, although swelling of any degree was reported by 72% of the sample. These symptoms were reported by the women to be present premenstrually and relieved during menstruation. They were distinct from menstrual dysmenorrhoea, present to a moderate degree in one third of the women although an association between the two complaints was apparent.

More recently, two large studies have been based in Scandinavia. Widholm (1985) surveyed 5000 adolescents and their mothers by questionnaire and reported that 68% of 5000 daughters had experienced premenstrual tension, with a prevalence of 75% among 1400 mothers. He found an association between premenstrual tension and dysmenorrhoea in 42% of the daughters and 62% of the mothers with a highly significant association between these complaints in mother-daughter pairs, suggesting either a genetic influence or an effect of familial conditioning. He also surveyed 865 women from three different professional groups and found that 88% overall reported premenstrual tension, with no differences between the groups. Around 40% of each group also complained of dysmenorrhoea. The severity of the symptoms was not assessed but their mean duration was 4 days.

Andersch et al (1986) surveyed a random sample of 1000 women in the Swedish city of Goteborg, concentrating on premenstrual complaints and using a descriptive self-rating scale in an attempt to assess symptom severity. Again symptom prevalence was high, with 92% reporting at least one premenstrual change and 72% a combination of mental symptoms and body swelling. With the exception of anxiety, symptoms were not age-related. Only 3% classified their symptoms as severe and 11% expressed a wish to seek medical help.

This extremely high prevalence of premenstrual problems suggests that the surveys are detecting a normal phenomenon, with severe problems in no more than 10 percent of women. This raises the question of whether we are seeing a normally distributed spectrum of problems, or whether there is in fact a discrete pathological entity with a separate

causation. However, there are methodological criticisms that are relevant to the interpretation of the results of these surveys. Firstly, the premenstrual phase of the cycle was being studied in isolation from the remainder of the cycle with assumptions that symptoms were confined to this phase. Moos (1969) found that women who had high premenstrual scores on his menstrual distress questionnaire also tended to score highly during other phases of the cycle. The association between premenstrual tension and menstrual dysmenorrhoea found in some of these studies raises questions about the extent to which they may be inter-related although they are traditionally regarded as being entirely separate. Secondly, the conclusions of the above surveys were based entirely on the results of single questionnaires. As discussed later (section 1.9.3), such results can be misleading. Detailed prospective studies of large numbers of randomly selected women pose considerable methodological difficulties but a number of small detailed studies have been reported and will be discussed below.

1.5 - Normal cyclical variation in mental and physical well-being

There have been a number of prospective studies of menstrual cycle symptomatology in groups of volunteer subjects. Dennerstein and Burrows (1979) and Sanders (1981) have reviewed 33 such studies in detail, 16 of which were examined by both authors. The numbers of subjects ranged from 2 to 172 (median 20) and the majority (28) were evaluated over one or two cycles. Only 13 of the studies were based on daily self-assessment, the remainder using evaluations made at intervals during the cycle. The methods used varied considerably (see section 1.9), including the Menstrual Distress Questionnaire, mood

Table 1.1 - SUMMARY OF PROSPECTIVE STUDIES OF CYCLICAL CHANGE

(From Dennerstein & Burrows, 1979; Sanders, 1981)

Studies reviewed		32
Median number of subjects		20 (range 5-172)
Nature of assessment:		
Daily rating of mood/symptoms	13	
Selected days only	13	
Objective performance tests	5	
Headache only	1	
RESULTS		
a) Mood:		
No overall change		4/26
Adverse premenstrual change		22/26
Adverse menstrual change		6/19
Adverse follicular phase change		2/20
Adverse midcycle change		2/26
Positive midcycle change		11/26
b) Physical symptoms:		
No overall change		0/9
Premenstrual exacerbation		8/9
Menstrual exacerbation		8/9
c) Objective performance:		
No overall change		4/5
Improved during luteal phase		1/5

adjective check lists, verbal anxiety scales, content analysis of speech, psychoanalysis of dreams and various objective performance tests. Thus the results may not be strictly comparable. Rather than repeat in detail the results of these studies which were very clearly and concisely summarised and tabulated by both the above authors, their overall conclusions are shown in table 1.1. Excluding the study with only two subjects, mood was evaluated in 26 of the 32 studies and only four studies demonstrated no cyclical changes. Adverse changes were identified premenstrually in 22 of the studies and during menstruation in six although menstrual evaluation was not invariably performed. Adverse symptoms at mid cycle were only reported by two authors but a peak in positive moods or a significant trough in negative symptoms was reported by 11 groups; positive symptoms including elation, euphoria, assertiveness and competitiveness. Two groups reported negative symptom peaks during the follicular phase.

Of the 9 studies which included assessment of physical symptoms, including pain, headache, breast discomfort and swelling, the majority found symptoms to peak premenstrually and during menstruation (table 1). Five additional studies were based entirely on objective performance tests, evaluating either motor or intellectual performance or a combination of both. Four of the five showed no cyclical variations and the fifth paradoxically found reaction and calculation time to be lowest during the luteal phase compared with other cycle phases. A recent study (Posthuma et al, 1987) identified no phase-related differences in motor performance in a group of carefully selected control subjects, while women screened for PMT showed some

premenstrual functional impairment in only one of the four tests (the one demanding finest coordination and balance).

1.6 - Sources of bias in menstrual cycle research

The results of these studies confirm the presence of cyclical variation in physical symptoms, particularly swelling and breast discomfort. There is also evidence for cyclical changes in mood, although not all the authors have confirmed this. The reasons for the discrepancies may in part be methodological, as many different methods of assessment have been used. In addition, there are differences in the subjects selected for study. Common recruits are students, particularly psychology students or student nurses, with bias towards the younger age groups. The subjects have to be willing to comply with the demands of the protocol, which are fairly intensive. There are other sources of bias, for example excluding women on oral contraceptives or screening out those with psychological problems. The study reported by Abplanalp et al (1979) positively screened for 'normality' and found no significant cyclical differences apart from a menstrual peak in anxiety and tension. On the other hand, studies based on volunteers may tend to attract those with an interest in menstrual cycle problems, perhaps because they themselves experience symptoms, as shown by the results of Sanders et al (1983) who recruited subjects for 'a research project on the menstrual cycle'. Of 44 volunteers, 21 were found to have significant changes in mood and physical symptoms. Some data on so-called normal controls was presented by Dennerstein (personal communication, 1985). Daily mood profiles from women who volunteered because of absence of premenstrual

problems showed a marked peak of negative affect during the postmenstrual phase of the cycle.

Two interesting studies have emphasised other sources of bias in the assessment of menstrual cycle symptoms. Ruble (1977) studied two groups of women who were told that the date of menstruation could be predicted from the result of an EEG and were thereby deliberately misled about the time when their next period was due. Ratings of premenstrual-type symptoms were significantly higher in the group who were told menstruation was due within the next couple of days, compared with those who were led to believe it was due in 7 to 10 days. The actual timing of menstruation did not significantly differ between the two groups. In a recent study, Olasov & Jackson (1987) compared daily symptom ratings over 40 days in a group of psychology students who had been shown a pre-recorded lecture emphasising the negative aspects of menstruation and mood change, with a group shown a lecture stating the case against any relationship between mood and the menstrual cycle. There were significant differences between the results; the group who saw the negative aspects lecture having significantly higher negative symptom scores both premenstrually and menstrually.

Studies in which the subjects are blind to the true objective of the investigation may be more likely to yield meaningful results than those in which the subjects are fully aware. Those of Wilcoxon et al (1976) and Slade (1984) concealed the purpose of the study and both confirmed cyclical variations in physical but not in mental symptom,

any apparent relationship of the latter to menstrual cycle phase being accounted for in Wilcoxon's study by coincidental stressful events.

Another group in whom awareness of menstrual cycle phase may be absent are women who have undergone hysterectomy with conservation of the ovaries. Backstrom et al (1981) monitored seven such women by daily visual analogue scales for one month prior to and two months following hysterectomy. All had complained of cyclical symptoms prior to surgery but five of the seven were unaware of such changes afterwards. However daily ratings revealed continuing 'premenstrual symptoms', although significantly reduced in magnitude compared with preoperative records. Beaumont et al (1975) studied women who had undergone hysterectomy in the past, also monitoring symptoms and steroid profiles daily. Here the differences did not reach significance but there was a trend towards higher scores in the late luteal phase. These women had been selected at random and their past history regarding cyclical problems was not stated. However such results do tend to throw some doubt on the theory that cycle-related symptoms are purely a result of expectation and conditioning.

The results of the above studies emphasise the complexity of the relationship between mood and the menstrual cycle. They also raise the question of the extent to which conditioning, personality and environmental factors influence such changes, and in particular, the tendency to complain about them. Some authors have examined these areas and they will be discussed in the next section.

1.7 - Premenstrual change, personality and psychiatric disorder

In their large, randomised study of women selected from various general practices, Coppen & Kessel (1963) investigated not only the presence of cycle-related symptoms but also personality, as assessed by the Maudsley Personality Inventory. They found the reporting of premenstrual psychological symptoms and also headaches and swelling to be significantly correlated with a high score for neuroticism. The only symptom unrelated to neuroticism was menstrual dysmenorrhoea. James & Pollitt (1974) also examined the relationship between premenstrual symptoms and personality, but in women recruited from a psychiatric clinic. Their finding of a significant correlation between premenstrual symptoms and personality extremes of obscessionality or hysteria may thus be biased by the population under study. Clare (1979) examined women selected at random from general practice, using the Moos Menstrual Distress questionnaire (MDQ) to assess premenstrual complaints and the General Health Questionnaire (GHQ) for psychiatric morbidity. Seventy five percent of the women scored positively on the MDQ, and had an even chance of a positive score on the GHQ. However, 87% of those scoring positively on the GHQ had a positive MDQ score and reported significantly more premenstrual symptoms, especially depression, irritability, tension, fatigue and anxiety than the GHQ negative women. Breast symptoms did not differ between the two groups. He also studied 170 women attending a premenstrual tension clinic and found a similar distribution of GHQ scores as in the normal population sample.

This relationship between psychiatric morbidity and premenstrual complaints has been demonstrated by other authors. Coppen (1965)

compared groups of patients attending a psychiatric clinic, with general practice controls and found a raised prevalence of menstrual problems in general among those classified as suffering from neurosis, with high scores for dysmenorrhoea, dyspareunia, and premenstrual problems. There was however a reduced prevalence among schizophrenics. Of those with affective disorders, only those of a depressive type were associated with a raised prevalence of menstrual problems. Other authors have also found a relationship between premenstrual problems and affective disorders in general (Wetzel et al, 1975; Endicott et al, 1981) to the extent that these authors use the term 'premenstrual affective disorder'. As assessments were interview-based, these studies may merely be showing a premenstrual or indeed menstrual, exacerbation of the underlying affective disorder as no information is available about the extent to which they were present during the remainder of the cycle. With the exception of acute schizophrenic crises (Abramowitz et al, 1982), an excess of acute psychiatric admissions has been shown to occur premenstrually (Glass et al, 1971; Diamond et al, 1976; Abramowitz et al, 1982) and menstrually (Janowsky et al, 1979; Abramowitz et al, 1982). However, a recent report of the timing of suicide attempts (Fourestie et al, 1986), related these to the menstrual phase of the cycle with the lowest incidence during the luteal phase.

These observations about the relationship between cycle phase and psychiatric disorders are of interest but assumptions cannot be made about women who complain of premenstrual symptoms in general. Like Clare (1979), Rees (1953) had found that many women reporting marked symptoms of premenstrual tension were of stable personality while many

severely neurotic women had no such complaints. However, in women classified as neurotic, a correlation was found between the degree of premenstrual tension and the severity of the neurosis. Wendestam (1980) also found a range of personality types in a study of 40 women diagnosed as suffering from the premenstrual syndrome. He compared them with a group selected for absence of premenstrual complaints, with a 'normal population' group and with a group of women with clinically diagnosed neurosis. The neuroticism scores of the women classified as sufferers from the premenstrual syndrome were similar in distribution to the normal population but higher than the group selected for absence of premenstrual symptoms, who were younger and less parous than the PMS group.

Not only personality but also social conditioning may alter perception of menstrual cycle changes, as mentioned in section 1.6. In a sample of 255 women, Paulson (1961) found those who had high scores for premenstrual tension, had more disturbed family relationships, psychosexual problems and negative attitudes to the menarche and menstruation. However 72% of the group as a whole were unmarried and thus it may be a biased population sample. Wood et al (1969b) found women with premenstrual complaints to have a higher incidence of marital difficulties, dissatisfaction with work and psychosexual problems compared with non-complainers, although the women on whom these conclusions were based were a self-selected sample who attended a health screening clinic (Wood et al, 1969a). Watts et al (1980) compared 25 women who had been carefully selected for the presence of premenstrual symptoms with 23 control subjects and found significantly higher neuroticism scores among the former group, as assessed by the

Eysenck Personality Inventory. They also showed more negative attitudes to sex, masturbation and the genital organs. Attitudes to menstruation, childbearing and child rearing did not differ between the two groups.

Despite the evidence from these studies, not all authors would agree that there is an association between personality, psychiatric morbidity and premenstrual and menstrual problems. Reid & Yen (1981) feel there is little evidence to support psychosomatic dysfunction in women with premenstrual tension. However, they use strict criteria for the diagnosis of the latter (section 1.3). Gannon (1981) draws attention to the similarities between items on menstrual distress questionnaires and standardised personality tests. In other words, symptoms which are truly menstrual cycle-related may be scoring on the personality inventories. The converse argument is of course true, as a neurotic individual is likely to give positive answers for many of the adverse menstrual symptoms. This emphasises the importance of prospective daily assessments before reaching conclusions about the relationship of symptoms to menstrual cycle phase.

The overall impression from this extensive literature is that the majority of women report adverse symptoms prior to or during menstruation (e.g. results of surveys by Pennington (1957) and Andersch (1986)). However, most women do not regard these changes as abnormal and it is apparent that the reported intensity of such symptoms or the tendency to complain about them is influenced by a number of factors, in particular social conditioning and personality. It is still not clear whether women classified in the literature as

'premenstrual tension' or 'premenstrual syndrome' sufferers do in fact suffer from a discrete disorder or whether their symptoms should be regarded as a pathologically exaggerated response to normal cyclical changes. The attempts to find an underlying endocrinological cause are covered in the next sections of this chapter and in chapter 3.

1.8 - Physiological changes during the menstrual cycle and their relevance to symptomatology

1.8.1 - Glucose tolerance and the menstrual cycle

The frequent reports of food cravings and other symptoms attributed to hypoglycaemia in association with adverse premenstrual symptoms led to the hypothesis that the symptom complex is attributable to a premenstrual impairment of glucose tolerance (Morton, 1950; Morton et al, 1953). The same author reported increased glucose tolerance in women tested premenstrually and during menstruation but did not distinguish between those who were symptomatic and asymptomatic. Later studies have produced inconsistent results, for example Jarrett & Graver (1968) found cycle related differences in oral glucose tolerance while Spellacy et al (1967) reported no such differences with intravenous tests. These authors did not select women on the basis of adverse symptoms. In a more recent study comparing symptomatic women with normal controls, Reid et al (1986) found no difference in oral glucose tolerance between the two groups or between the follicular and luteal phases. However the group complaining of premenstrual symptoms including 'hypoglycaemia' reported hypoglycaemic symptoms during the course of the OGGT in both cycle phases, although

their blood sugar levels remained well within the normal range throughout the course of the tests! The same authors point out that many of the earlier studies did not adequately control for dietary alterations which may have been related to the menstrual cycle, for example binge eating indulged in by many women premenstrually. The physiological changes, if any, underlying the latter problem remain unexplained but such eating habits may contribute to sensations of abdominal fullness and bloating and may in part explain the poor correlation between symptoms frequently attributed to fluid retention and objective assessment of the latter (see below).

1.8.2 - Fluid and electrolyte balance

The role of abnormalities of fluid and electrolyte metabolism in the aetiology of premenstrual symptomatology remains a subject of controversy. Swelling, peripheral oedema, abdominal bloating and generalised oedema have all been reported in association with other clinical features of severe premenstrual tension (Frank, 1931; Sweeney, 1934; Rees, 1953), leading to the assumption that fluid retention was the major aetiological factor (Sweeney, 1934; Greenhill & Freed, 1941; Bickers, 1952). Similar symptoms are also frequently reported by normal women during the premenstrual phase of the cycle (see section 1.5). A number of studies based on daily weighing of volunteer subjects have demonstrated net weight gain premenstrually, interpreted as indicative of fluid retention (Thorn et al, 1938; Abramson & Torghele, 1961; Watson & Robinson, 1965). The latter two authors also reported a small peak at the time of ovulation, when adverse symptoms are characteristically minimal (section 1.5). A link between the degree of premenstrual weight gain and the magnitude of

adverse premenstrual symptoms was reported by Abramson & Torghele (1961) while others have failed to find a relationship between weight gain and overall symptomatology (Thorn et al (1938); Appleby, 1960; Bruce & Russell, 1962; Reeves et al, 1971). Indeed, Golub et al (1965) were unable to demonstrate any premenstrual weight gain in a group of college girls, many of whom complained of premenstrual swelling. One source of confusion in the literature is the use of terms such as swelling, oedema, bloating, and water retention to describe what are entirely subjective sensations of discomfort. The assumption that they are indicative of 'fluid retention' may frequently be erroneous. As mentioned above, abdominal bloating, which is a very common premenstrual complaint, may be attributable to other factors.

Detailed studies of fluid and electrolyte balance have also yielded conflicting results. Bruce & Russell (1962) reported premenstrual retention of sodium and water in both control and symptomatic subjects while Klein & Carey (1957), Michelakis et al (1971) and O'Brien et al (1980) failed to demonstrate significant cycle related differences. In the studies of Andersch et al (1978), no overall differences in total body water were apparent between cycle phases in control or symptomatic subjects although late luteal phase water/potassium ratio was significantly elevated in the symptomatic women, suggesting a shift of fluid from the intravascular to the extravascular compartments. Observations of changes in capillary permeability during the menstrual cycle were first made by Petersen & Milles (1926) and more recently Wong et al (1972) reported significant changes in capillary filtration coefficient during the luteal phase in

symptomatic compared with non symptomatic women, indicating a transfer of fluid from intravascular to extravascular compartment in the former group. Jones et al (1966) also demonstrated increased permeability of the capillary walls to proteins during the luteal phase of the cycle in a group of volunteer women but with no correlation between symptom severity and degree of capillary permeability.

In summary, these studies suggest that changes in fluid and electrolyte balance occur during the menstrual cycle with associated fluid shifts between vascular compartments and perhaps a small net premenstrual fluid gain. However the relationship between these changes and premenstrual symptomatology is unclear and does not provide a convincing explanation for their diverse nature, even in cases where symptoms possibly attributable to fluid retention predominate.

1.8.3 - Effectiveness of diuretic therapy

In view of the confusion about fluid and electrolyte changes and menstrual cycle symptoms, it is not surprising that studies of the use of diuretics have also been inconclusive. The subject has been reviewed by Reid & Yen (1981) and O'Brien (1982). Only three out of six placebo-controlled studies have shown a significant benefit from active therapy although criteria for inclusion were not uniform. One of these positive studies selected only women who demonstrated a net premenstrual weight gain prior to therapy (Werch & Kane, 1976). Another used the aldosterone antagonist, spironolactone and it was postulated that the benefit was due to the mild diuretic effect of aldosterone antagonism (O'Brien et al (1979), a reduction in

premenstrual weight gain being observed in treated cycles. Both these studies showed a significant improvement in psychological symptoms in addition to those attributed to fluid retention.

1.8.4 - Renin-angiotensin-aldosterone system

It is of interest to examine the possible physiological basis for any changes in the distribution of fluid and electrolytes during the menstrual cycle. Progesterone itself is known to have a natriuretic effect (Landau & Lugibihl, 1958) but this is compensated for by a rise in plasma renin activity and angiotensin II and aldosterone concentrations (Oparil et al, 1975). These changes are observed both during normal ovulatory cycles (Sundsfjord & Aakvaag, 1970; Michelakis et al, 1975) and following an intramuscular bolus of progesterone (Oelkers et al, 1974) but do not appear to occur in the absence of ovulation (Michelakis et al, 1975). There is no evidence that aldosterone levels differ between symptomatic and asymptomatic women (O'Brien et al, 1980; Munday et al, 1981) and the mechanisms underlying the increased capillary permeability described above have not been clarified. While alterations in renin, angiotensin and aldosterone concentrations may explain some of the normal physiological changes of the cycle, there is no current evidence to support or refute an abnormality of the renin-angiotensin system in the aetiology of more severe degrees of cyclical swelling and the mental changes experienced by symptomatic women.

1.8.5. - Cyclical oedema

The problem of severe premenstrual swelling is sometimes confused in practice with a similar but separate clinical entity which also occurs

in women and is known as cyclical oedema (Thorn, 1957). In its clinical manifestations, it is also often associated with headache, increased irritability and other mental changes but is characterised by the absence of any obvious systemic abnormality and by being unrelated to menstrual cycle phase. Most authors stipulate a minimal weight gain which must be recorded in order to make the diagnosis (Edwards & Bayliss, 1976) although women with complaints of severe abdominal distension in the absence of overall weight gain have been described (Thorn, 1968), the latter being reminiscent of many patients complaining of premenstrual swelling.

The problem has been attributed to a shift of albumin from the intravascular compartment to extravascular tissues because of increased capillary permeability, combined with a compensatory reduction in renal fluid and electrolyte excretion in the upright position (Edwards & Bayliss, 1976). Reduced urinary dopamine excretion in women with idiopathic oedema compared with normal controls has been reported by Kuchel et al (1977) raising the possibility that both cyclical oedema and premenstrual swelling may be a consequence of an abnormality in renal dopaminergic function. Renal dopamine is an important natriuretic agent although its precise role in homeostasis is uncertain (Lee, 1986) and preliminary studies indicated no alteration in renal excretion of dopamine during the normal menstrual cycle in healthy volunteer women (Perkins et al, 1981). Young et al (1983) provide evidence for an underlying hypothalamic disturbance in cyclical oedema by virtue of differences in response to TRH and LHRH between patients and control subjects but

similar studies have not been done in women with severe premenstrual symptomatology.

A link between stress, psychological disturbance, mental symptoms and cyclical oedema is recognised (Thorn, 1968; Edwards & Bayliss, 1976; Pelosi et al, 1986), giving further support to the theory that its aetiology may be similar to that of some cases of premenstrual tension associated with swelling and oedema. However, at present the underlying pathological mechanisms remain obscure.

1.8.6 - Prolactin and the use of bromocriptine

For a time, it was postulated that an abnormality of prolactin secretion may underlie premenstrual symptomatology. The reasons for this were twofold. Firstly, reduced levels of progesterone in the luteal phase in symptomatic women were reported by several authors (see section 3.2) and prolactin is known to inhibit production of progesterone by the corpus luteum (McNatty et al, 1974). Secondly, it was believed that prolactin played a crucial role in salt and water balance (Horrobin et al, 1971; Buckman et al, 1973). However this was later discredited by showing that the ovine prolactin which had been given to healthy volunteers was contaminated by vasopressin (Bond et al, 1976). Also, elevations of endogenous prolactin stimulated by TRH failed to alter renal salt and water excretion (Baumann & Loriaux, 1976). Studies of circulating prolactin throughout the menstrual cycle have also yielded contrasting results, with some studies showing no change (McNeilly & Chard, 1974) while others identified a peak at ovulation and higher concentrations during the luteal phase (Franchimont et al, 1976; Vekemans et al, 1977). However conclusions

based on small numbers of blood samples may be misleading because of the episodic nature of prolactin secretion with a marked diurnal variation (Ehara et al, 1973). Thus it is not surprising that conflicting results were obtained in women complaining of cyclical symptoms. Halbreich et al (1976) reported a significant elevation of serum prolactin concentrations in symptomatic women compared with normal controls although they could find no correlation with symptom scores. Later reports (Anderson et al, 1977; Andersch et al, 1979) failed to demonstrate a difference. Circulating prolactin has been shown to rise in response to stress (Noel et al, 1972) and this may account in part for the discrepancy between these studies.

Several placebo-controlled trials of bromocriptine therapy have been conducted, again with inconsistent results. The one demonstrating greatest benefit studied women presenting with infertility rather than with a primary premenstrual tension problem (Benedek-Jaszmann & Hearn-Sturtevant, 1976) permitting only limited conclusions to be drawn. Harrison et al (1976) reported a beneficial effect with bromocriptine while Ghose & Coppen (1977) found no difference. Anderson et al (1977) reported a significant improvement in breast symptoms but psychological problems were unchanged. Greater benefit was reported by Andersch et al (1979), but this was independent of prolactin levels. The method of symptom recording and measurement in most of these studies was by use of retrospective interviews and is thus open to criticism (see section 1.9.3) but overall there is no good evidence to support a role for prolactin in the aetiology of premenstrual problems.

1.8.7 - The menstrual cycle and the breast

Subjective awareness of breast swelling and discomfort during the premenstrual phase of the menstrual cycle is accompanied by well documented physical changes. These have been described in detail by Vorherr (1974) and include increased mammary blood flow, ductular-acinar sprouting and interlobular oedema. Slight secretory activity also occurs in the alveolar lining which becomes more marked with the fall in sex steroid levels at the onset of menstruation but is followed by regressive changes with loss of oedema and condensation of the stroma during the early follicular phase. Premenstrual increase in breast volume has been demonstrated in volunteer subjects (Milligan et al, 1975) using a water displacement technique. Subjective awareness of breast changes may thus be regarded as normal although they vary considerably in magnitude and perception. The problem of 'cyclical pronounced mastalgia' is very common in clinical practice (Preece et al, 1976) and may occur in association with other cyclical symptoms or in isolation. Mammograms of these women with marked symptoms frequently show areas of fibroadenosis (Preece et al, 1976) although the diagnosis of cyclical mastalgia usually depends on the reported severity of the discomfort. A study based on luteal phase blood samples (Sitruk-Ware et al, 1977) showed sufferers from benign breast diseases to have significantly lower progesterone levels than normal controls. However single samples only were taken and timed according to basal body temperature, which may lead to inaccuracies (see section 3.2). Their findings have been confirmed by others (Rolland et al, 1979) but the subjects studied included those with non-cyclic breast pain and both with and without demonstrable structural changes. The relationship between cyclical breast

discomfort, hormonal and structural change is still unclear, as is the association between breast symptoms and other premenstrual problems.

Despite the lack of understanding of its cause, the management of cyclical breast pain has resulted in more consistent success than that found with other cyclical symptoms. Bromocriptine has been mentioned above (section 1.8.6) and significant benefit over placebo has been reported by Mansel et al (1978) in a 6 month cross-over study of women with cyclical breast pain. Of other cyclical symptoms, only irritability showed a significantly better response to active therapy with bromocriptine. However it did not relieve non-cyclic breast symptoms. In a similar study, the same group also found a significant response to danazol in 28 subjects with cyclical mastalgia, although the incidence of treatment-related weight gain and menstrual abnormalities was high (Mansel et al, 1982). The mode of action of danazol is described in a later section (4.4). More recently the anti-oestrogen tamoxifen has been shown to be effective in women with both cyclic and non cyclic breast pain (Fentiman et al, 1976). The success of these therapies presumably reflects the hormonal dependency of breast tissue although their exact mechanism of action is not known.

In section 3.5, the effects of oral contraceptives on cyclical symptoms are reviewed. Milligan et al (1975) showed that breast volume increases premenstrually in pill cycles as well as natural cycles although changes are smaller in the former group. Long term oral contraceptive usage appears to reduce the incidence of benign breast disease (Boston Collaborative Drug Surveillance Programme,

1973; Ory et al, 1976; Vessey et al, 1976) and one study (Royal College of General Practitioners, 1977) indicated a negative correlation with the dose of progestogen in the pill. However the role of oral contraceptives in the management of women with established breast symptoms is less clear.

1.9.- Methods of measurement of mood and physical change

Some of the discrepancies in the literature discussed earlier are likely to be attributable to the variety of methods used to assess menstrual cycle symptomatology. This is not intended to be a comprehensive review of all the methods in past and current use but covers those used in the majority of the studies cited, particularly those related to therapy. Some of the differences in methodology may be a reflection of the different backgrounds of individuals and groups involved in menstrual cycle research. These include general practitioners (Dalton, Williams), gynaecologists (O'Brien, Backstrom, Magos & Studd, Wood), endocrinologists (Reid & Yen, Butt), psychiatrists (Moos, Coppen & Kessel, Sampson, Dennerstein, Bancroft, Halbreich, Rubinow) and psychologists (Paulson, Paige, Wilcoxon, Sanders, Endicott, Slade). In addition, the methods used will vary according to the nature of the study and the population under investigation, for example more detailed assessments will be necessary to monitor the results of therapy, compared with simpler methods suitable for large population surveys.

1.9.1 - Retrospective interviews and questionnaires

Most large surveys rely on data from single interviews or postal questionnaires, and consequently the methods used must be simple and comprehensive, in order to encourage maximum compliance. Such methods were used in the prevalence studies described above, although only those of Coppen & Kessel (1963) and Andersch et al (1986) attempted to quantify the severity of the symptoms, rather than asking for a yes/no response. The former used a simple (nil to severe) scoring system,

while the latter attempted to standardise the replies by giving descriptive statements to assist in the grading.

1.9.2 - Special methods of assessment

For more detailed assessment, several methods have been devised which enable quantification and the application of statistical analysis. Some groups have used complex methods such as content analysis of speech (e.g. Paige, 1971) based on recorded interviews. For assessment of individual parameters of mood there are a number of specific inventories familiar to psychiatrists (e.g. Hamilton depression scale, Beck's depression inventory, Speilberger's state anxiety inventory). Also used frequently for self-assessment are various Mood Adjective Check Lists (MACL - McNaire & Lorr, 1964; Mackay et al, 1978). These comprise a list of dimensions, each of which is described with a few adjectives e.g. not at all, a little, quite a bit, extremely.

A number of detailed questionnaires, intended specifically for self-assessment of menstrual cycle-related complaints have also been developed of which the Menstrual Distress questionnaire (MDQ; Moos, 1968) is the best known. It comprises 47 symptoms, arranged in eight clusters, each of which is scored on a six-point scale. Steiner et al (1980) have devised a separate 36 item 'Self Rating Scale for Premenstrual Syndrome', consisting of a list of descriptive statements with each one requiring a yes/no answer. Halbreich et al (1985) have recently compiled a different Premenstrual Assessment Form, listing 95 items rated on a six-point scale. This differs from others in scoring for severity of change rather than for symptom

severity per se. There has been no degree of uniformity in the application or use of these various methods and with the exception of a recent study by Casper & Powell (1986) (see below) no published reports of attempts to critically compare their validity and efficacy.

1.9.3 - Prospective daily assessment

All the above methods may be used for single assessments or for serial measurements. However, it has become increasingly evident that single retrospective assessments of menstrual cycle related symptoms may be inaccurate and misleading. In one of the earliest detailed studies, McCance et al (1937) found the discrepancy between retrospective and daily reports to be 'so frequent as to throw considerable doubt on the value of any work based on history or questionnaire'. Abplanalp et al (1979) were unable to demonstrate any significant premenstrual changes in mood in 33 subjects assessed daily, while a retrospectively completed MDQ had indicated significant premenstrual problems. Halbreich et al (1985) found that less than half the women diagnosed as having premenstrual change on retrospective assessment have this confirmed prospectively. On the other hand, Taylor (1979) found a good correlation between a single MDQ and daily assessment. However he does comment that the subjects who scored highly premenstrually also scored highly during the remainder of the cycle, and these might not have met the criteria for premenstrual change used by other authors.

In view of the overall consensus that retrospective interviews and questionnaires are inadequate for the assessment of cyclical symptoms,

most recently published studies have been based on daily recordings, although again a wide variety of methods have been employed.

1.9.4 - Detailed methods of daily assessment

Many of the above methods have been used for daily self-assessment, for example the study of symptom profiles in small selected numbers of volunteers where a combination of methods has sometimes been used, for example the MDQ and MACL (Silbergeld et al, 1971; Wilcoxon et al, 1976). The MDQ has also been successfully used for monitoring the results of therapy, for example by Sampson (1979) and Magos et al (1986), the latter group using a shortened version of 34 symptoms in six clusters, scoring each item from 0 to 3.

1.9.5 - Simple descriptive scales

The methods used for daily self-monitoring in treatment trials have in general been simpler than the detailed methods described above, presumably because of the need to ensure maximum compliance over a period of several months. Again, there has been no uniformity of method, each group drawing up a list of symptoms and devising a simple numerical scoring system using a four to six-point scale (Williams et al, 1983; Dennerstein et al, 1986, 1987; Watts et al, 1987). In general, validation of their use in comparison with other methods has not been described although there has been a recent study (Casper & Powell, 1986) in which results of assessment by a set of visual analogue scales (see below) have been compared with two descriptive methods, one employing a simple numerical scoring system (1 to 3), the other a yes/no response to a list of statements (Steiner et al, 1980). The results from the three methods were very highly inter-correlated

which is encouraging when comparing the results of studies based on so many different methods of measurement.

1.9.6 - Visual analogue scales

The visual analogue scale (VAS), (Aitken, 1969) is another method frequently used to quantify mood and physical state, for example in research into the effectiveness of analgesic drugs (Huskisson, 1974). Its reliability and reproducibility has been demonstrated in the latter context (Revill et al, 1976). It is a straight line or set of lines representing individual parameters, marked at both ends, usually measuring 10cm, and with both ends defined as extremes of a range for the particular parameter being measured (e.g. from 'none' or 'not at all' to 'as bad as I can imagine'). Subjects are asked to define their own extremes and then to assess the severity of each symptom serially by marking the line as they feel appropriate. Visual analogue scales can also be used for bipolar measurements, for example 'most depressed - most happy' (Rubinow et al, 1984).

Sanders (1981) found the method to be acceptable for the measurement of cyclical changes in a group of 14 women, who preferred it to the MACL and more complex descriptive methods. Similarly Faravelli et al (1986), testing it against standard scales for the measurement of depression found it to be more popular with the patients although 8 out of 100 were unable to use it. The VAS has been used for measurement of menstrual cycle symptoms by O'Brien et al (1979; 1980), Sanders et al (1983), Backstrom et al (1981), Abraham et al (1985) and Rubinow et al (1984). Sanders (1981) has validated a set of visual analogue scales by comparison with simultaneous recordings made on the

Lorr-McNaire MACL, finding highly significant correlations between the two methods. She cited other studies which have similarly validated their use in the measurement of specific dimensions of mood (e.g. Zeally & Aitken, 1969).

1.9.7 - Statistical methods

Until fairly recently, statistical comparisons of mood and physical change across the menstrual cycle have largely employed parametric methods, in particular analysis of variance (e.g. Wilcoxon et al, 1976, Silbergeld et al). As measurement of mood is based on allocation of a score to indicate severity and the numerical data is thus ordinal in nature, this practice is open to criticism (Siegal, 1956). However parametric methods are still used for paired comparisons in therapy trials where results are based on simple descriptive scales (e.g. Dennerstein et al, 1985, 1986; Watts et al, 1987).

One of the advantages of the use of the VAS was said to be its suitability for the application of parametric methods of statistical analysis (Aitken, 1969). The validity of this has been questioned (Forrest & Andersen, 1976) as the VAS is essentially an ordinal scale, its limits being defined by the individual. Maxwell (1978) has compared parametric and non-parametric statistical tests for both within-subject and between-subject comparisons using the VAS and concluded that parametric methods are valid for within-subject comparisons.

1.9.8 - Criteria for diagnosis based on quantitative methods of assessment

Development of these methods of measuring menstrual cycle symptomatology quantitatively on a continuous basis should have resulted in more precise diagnostic criteria. However some groups still specify the need for a 'symptom-free interval' (Williams et al (1983); Dennerstein et al (1985) which presumably implies scores of zero for all parameters during the postmenstrual phase. This, as seen in chapter 2, only applies to a very small proportion of women who present with premenstrual complaints. Watts et al (1987) refer to an 'appreciable' increase in symptom scores premenstrually without being any more precise but O'Brien et al (1979) were happy to accept premenstrual scores consistently higher than those present postmenstrually. Halbreich et al (1985) regard significant change between the premenstrual and postmenstrual phases as being at least 2 points on a six-point scale and also specify a minimum acceptable level of symptomatology during the post-menstrual phase. Using the VAS, Rubinow et al (1974) used an increase of 30% during the premenstrual week as indicative of 'menstrually-related mood syndrome'.

Some groups have devised sophisticated methods of assessing the significance of individual cyclical changes, with the help of computerisation, for example the least mean square method of fitting sine waves described by Sampson & Jenner (1977), using the MDQ. Magos et al (1986) described a method of trend analysis for assessing level of change in individuals. For group comparisons, they calculate maximum and minimum exponentially smoothed averages, representing

peaks and troughs in symptoms, applying non-parametric methods to measure statistical differences. Such methods are likely to assign statistical significance to small differences and may be less useful than the simpler methods described above as they do not indicate the baseline level of symptoms in an individual and are difficult to apply in an ordinary clinical situation.

1.10 - Methods of measurement used in this thesis

1.10.1 - Visual analogue scales

The majority of the measurements used in the studies described in the later sections of this thesis were made using a standard set of 10cm visual analogue scales (figure 1.3), completed by the subjects on a daily basis throughout the period of observation. The dimensions listed were based directly on those used by Sanders (1981) during the course of her studies done in this department, under the supervision of Dr J. Bancroft and in collaboration with Dr T. Backstrom. Her original list was selected on the basis of earlier studies in the literature and comprised scales for cheerful and happy, energetic and active, sociable and friendly, relaxed, changeable, depressed and unhappy, fatigued and tired, aggressive, irritable, tense and anxious. The physical symptoms, swelling, headache and breast discomfort, were rated on a four-point scale. In the present studies, it was decided to use the 10 cm scales for swelling, breast tenderness and menstrual bleeding so that methods were uniform. The items of mood were reduced to five, including those most frequently reported by symptomatic women, namely tense/anxious, fatigued/tired, irritable, depressed/unhappy. Only one positive item (cheerful and happy) was

Figure 1.3

NAME: DATE:

FOR EACH ITEM MARK HOW YOU HAVE BEEN FEELING ACCORDING TO YOUR OWN DEFINITION

	Not at all		Extremely
1. Cheerful and happy	0	———	10
2. Tense and anxious	0	———	10
3. Fatigued and tired	0	———	10
4. Irritable	0	———	10
5. Depressed	0	———	10
6. Breast tenderness	0	———	10
7. Feeling of swelling	0	———	10
8. Pelvic pain	0	———	10
9. Menstrual bleeding	0	———	10

Tablets - dose and number

Events during the day, other feelings, comments:

retained as it was felt that too lengthy a list might reduce compliance. During the course of the initial study an additional 10cm scale was added for the measurement of 'pelvic pain' (see section 2.3.5)

In the initial study (chapter 2), the method described above was used for daily prospective assessment of 100 women who consecutively presented with premenstrual problems. The analysis was based on three phases of the cycle, the premenstrual week, the initial 5 days of menstruation and the postmenstrual week (days 6-12). These correspond to the following phases studied by Sanders et al (1983), namely, late luteal (days 23-28), early follicular (days 1-5) and mid-follicular (days 6-10). The latter study had demonstrated maximum intensity of negative moods during the late luteal phase with a trough of negative moods during the late follicular phase, i.e. around the time of ovulation. It also showed a peak of positive moods around ovulation. However, in view of previous reports that adverse symptoms may be related to ovulation (Dalton, 1977; Reid & Yen, 1981) it was decided to omit this phase from the analysis and take the mid-follicular phase as the baseline week.

Mean scores for both mental and physical symptoms were calculated for each subject for each of these three cycle phases to enable comparisons between the phases to be made. This is described in more detail in section 2.2.3. Where cycle phase scores were compared between groups of individuals, results were expressed as the median and range (or interquartile range) for analysis by non-parametric statistical methods (see section 1.9.7).

The method selected to classify and compare the individual subjects has not been used before in any published study. Magnitude of the premenstrual symptom change can be measured simply by subtracting the postmenstrual score from the premenstrual score, the method used by O'Brien et al (1979). The disadvantage of this is that it does not take account of basal symptom levels. As discussed in section 1.3, many authors have emphasised the importance of symptom relief following menstruation. The degree of symptom relief can be calculated by expressing the difference between the premenstrual and postmenstrual scores as a percentage of the premenstrual score as follows:

$$\text{Post-menstrual relief} = \frac{\text{premenstrual score} - \text{postmenstrual score}}{\text{premenstrual score}} \times 100\%$$

Similarly, the degree to which symptoms are relieved during menstruation can be calculated. The terms postmenstrual or menstrual mood/physical symptom relief will be used in the text to refer to the percentage change derived in this way. The method is not only applicable to scores obtained with visual analogue scales but can also be used where other methods of measurement have been used, for example the simple descriptive scale described below. It has the advantage of simplicity and is self-explanatory, not requiring the introduction of elaborate and confusing terminology.

This method measures only degree of change and does not indicate the severity of the premenstrual symptoms in an individual. For example,

premenstrual scores of 8.0 and 1.0 would both be relieved by 100% if the postmenstrual scores were zero. However assessment of severity is subjectively defined and thus any classification based on comparison of the cycle phase scores between individuals would not be very meaningful anyway.

In the second study, (chapter 4) the effects of suppression of ovulation with two progestogens were compared with placebo. The same set of visual analogue scales was used in the measurement of response, again using daily recordings over a period of at least three months. Suitability for inclusion in the study was based on the degree of postmenstrual mental relief calculated by analysing the results of two pre-treatment cycles as above (for details of proposed diagnostic categories see chapter 2). To determine the effects of therapy, mean cycle phase scores were compared as described in detail in section 4.2.5. Parametric methods, in this case analysis of variance, were used to assess statistical significance, as repeated measurements were being made by the same individuals (see section 1.9.7). Where any between group comparisons were made, non-parametric tests were used.

1.10.2 - A simple descriptive scale

In the third study, a different method of self-assessment was used, based on a simple descriptive scale (see section 1.9.5). It was first tested in a small pilot study (described in section 2.6) where it was compared with the visual analogue scales in a sample of subjects. The reason for selecting an alternative method was the length of time over which recordings would be made. Therapy with the LHRH agonist would last 6 months and this, including pre and post-treatment cycles, would

Figure 1.4

MENSTRUAL CYCLE SYMPTOM CHART Name:

Date																												
Day	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Bleeding																												
Pelvic pain																												
Breast discomfort																												
Irritability																												
Swelling																												
Depression																												

Daily score:
0 = none
1 = mild/slight
2 = moderate
3 = severe

For bleeding:
1 = scant/spotting
2 = normal
3 = heavy/excessive

make the total duration of the study at least 9 months. As some of the subjects would be women who had not primarily presented with premenstrual complaints, it was felt that compliance would be reduced if the method of recording was too detailed. Failure of subjects to complete the VAS charts was a problem encountered in the progestogen study (chapter 4), where the duration of recording did not exceed 6 months. For a similar reason, the items listed on the simple chart were reduced to 6, namely, bleeding, pelvic pain, irritability, depression, breast discomfort and swelling (figure 1.4). Spaces were left for other problems to be rated daily if appropriate. The subjects were asked to score each symptom daily on a four-point scale, indicating the severity from 0 to 3 (severe). Non-parametric tests were used for the statistical analysis.

1.11 - Conclusions

1) The endocrine changes of the menstrual cycle are complex, involving the ovary, anterior pituitary, hypothalamus and the central nervous system.

2) Cycle related changes in mood and physical symptoms are reported by such a high proportion of the female population that their presence cannot always be regarded as pathological although they appear to be a cause of significant morbidity in a minority of women.

3) The relationship between the menstrual cycle and physical symptoms appears to be more clear cut than mental change where factors such as social conditioning, personality and psychiatric morbidity all appear to play a variable but important role.

4) The physiological basis of the adverse physical symptoms is not clear. Alterations in fluid and electrolyte balance and breast morphology with menstrual cycle phase are recognised but differences accounting for symptomatology and their relationship to psychological symptoms have not been identified.

5) There is considerable lack of uniformity between investigators with regard to basic definitions of menstrual cycle-related problems and the methods used in their investigation. The most useful methods are those based on prospective daily self-rating, of which several have been validated.

In chapter 3, the relationship between hormones and mood will be further considered. Chapters 2, 4, 6 and 7 of this thesis will be concerned with women who present for help with premenstrual problems and the role of hormonal manipulation in their management. The methods of assessment described above (section 1.10) will be used in their evaluation.

CHAPTER 2

THE CHARACTERISTICS OF 100 WOMEN PRESENTING WITH PREMENSTRUAL PROBLEMS

2.1 - Introduction

In chapter 1 of this thesis, some of the difficulties and discrepancies surrounding our current understanding of menstrual cycle related problems have been outlined. Even the basic nomenclature and definition is a source of controversy. This chapter is concerned with the group of women who suffer from disturbances of mood which they relate to the menstrual cycle, specifically the premenstrual phase, and which are sufficiently severe for them to seek medical help, thereby posing a management problem for both general practitioners and hospital specialists.

Prior to 1980, when this study commenced, there were no published reports of profiles of mood and physical symptoms throughout the menstrual cycle in women presenting with premenstrual tension. There was a large literature of published clinical trials involving numerous approaches to therapy, mostly with negative results. In addition, a number of studies had examined hormone profiles but usually without defining symptom patterns and severity in the cycles under study (see section 3.2). It was evident that in order to clarify the situation with regard to diagnosis, cause and treatment, a reappraisal of the condition was urgently needed. Accurate delineation of the problem within a group of symptomatic women would provide a basis for drawing up diagnostic criteria, reveal possible subsets of patients for study

of aetiology and should lead to rationalisation of therapy, both in the selection of subjects for clinical trials and for management of individual patients.

The object of this study was therefore to assess prospectively a series of women who consecutively presented to a specialist clinic because of problems attributable to 'premenstrual tension', in order to clarify the relationship of their symptoms to the premenstrual phase of the cycle and to menstruation itself. In addition, other factors that might be related to their problem could be studied with the aim of devising a simple system of classification as a basis for further research.

2.2 - SUBJECTS AND METHODS

2.2.1 - Subjects

All the women included in this report were referred to the Reproductive Endocrine clinic of the Edinburgh Royal Infirmary with cyclical mood changes thought by themselves and/or by the referring practitioner to be attributable to premenstrual tension. The criteria for inclusion included a complaint of one or more of the symptom triad of irritability, tension and depression with or without the other physical and mental symptoms commonly associated with the condition. Also for inclusion in the study, the women had to give a history of relief of their symptoms during or following menstruation. All the women were sufficiently distressed by their symptoms to seek specialist help and the majority had received various therapies in the

past although none were on any specific therapy, hormonal or otherwise, during the period of observation. Women were not excluded on the basis of a past history of psychiatric illness or treatment because the object of the study was to gain information about the entire population of women referred with cyclical problems of this nature.

2.2.2 - Assessment of symptoms

At the initial visit a full medical, social, psychiatric and gynaecological history was taken and the women screened for the presence of significant general or pelvic disease. The psychiatric history was recorded as positive if they had received treatment for any past or current problems or had at any time attended a psychiatric clinic for treatment or been hospitalised for a psychiatric problem. Attendance or treatment for problems specifically related to the menstrual cycle or puerperium were not considered indicative of a positive psychiatric history. Those who were eligible on the basis of their presenting symptoms were asked to complete a standard set of visual analogue scales (figure 1.3) each evening for at least 35 and usually 60 days (see sections 1.9.6 and 1.10.1 for a description of the method). The parameters being assessed were tension/anxiety, lethargy/tiredness, cheerfulness, irritability, depression, breast discomfort, swelling and menstrual bleeding. During the course of the study the charts were modified to include pelvic pain in the symptom list. The women were asked to define their own limits for each parameter between 0 (not at all) and 10 (extreme) and mark the 10cm line accordingly.

2.2.3 - Data analysis

For the analysis, three separate phases of the menstrual cycle were studied (see section 1.10.1). The premenstrual phase included the 7 days prior to but not including day 1 of menstruation (days -7 to -1 inclusive). The menstrual phase included the first 5 days from the onset of menstruation (days 1 to 5), regardless of the duration of bleeding. The post-menstrual phase was taken from day 6 to day 12 of the cycle, inclusive. Overall mean scores for both mental and physical symptoms were calculated for each subject for each of these three cycle phases to enable comparisons between the phases to be made. The scores for irritability, tension, depression and lethargy were combined for each phase and a mean 'adverse mood' score calculated. Mean physical symptom scores were calculated by combining breast discomfort and swelling in a similar way. If data from two complete menstrual cycles was available, calculation of the mean score was based on both cycles.

The level of change of the symptoms between the premenstrual and the postmenstrual phases of the cycle was then calculated for the physical and the mental symptoms in turn for each subject. The mean postmenstrual symptom score was first subtracted from the mean premenstrual score. This symptom difference was then expressed as a percentage of the premenstrual score to give the degree of 'postmenstrual mood/physical symptom relief' for each individual subject, as shown in section 1.10.1. The degree of menstrual mood/physical symptom relief was then similarly calculated. The analysis was performed with the assistance of 'Minitab data analysis software' using an IBM-PC compatible microcomputer system.

Descriptive analysis of the data was then performed as described in the results section. Statistical comparisons were made using non-parametric methods of analysis. The Mann-Whitney two-sample test was used to compare two groups, the Kruskal-Wallis one-way analysis of variance for comparison of more than two groups, Chi-squared test to compare categories and Spearmann's rank correlation coefficient as a measure of correlation.

As an additional assessment of day to day changes in individual symptoms throughout one complete menstrual cycle, mean daily symptom scores were also calculated. For this, it was necessary to standardise all the cycles to 28 days. Day 1 was taken as the onset of bleeding (excluding spotting) and day 28 was the day immediately prior to its onset. The days were counted backwards to day 12 and then forwards for 11 days so that any ajustments for length were made in the mid-late follicular phase, regarded as the 'baseline' phase both symptomatically and hormonally (section 1.10.1). The results were computed and plotted out for the entire sample of 100 women and also for the sub-groups identified during the above analysis (see results section). Statistically significant cyclical changes were detected using analysis of variance for repeated measures.

Any cycles which were markedly atypical in terms of length or bleeding pattern were excluded from the analysis as were those complicated by coincidental major life events such as bereavement or significant physical illness likely to upset the normal cyclical mood pattern.

2.2.4. - Endocrine measurements

A random subsection of the subjects underwent simple assessment of ovarian function by estimation of total oestrogen and pregnanediol excretion in early morning samples of urine, collected weekly and stored in the subjects' own domestic freezers in between visits to the hospital. The results were to act as a baseline for a parallel study of the effect of ovulation suppression with certain progestogens (see chapter 4) and those women who expressed an interest in this study were asked to collect urine samples. In addition it was hoped to detect some spontaneous anovular cycles in order to study differences in symptom profiles between these and normal cycles in the same individuals. Those women in particular with a history of occasional atypical cycles or variable symptom patterns were asked to collect weekly urine samples.

2.2.5 - Assay methods

Total urinary oestrogens were measured by fluorimetry after semi-automatic extraction, using the method described by Brown et al (1968). Pregnanediol was measured by gas-liquid chromatography (Chamberlain & Contractor, 1968). Results were expressed as the steroid:creatinine ratios.

2.3 - RESULTS

2.3.1 - Characteristics of the subjects

The mean age of the women was 35.2 years (range 24-49). Their marital status, parity, current method of contraception and socio-economic status are summarised in tables 2.1.1 - 2.1.4. Women using hormonal contraception had not been specifically excluded from the study but only four were in this category, two of them using a progestogen-only pill. In none of them had the pill been prescribed as a remedy for their cyclical symptoms. For those women in part or full-time employment, the occupation stated is their own, in the case of housewives the occupation of the spouse is given. The mean duration of their symptoms at presentation was 5.4 years (range 6 months to 22 years). The distribution of symptom duration is shown in table 2.1.6. The source of the original referral to the clinic is shown in table 2.1.5.

2.3.2 - Compliance

Of the 100 women initially eligible for the study, none expressed any misgivings about completing the visual analogue scales as instructed. However 16 failed to satisfactorily complete or return the charts. In order to collect data from 100 patients, the next 16 completed sets of charts received from eligible patients were also analysed. The characteristics of the non-compliars, together with their reasons for not completing the study are shown in table 2.2. Although there appears to be a higher proportion of single and nulliparous women among the non-compliars, the only statistical difference between this group and those who completed the charts was in relation to

TABLE 2.1 - CHARACTERISTICS OF THE IOO SUBJECTS

2.1.1	PARITY:	0	12
		1	13
		2	57
		3+	18
2.1.2	MARITAL STATUS:	married	76
		single	6
		sep/div	18
2.1.3	METHOD OF CONTRACEPTION:		
	Female sterilisation		52
	Male sterilisation		14
	IUCD		9
	Diaphragm/sheath		19
	Pill		4
	None		8

TABLE 2.1 - CHARACTERISTICS OF THE 100 SUBJECTS (cont)

2.1.4	OCCUPATION		
	Employed outside the home	68	
	Domestic/manual		15
	Clerical		30
	Professional		21
	Other		2
	Housewife	30	
	Husband manual		14
	Husband clerical		1
	Husband professional		10
	Div/sep		5
	Not known	2	
2.1.5	SOURCE OF REFERRAL		
	General practitioner		62
	Gynaecologist		31
	Family planning clinic		5
	Psychiatrist		2
2.1.6.	DURATION OF SYMPTOMS		
	Less than 2 years		9
	2-5 years		38
	5-10 years		32
	More than 10 years		17

TABLE 2.2 - CHARACTERISTICS OF THE 16 NON-COMPLIARS

2.2.1.	PARITY:	0	4
		1	2
		2	6
		3+	4
2.2.2.	MARITAL STATUS:	married	10
		single	3
		sep/div	3
2.2.3.	OCCUPATION:	domestic	3
		clerical	5
		professional	7
		housewife	1

2.2.4. REASONS FOR NON-COMPLIANCE

Charts mislaid	2
Too time consuming	3
Incomplete/incorrectly filled out	6
Problem resolved	4
Wrong diagnosis	1

occupation. Significantly fewer of the non-compliars were housewives (Chi-squared = 4.12, 1 degree of freedom; $p<0.05$).

When the charts were incorrectly filled out (table 2.2.4), this was generally due to failure to mark the line appropriately, giving a descriptive term instead. Of those who felt their problems had resolved during the course of the assessment months, all had remained well when contacted 6 months later. There were several subjects who realised during the course of completion of the daily records that their problems were not truly related to the menstrual cycle. However only one of them actually stopped completing the charts. The others are included in the main analysis as previously they had attributed their problems to premenstrual tension.

2.3.3.- Menstrual and postmenstrual relief of mood and physical symptoms

A classification of the extent to which the premenstrual mental and physical symptoms were relieved during the postmenstrual and menstrual phases of the cycle respectively is shown in table 2.3. Fourteen of the women actually showed a postmenstrual exacerbation of their mental symptoms and near complete relief (75% or more) was apparent in only one third. However two thirds of the women showed relief of physical symptoms, when present, of 75% or more. During menstruation itself, both mental and physical symptoms actually worsened in a third or more of the subjects. Mental symptoms were relieved by 50% or more in only 20 women. Menstrual data was obtained from only 98 of the women, due to failure of two to complete the charts during menstruation.

TABLE 2.3

Postmenstrual relief of mental and physical symptoms

Degree of relief	Mental	Physical
75% or more	32	62
50-74%	15	9
25-49%	20	7
0-25%	19	5
symptoms exacerbated	14	10
no cyclical symptoms	--	7

Menstrual relief of mental and physical symptoms

Degree of relief	Mental	Physical
50% or more	20	34
0-49%	35	24
exacerbated* 0-49%	25	14
exacerbated* 50% or more	18	19

*No relief as symptoms worse during menstruation

Further analysis was performed to study mental and physical symptom profiles before, during and after menstruation, subdividing the women into five groups according to the degree of postmenstrual relief of the mental symptoms as classified in table 2.3. Analysis of the mental symptoms is shown in figure 2.1, where results are expressed as the median and interquartile range for each cycle phase within the groups. While the severity of symptoms during the premenstrual phase of the cycle did not differ significantly between the groups ($H=3.357$, $p=0.50$; Kruskall Wallis one-way analysis of variance), a marked difference in median symptom severity was seen during menstruation itself ($H=15.21$, $p<0.01$). The median mental symptom score was actually greater during menstruation than premenstrually in the two groups with least postmenstrual relief. The median menstrual score was lowest in the group with greatest postmenstrual relief of mood.

The physical symptom profiles were similarly analysed according to the degree to which the mental symptoms were relieved postmenstrually (figure 2.2). Median severity of the physical symptoms during the premenstrual phase did not significantly differ between the groups ($H=2.819$) and here differences during the menstrual phase just fell short of significance ($H=8.754$, $p<0.10>0.05$). An overall improvement of physical symptoms was seen during menstruation in all the groups with the exception of the one in which mental symptoms were exacerbated postmenstrually. Here a marked menstrual peak was seen. However even in this group, median physical symptom score was reduced postmenstrually, compared with the premenstrual score.

Figure 2.1 - Severity of mental symptom (median & interquartile range) before, during and after menstruation subdivided according to their degree of relief post menstrually.

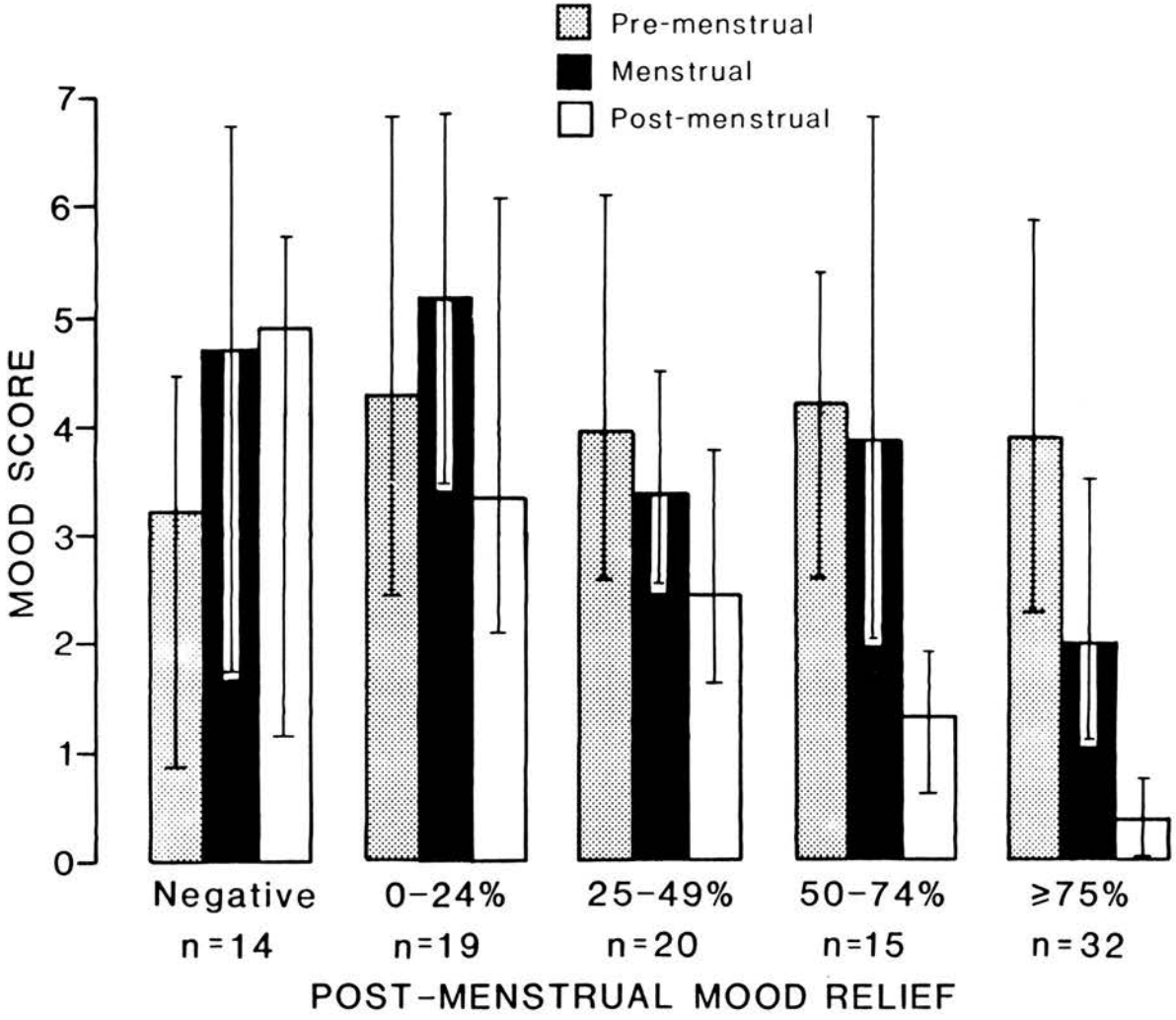
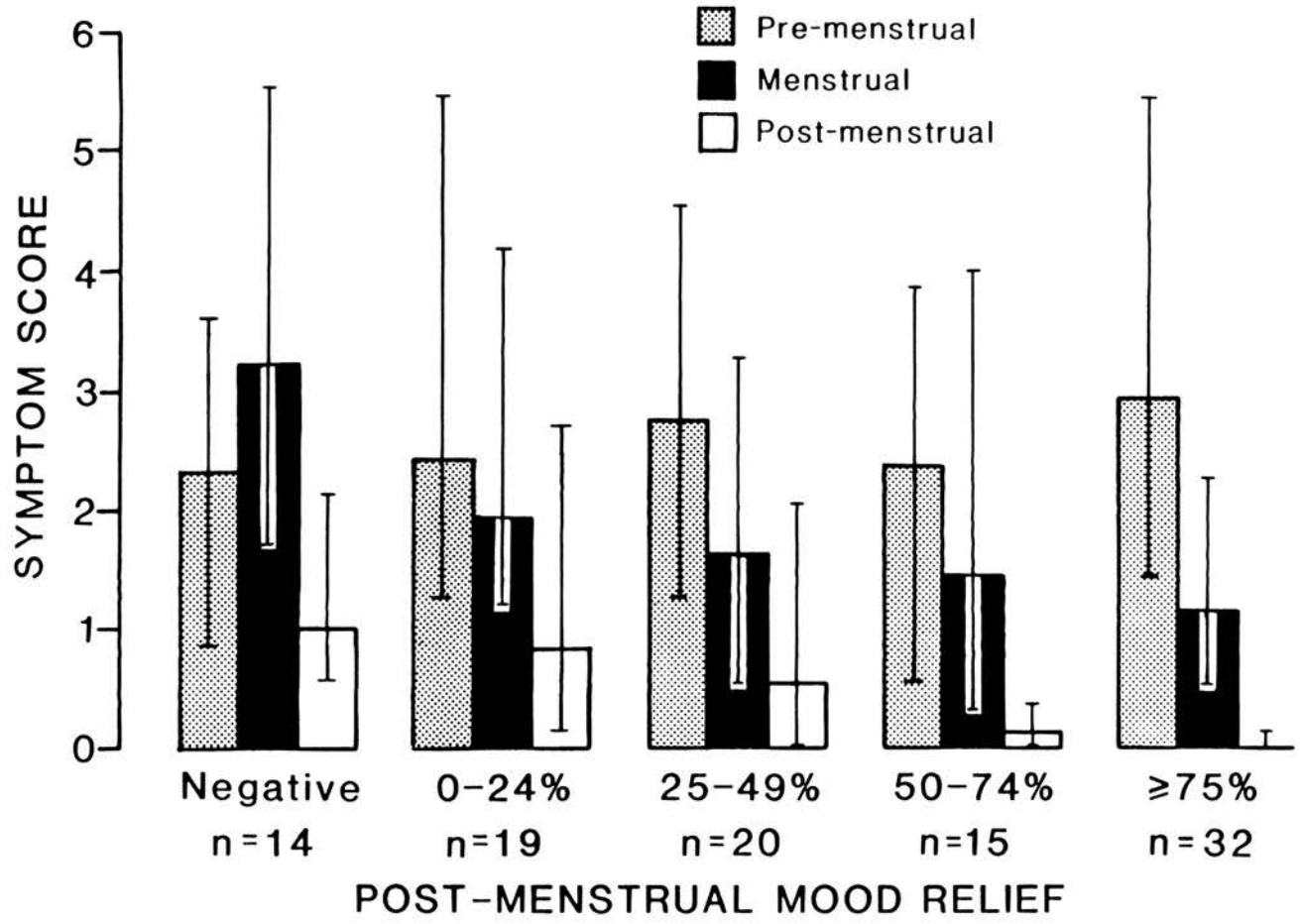


Figure 2.2 - Severity of physical symptoms (median & interquartile range) before, during and after menstruation grouped according to the degree of postmenstrual relief of the mental symptoms.

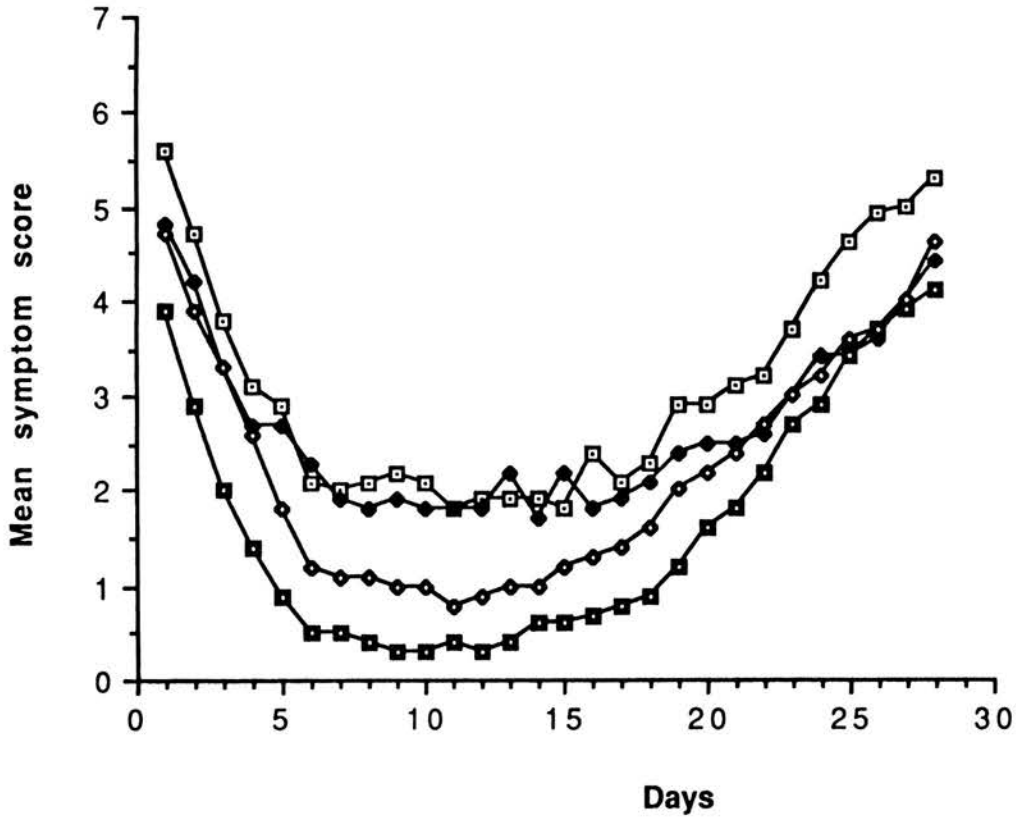


This method of analysis of the data expresses only magnitude of change of the symptoms and does not detect individual women with low levels of symptomatology. There were seven women with no complaints of physical discomfort, distributed throughout all five groups. Because of the subjective nature of the ratings, comparison between individual absolute scores may be invalid, but 11 women consistently had a mean score below 2.5 in all three cycle phases for both mental and physical symptoms. They were distributed between all five of the subgroups. Three of them consistently had mean scores below 1.0, one from the group with greater than 75% relief postmenstrually. Review of their clinical notes did not reveal any other predominant symptoms which were not included among those on the VAS forms. Examination of the latter showed that adverse symptoms had lasted for between one and three days only but presumably had caused distress and led to their presentation.

2.3.4 - Symptom profiles throughout the menstrual cycle

The mean daily symptom scores throughout one complete menstrual cycle for the whole group of 100 women are shown in figure 2.3. Because of similarities between the profiles for the individual psychological symptoms, only those of irritability and depression are displayed. The results of analysis of variance indicate significant cyclical chances in symptoms (figure 2.3). Symptoms all reached a sharp peak, maximal one day prior to and on the day of onset of menstrual bleeding. A steep increase in the intensity of the physical symptoms occured from day 20 of the cycle, parallelled by a similar slightly earlier rise in psychological symptom intensity.

Figure 2.3 - Daily symptom profiles throughout one complete menstrual cycle. Data from 100 women showing mean daily scores for individual symptoms.



F values (df 27, 2772)

Irritability	F = 19.4
Depression	F = 9.0
Breast discomfort	F = 32.3
Swelling	F = 20.6

All significant at P<0.01

Symptom profiles were also plotted for the five subgroups identified by calculation of the postmenstrual mood relief as described above. These are shown in figures 2.4.1 - 2.4.3, where the groups are numbered in ascending order of degree of postmenstrual relief as indicated in the legends. Results confirm that there was little relationship between mood and the menstrual cycle in the two groups with least postmenstrual mood relief, although physical symptoms were clearly related to cycle phase. In particular, daily scores for depression show no significant variance in either subgroup. Those women with intermediate degrees of relief (25-75% - figure 2.4.2) showed significant cyclical changes in mood but with raised and fluctuating scores in the middle phase of the cycle. This contrasts with the profiles seen in the group with greatest relief (figure 2.4.3). The pattern of the premenstrual symptom rise was similar in the three latter groups, although the sharp increase in symptom intensity occurred earlier in the women from group 5.

2.3.5 - Factors associated with degree of postmenstrual relief

In order to examine factors that might have influenced the patterns of mood change identified in section 2.3.3, the subjects were similarly categorised according to the degree of postmenstrual relief of the mental symptoms. The association with past psychiatric history, marital status and parity is shown in table 2.4. Women with postmenstrual mental symptom relief of 75% or more included significantly fewer with a past history of psychiatric treatment or marital breakdown than those with postmenstrual mood relief below 75%. There were also significantly fewer with three or more children. Occupation did not differ between the groups (not illustrated).

Figures 2.4.1 - 2.4.3
Symptom profiles throughout one complete menstrual cycle, showing mean daily scores for individual symptoms. The women are grouped according to the degree of postmenstrual relief of the psychological symptoms.

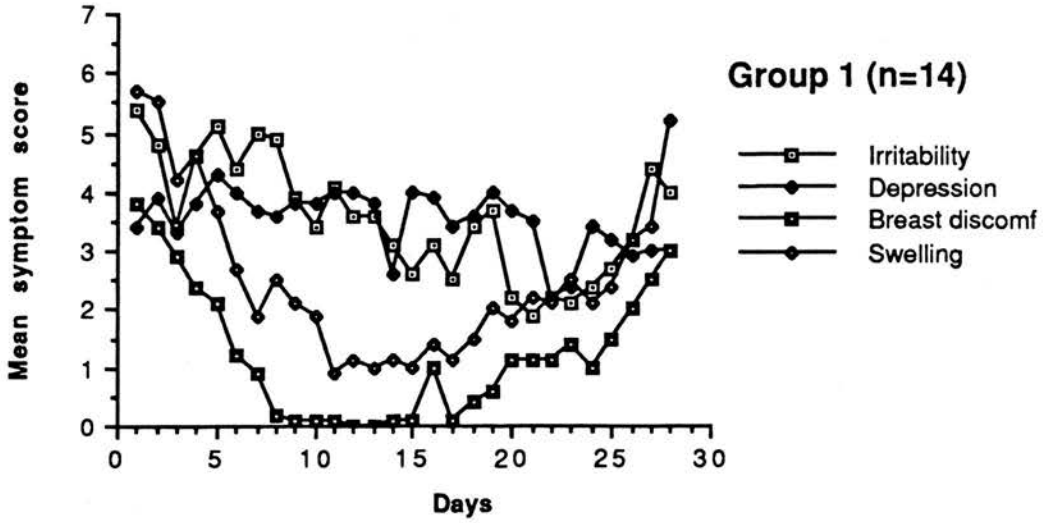
Key and F-values derived by analysis of variance
Unless stated P<0.01

	Group 1	Group 2	Group 3	Group 4	Group 5
Relief	None	1-24%	25-50%	50-74%	75-100%
Irritability	1.45 *	1.56 +	7.70	4.95	20.73
Depression	0.90 *	0.95 *	2.44	4.41	14.25
Breast pain	4.04	3.78	7.78	4.90	19.70
Swelling	3.80	2.70	4.63	2.65	14.71
Degrees of freedom	27/364	27/504	27/532	27/392	27/868

* Not significant
+ P<0.05

Figure 2.4.1
Daily symptom profiles throughout one complete menstrual cycle.

a) Group 1 - Women with no postmenstrual relief of mood.



b) Group 2 - Women with postmenstrual mood relief below 25 prcent.

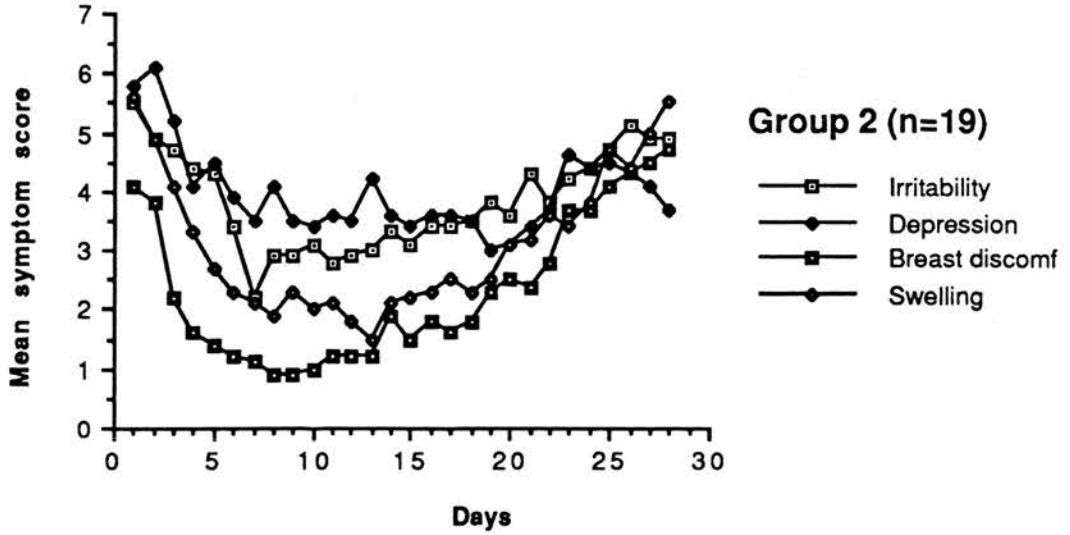
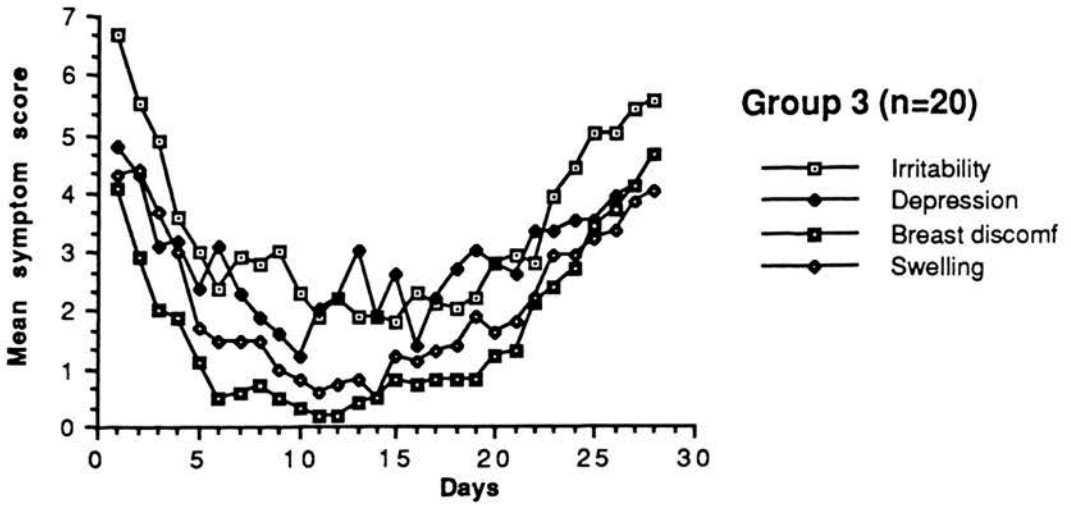


Figure 2.4.2
Daily symptom profiles throughout one complete menstrual cycle.

a) Group 3 - Women with postmenstrual mood relief between 25 & 49%.



b) Group 4 - Women with postmenstrual mood relief between 50 & 74%.

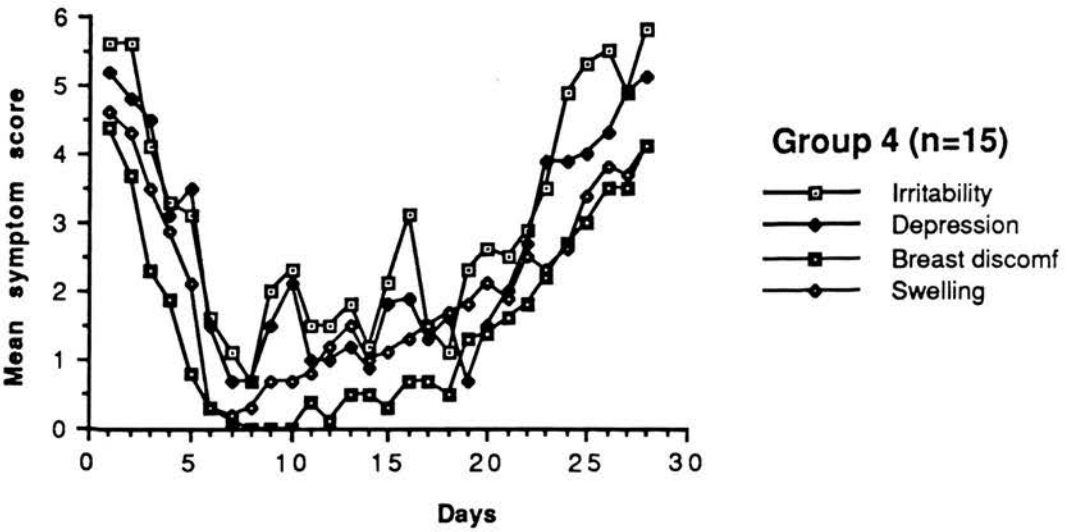


Figure 2.4.3 - Daily symptom profiles throughout one complete menstrual cycle. Group 5 (women with postmenstrual mood relief of 75% or greater).

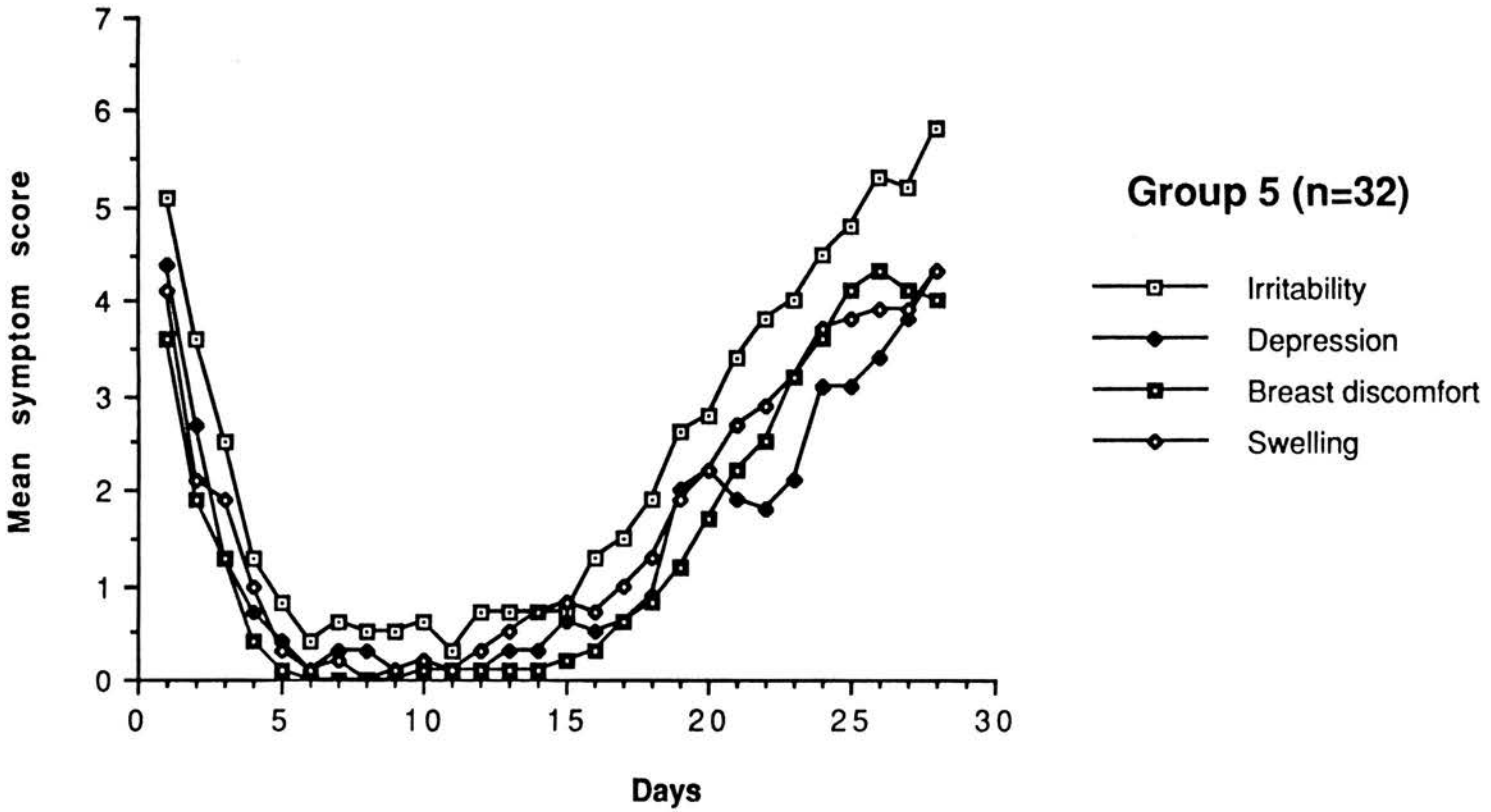


TABLE 2.4

Factors associated with the degree of postmenstrual mood relief

	Postmenstrual mood relief						
	None	1-24%	25-49%	50-74%	75-100%		P
	n=14	n=19	n=20	n=15	n=32	(df=1)	
Psychiatric history	5 (26%)	13 (68%)	8 (40%)	8 (53%)	5 (16%)	10.81	<0.01
Divorced/separated	2 (14%)	6 (32%)	6 (30%)	3 (20%)	1 (3%)	7.05	<0.01
Parity 3 or more	2 (14%)	5 (26%)	6 (30%)	3 (20%)	2 (6%)	4.40	<0.05
Menstrual exacerbation *	11 (79%)	10 (53%)	9 (45%)	7 (47%)	6 (19%)	12.18	<0.001
	(7)	(4)	(0)	(3)	(3)		

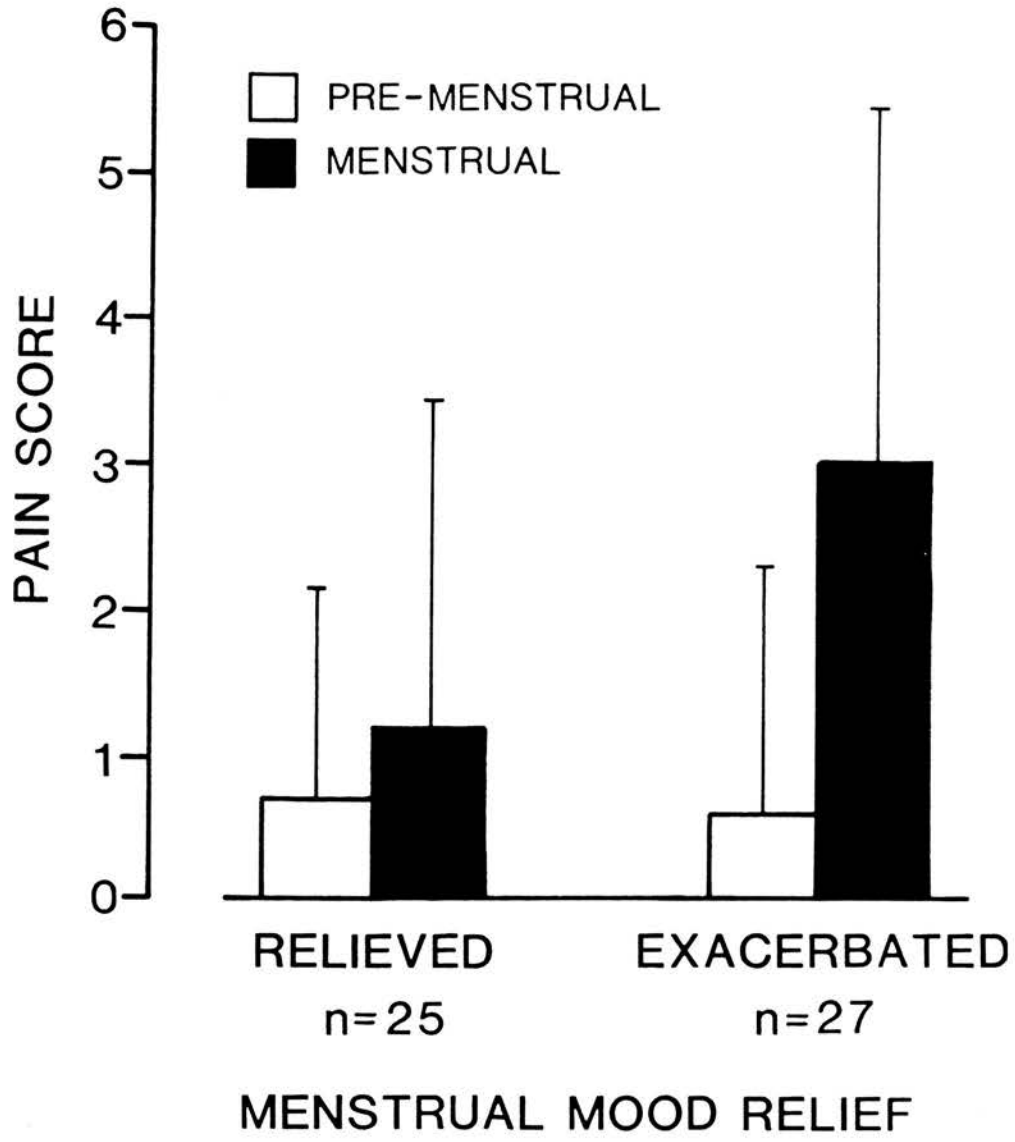
* Figures in brackets below indicate those with menstrual exacerbation of 50% and over

The association between menstrual and postmenstrual mood relief (see figure 2.1) is also shown in table 2.4. The majority of the women with no postmenstrual relief of mood recorded their mental symptoms at maximum levels during menstruation itself. Worsening of adverse mood during menstruation was also present in around half the subjects with minimal or intermediate degrees of postmenstrual mood relief. The difference between these groups and the women with postmenstrual relief of 75% or more is highly significant. However a marked exacerbation of the mental symptoms during menstruation (50% or more) was more frequent in the groups with minimal or no postmenstrual relief (less than 25%).

2.3.6 - Pelvic pain and menstrual relief of symptoms

The influence of a history of psychiatric treatment, marital breakdown or larger family size on mood relief during menstruation was also examined. However all three factors were equally prevalent among those with exacerbation of symptoms compared with those whose symptoms were relieved. The persistence of the adverse mood state during menstruation in such a high proportion of the women prompted an investigation into the extent to which this was related to any associated menstrual pain. The daily charts were thus modified during the course of the study to include an additional 10cm line for assessment of 'pelvic pain'. Data was available from 52 cycles. A poor correlation was obtained between menstrual mood scores and menstrual pain scores (r=0.274). However when the cycles were subdivided according to whether adverse mental symptoms were relieved (n=25) or exacerbated (n=27) during menstruation (figure 2.5), a

Figure 2.5
Pelvic pain score (median and 3rd quartile) premenstrually and during menstruation subdivided according to whether mental symptoms are relieved or exacerbated during menstruation



significantly higher median menstrual pain score was evident in the group whose mental symptoms were exacerbated during menstruation (w=824; P=0.048 by Mann-Whitney test). Median premenstrual pelvic pain scores were similar in the two groups.

2.3.7 - Individual comparison between cycles

Complete data from all three phases of two consecutive menstrual cycles was obtained from 54 of the women. Highly significant (P<0.001) correlations were obtained between the two cycles when comparing the premenstrual (r=0.650), menstrual (r=0.617) and postmenstrual (r=0.762) mood scores and the menstrual (r=0.410) and postmenstrual (r=0.597) relief. The overall data from the two cycles did not show a worsening or improvement of symptoms during the period of observation.

2.3.8 - Menstrual cycle data and results of endocrine monitoring

Of the menstrual cycles studied, the mean length was 28.7 days (range 23-57 days). In ninety four percent of the subjects, the length fell within the limits of 25 to 35 days (table 2.5). Weekly monitoring of urinary ovarian steroid metabolites enabled adequate assessment of ovulation to be performed over at least one cycle in 58 women. Three anovular cycles were detected in three individuals and were all atypical in terms of length and bleeding pattern. Normality of the luteal phases was assessed on the basis of the following criteria:

Two consecutive urinary pregnanediol:creatinine results of at least 1.5 mg/g taken at an interval of at least 7 days.

TABLE 2.5

MENSTRUAL CYCLE CHARACTERISTICS

2.5.1 - LENGTH	<25 days	4
	25-27 days	33
	28-30 days	45
	31-35 days	16
	>35 days	2
2.5.2 - NATURE*	Ovulatory	51 (88%)
	Anovular	3 (5%)
	Inadequate luteal phase	4 (7%)

* Data from 58 subjects

OR one result above 2.0 mg/g preceded or followed by one of at least 1.0 mg/g and separated by a 7 day interval.
In addition, in all the cycles judged to be normal, the urinary pregnanediol:creatinine concentration had reached 1.0 mg/g by day 17 of the cycle.

These were the standard criteria used by the clinical laboratory in which the assays were performed. As shown in table 2.5 only four cycles were classified as having an inadequate luteal phase. In all four, bleeding paterns were normal and they had been included in the detailed symptom analysis, unlike the anovular cycles which had been excluded because of their abnormal nature. These abnormal cycles were distributed evenly throughout all the symptomatic groups.

Urinary steroid excretion profiles were calculated for the group as a whole and for the three main sub-groups identified during the course of analysis of the psychological symptoms (section 2.3.3). The cycles were standardised to 28 days as described in section 2.2.3. Mean urinary total oestrogen:creatinine concentration and pregnanediol:creatinine concentration were calculated for each 3-4 day interval throughout one complete menstrual cycle. The results are given in table 2.6. There were no statistically significant differences between the results for the three groups, assessed by multiple Mann-Whitney tests. The steroid excretion profiles for the group as a whole are shown in figure 2.6. The relationship between symptomatic changes and pregnanediol excretion for the group as a whole is illustrated in figure 2.7. Although the rise in symptom intensity does follow the luteal phase rise in progesterone, the two

TABLE 2.6

RESULTS OF MONITORING OF URINARY STEROID EXCRETION (MEAN ± SD)

DAYS	WHOLE GROUP	RELIEF <25%	RELIEF 25-75%	RELIEF >75%
A - TOTAL URINARY OESTROGEN:CREATININE				
1-3	8.3 ± 5.6	6.3 ± 2.8	8.4 ± 3.5	10.1 ± 8.3
4-6	8.7 ± 4.8	9.2 ± 4.5	9.7 ± 6.6	7.7 ± 3.8
7-10	9.4 ± 5.2	9.8 ± 7.1	7.9 ± 4.5	10.8 ± 4.9
11-13	14.6 ± 6.6	13.2 ± 4.9	14.0 ± 9.0	17.7 ± 4.6
14-16	21.1 ± 12.1	20.0 ± 7.2	20.5 ± 15.1	22.7 ± 10.8
17-19	16.8 ± 7.6	18.4 ± 6.4	18.2 ± 8.3	15.1 ± 7.6
20-21	17.1 ± 8.8	15.9 ± 8.9	17.2 ± 9.4	18.5 ± 8.2
23-25	16.0 ± 8.0	17.9 ± 4.4	15.3 ± 9.9	15.9 ± 7.7
26-28	13.5 ± 8.6	11.9 ± 4.2	14.4 ± 11.9	13.7 ± 6.2
B - URINARY PREGNANEDIOL:CREATININE				
1-3	0.59 ± 0.34	0.40 ± 0.23	0.65 ± 0.27	0.71 ± 0.44
4-6	0.43 ± 0.24	0.54 ± 0.24	0.42 ± 0.24	0.35 ± 0.23
7-10	0.35 ± 0.23	0.31 ± 0.28	0.32 ± 0.17	0.40 ± 0.22
11-13	0.37 ± 0.23	0.29 ± 0.16	0.31 ± 0.21	0.28 ± 0.12
14-16	0.61 ± 0.44	0.53 ± 0.27	0.58 ± 0.36	0.92 ± 0.56
17-19	1.79 ± 1.86	1.32 ± 1.29	1.32 ± 0.85	2.38 ± 2.46
20-22	3.34 ± 3.02	3.06 ± 2.20	3.00 ± 2.44	4.42 ± 4.78
23-25	2.91 ± 1.13	3.24 ± 1.38	2.74 ± 0.95	2.91 ± 1.20
26-28	2.02 ± 1.33	1.82 ± 1.27	1.77 ± 1.04	2.54 ± 1.65

Figure 2.6 - Urinary excretion of total oestrogen and pregnanediol throughout one complete menstrual cycle (mean ± SEM). Results are expressed as the steroid:creatinine ratios for each 3-4 day interval.

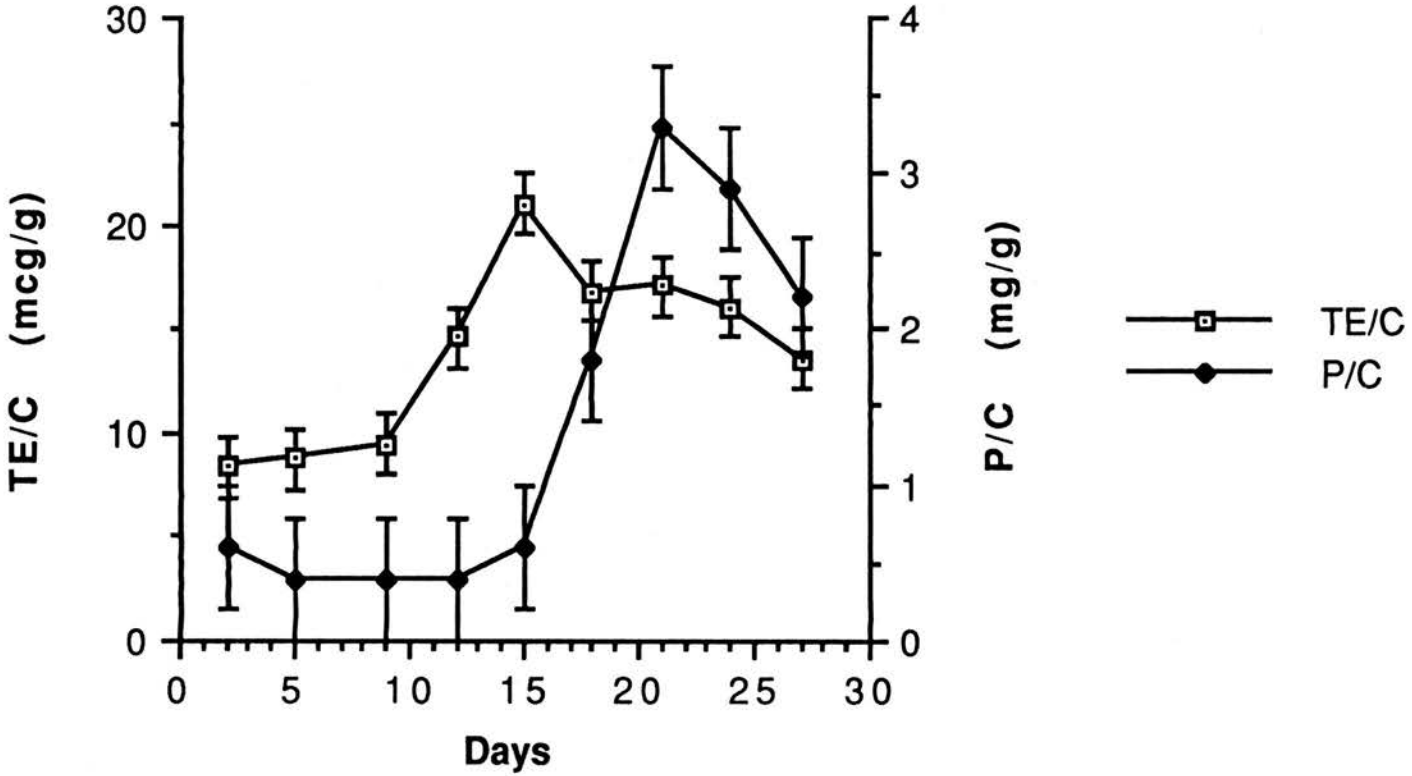
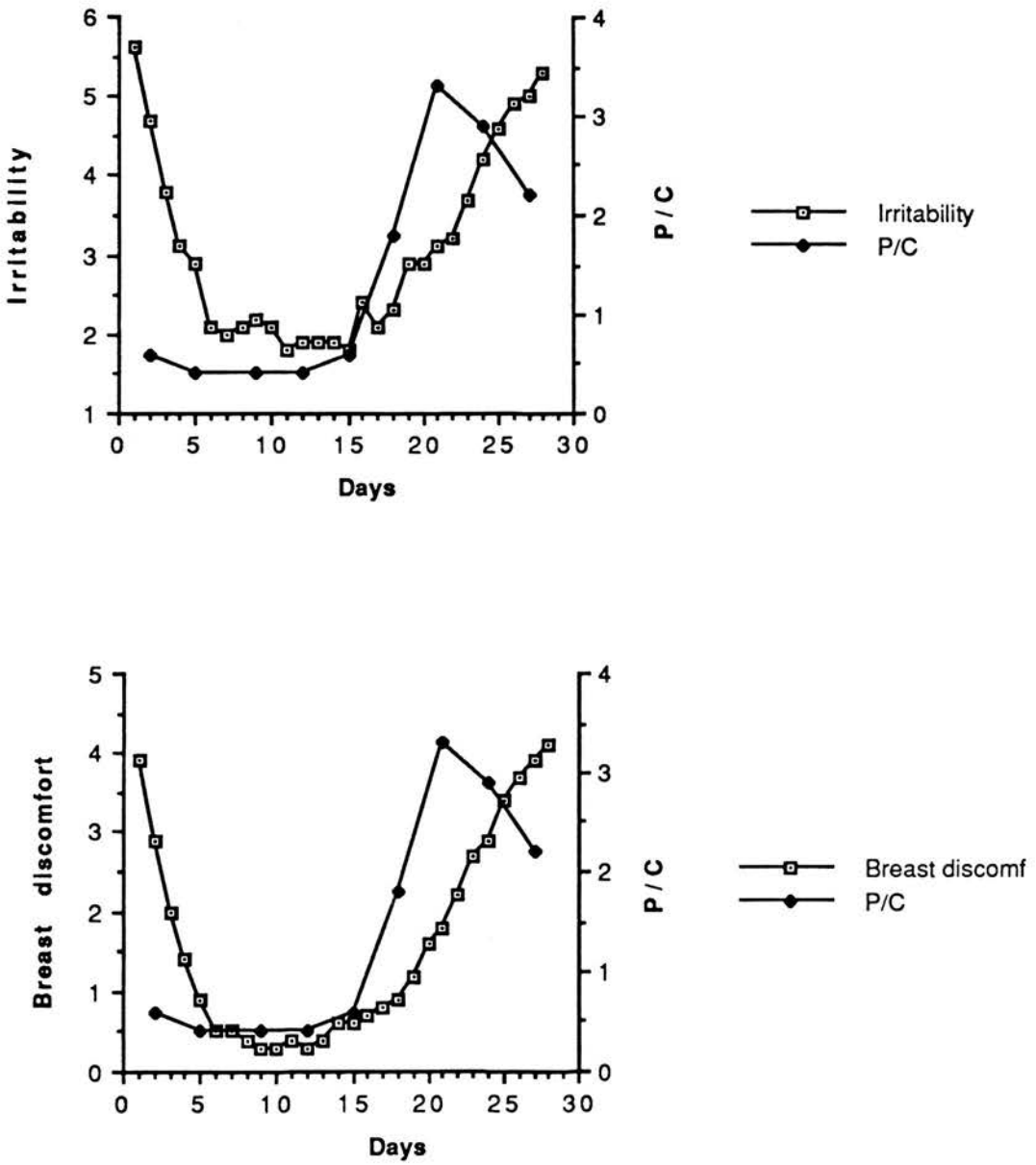


Figure 2.7
Urinary pregnanediol:creatinine excretion throughout one complete menstrual cycle, compared with symptom profiles for irritability and breast discomfort. Results are mean values for the whole sample of women.



are not parallel. The peak of adverse symptoms appears to correspond to the phase of withdrawal of both oestrogen and progesterone.

2.4 - DISCUSSION

The results of this study confirm the unreliability of assessment of premenstrual complaints based on history taking alone (see section 1.9.3). Of these women who all related their problems to the premenstrual phase of the cycle, prospective assessment showed the symptoms to peak around the onset of menstrual bleeding in the group as a whole. However only one third of the sample recorded complete or near complete relief of their psychological symptoms following menstruation. Physical symptoms were more consistently related to menstrual cycle phase.

The population studied here may be regarded as representative of women who seek medical help for their problems. They are biased in that they have been referred to a hospital clinic and this will reflect the different attitudes of individual general practitioners. There may be an additional source of bias in that referrals are also made to a psychiatrist working in the same department and there may be differences in the characteristics of these two groups. For example, the high proportion of women in this analysis whose symptoms centred around menstruation may reflect that they had been referred to a gynaecologist although no particular emphasis on gynaecological history was made in the initial interview and gynaecological pain was not initially one of the listed symptoms. In addition, the clinic they attended was one specifically associated with reproductive endocrine disorders rather than general gynaecology.

The analysis has identified a subgroup of women presenting with premenstrual complaints whose symptoms were more clearly related to

the premenstrual phase of the cycle compared with the remainder of the sample (those with postmenstrual relief of 75% and over). They differed significantly from the women with lesser degrees of postmenstrual mood relief in terms of their psychiatric history, marital status and family size. These women may represent sufferers from classical 'premenstrual tension' (Frank, 1931 - see section 1.3). This would be the group on which to concentrate research into possible underlying causes, and to focus initially in treatment trials. Some studies (e.g. Dennerstein et al, 1985; 1986) claim to have screened out this group for therapy but the majority of studies have been less specific in their selection criteria, which possibly accounts for some of the discrepant results between the various trials.

One third of the women showed little relationship between adverse mood and menstrual cycle phase, although physical symptom profiles maintained a cyclical pattern. High levels of adverse psychological symptoms were present throughout the cycle. The term 'menstrual distress' was used by Dalton (1977) to describe women with premenstrual symptoms which were not followed by a 'symptom free' week postmenstrually. It was also used by Dennerstein et al (1984) to classify women with premenstrual exacerbation of underlying diagnosable psychiatric problems. On the basis of the above results, it is suggested that the term is appropriate for those women with postmenstrual mood relief of less than 25%. This symptom profile indicates that the distress is an accentuation of an underlying problem which is present throughout the cycle whether or not there is a diagnosable psychiatric condition present. It is important to recognise these women in general gynaecological practice as they may

be inappropriately subjected to hysterectomy for non-specific menstrual complaints. One study of psychiatric morbidity in a gynaecological clinic (Byrne, 1984), used the General Health Questionnaire to assess the presence or absence of psychiatric disorders. A high prevalence of such problems, together with a history of marital breakdown was found, particularly among women who presented with complaints of pelvic pain. There was also an association with stressful life events as measured by the Present State Examination, with significantly lower scores in a control group.

A third of the subjects showed intermediate degrees of postmenstrual relief (between 25 and 75 percent according to the classification used here). This is numerically a wide range and there is likely to be overlap with the other two groups. Their psychological and physical symptom profiles were similar to those of the women with greater postmenstrual relief but with higher baseline levels of the psychological symptoms. They differed from those women with more complete degrees of postmenstrual relief by including significantly more with a history of past psychiatric problems, marital breakdown or larger family size. When compared with those with minimal or no postmenstrual relief, a similar number had a history of these latter factors. It is therefore not clear whether the women in this group actually differ from those whose problem has been labelled 'menstrual distress' except in relation to degree of relief of their symptoms during and following menstruation.

Comparison of the endocrine profiles of the women in these different groups did not identify any hormonal basis for the difference. The majority of the menstrual cycles which were monitored hormonally were normal in terms of the characteristics of their luteal phases and there was not an abnormal prevalence of anovular cycles. The evidence for and against a specific disorder of ovarian function is discussed in detail in the next chapter. From the results of the present study, it is not possible to reach any more detailed conclusions about the nature of the monitored cycles in the absence of data from control subjects and without accurate timing of ovulation with serial LH assay (see chapter 3). The profiles illustrated in figures 2.6 and 2.7 would not give support to a simple relationship between symptoms and either oestrogen or progesterone although an underlying hormonal basis seems likely. Equally, the psychological symptom pattern could be related to anticipation of impending menstruation, signalled by the physical symptoms. In later chapters of this thesis, suppression of ovulation and menstruation in women with cyclical symptoms is investigated. In practical terms, women with minimal or no postmenstrual relief are unlikely to benefit from any form of endocrine manipulation. For those in the intermediate category, anticipated benefit should be proportional to the magnitude of the relief although this hypothesis has never been tested.

It is possible that for many women who complain of adverse premenstrual mental changes, exaggerated physical symptoms are acting as a cycle marker so that they are making false assumptions about the relationship of other symptoms to cycle phase, for example the women illustrated in figure 2.4.1a. Similarly, in a subgroup of the women,

menstrual discomfort may be causing an exacerbation of mental symptoms during menstruation. It is also possible that some of these women have decreased tolerance to normal degrees of physical discomfort present premenstrually and during menstruation. Wood et al (1979a, 1979b) found a significant association between emotional difficulties and psychosexual problems and complaints of both premenstrual tension and menstrual pain. The only way of clarifying the relationship between the two groups of symptoms would be to abolish the physical components of the cycle and assess mental change in isolation. This approach is discussed in greater detail in a later section of this thesis.

Assessment of personality was not undertaken in this investigation because of potential difficulties in interpretation (see section 1.7). However it would have been interesting to correlate personality with degree of postmenstrual relief. As discussed earlier (section 1.7), an association between premenstrual complaints and neuroticism has been reported, also a relationship with psychiatric disorder. The results of the present study distinguish between premenstrual complainers whose symptoms are relieved postmenstrually and who are free of psychiatric problems and those with lesser degrees of postmenstrual relief. These latter women frequently have a background of psychiatric problems. Because psychiatric assessment was based only on reported past history, it might have underestimated the prevalence of psychiatric disorder in this group, in particular disorders of personality.

Both marital status and number of children were significantly associated with the degree of postmenstrual mood relief. A past history of marital breakdown may be an indicator of current life stresses, of minor psychological upset or alternatively of difficulties with personal relationships. Similarly, family size may be associated with environmental stress. It would have been relevant to assess formally the presence of stressful life events as there was an impression, while interviewing some of the women, that such factors were important. The role of stress in the aetiology of menstrual cycle related symptoms is of potential relevance. It is possible that there is an underlying physiological reason why women may be more vulnerable to stressful events premenstrually. Past studies have demonstrated that a wide range of medical conditions such as asthma and epilepsy may be worsened premenstrually (Magos & Studd, 1985) and the exacerbation of certain psychiatric disorders has already been discussed (section 1.7). Accidents, petty crime (Dalton, 1960a&b; 1961) and also major crime (Brahms, 1981) have been attributed to the 'premenstrual syndrome'. However, it is more likely that a tendency to poor performance and to perform violent and criminal actions is being exacerbated in a predisposed individual. The exact nature of any physiological factor is as yet unknown. One recent study of blood pressure patterns in women showed a premenstrual rise in blood pressure only when the measurements were made in the laboratory situation. When repeated in familiar surroundings, no premenstrual rise was seen (Greenberg et al, 1985). This suggests that the minor stress of the experimental situation was provoking this premenstrual blood pressure rise which was not seen during other phases of the cycle or when the stress was removed. Variation in the response of

the autonomic nervous system to stress according to menstrual cycle phase may be an important factor in the aetiology of cycle related symptoms. This theme is discussed in greater detail in chapter 7 of this thesis.

The visual analogue scales used here appear to be a suitable method of prospective assessment, adequately completed by 84% of the original sample. Their major disadvantage is that they are time consuming to analyse and thus are not suitable for routine screening purposes in a busy out-patient clinic or surgery. An alternative chart for routine use has been devised and its use is described in a later section (2.6). An assumption is being made that data obtained by monitoring one or two menstrual cycles is representative of the majority of such cycles experienced by an individual over several months. However good correlations were obtained between consecutive cycles in cases where sufficient data was available. Validity of the method might also be affected by a tendency for individuals to exaggerate the severity of their symptoms during assessment. One study has demonstrated that symptom scores using the VAS tend to be shifted towards the severe end of the scale compared with other methods (Faravelli et al, 1976). However, the method of analysis used here, based on severity of change in relation to baseline recording should allow for that tendency.

There are two recently published studies in which premenstrual complainers were assessed prospectively using visual analogue scales. One was based on a psychiatric clinic (Rubinow et al, 1984), the other on women referred to a gynaecological department (Abraham et al, 1985). A third group has reported a similar investigation (Halbreich

et al, 1985) using a different method of continuous assessment. All have come to very similar conclusions about the various patterns of symptomatology and the overall low proportion of women who actually exhibit a clear cut 'premenstrual tension syndrome'. One of the groups attempted to study a control population (Abraham et al, 1975) and found a similar prevalence of premenstrual symptoms among the volunteers. The patient group had higher symptom ratings during menstruation, again confirming the high prevalence of menstrually related complaints among the population of 'premenstrual complainers'. However, these results, like those presented in this chapter, do question the degree to which the reporting of cyclical symptoms depends on individual perception and attitudes rather than to the actual severity of the symptoms.

2.5 - Conclusions

Women who present for help with emotional problems which they attribute to the menstrual cycle should be asked to keep a prospective daily record of their symptoms, in order to determine their relationship to menstrual cycle phase. Their assessment must include a full social and psychiatric history and ideally an evaluation of personality and the presence of stressful life factors. The term 'premenstrual syndrome' does not appear to add anything positive to our understanding of the problems of these women. It merely refers to a group of symptoms and does not distinguish between normal physiological variation and a pathological condition. Nor does it allow for the fact that symptomatic women exhibit different symptom patterns. The alternative term 'menstrually related mood disorder' (Rubinow et al, 1984), although rather cumbersome is more appropriate

and clinically applicable. Its use is supported by the results of the present investigation.

It is suggested that classification of menstrually related mood disorder should be based on quantification of the degree of postmenstrual 'relief' of symptoms. This will be more informative than methods which do not take the baseline symptom levels into consideration. It is proposed that the term 'premenstrual tension' be restricted to women whose adverse mental symptoms are considerably relieved during the postmenstrual week. An arbitrary quantitative limit of relief by 75% or more postmenstrually could be used, although this may need to be altered in the light of further information from larger numbers of women. Where postmenstrual relief is negative or minimal (less than 25%), the term 'menstrual distress' is appropriate as symptoms usually persist throughout the cycle with slight exacerbation at menstruation. Between these limits there is a group of women who exhibit perimenstrual exacerbation of symptoms present to a varying degree throughout the cycle. These may be related to underlying problems which need to be defined for each individual, for example home stresses or a mild depressive illness. In practice there is bound to be overlap between these groups but it is necessary to set some limits when deciding about the suitability of therapy or criteria for inclusion in a treatment trial. Evaluation of responses to treatment should be performed with reference to pre-treatment degrees of postmenstrual mood relief. Not only will this assist with interpretation of results but also lead to further information about the relationship between symptom patterns and various causative factors.

2.6 - Evaluation of a simple descriptive scale in patients with premenstrual complaints

2.6.1 - Introduction

The visual analogue scales used for evaluation of women with premenstrual complaints in the study described in this chapter have previously been validated and are already in use in this context (see section 1.9.6). However, they are time consuming to analyse and not well suited for use in a busy gynaecological clinic or in a general practitioner's surgery where rapid on-the-spot analysis is necessary as an aid to diagnosis and further management. The object of the small study described below was to evaluate a simple descriptive chart in a population of women similar to those of the main study.

2.6.2 - Subjects and methods

All the women evaluated in this way were consecutively referred to the Reproductive Endocrine Clinic of the Edinburgh Royal Infirmary with premenstrual complaints. The criteria for inclusion were similar to those of the initial study (see section 2.2.1), except that women on oral contraceptives were specifically excluded. All the women were asked to complete the charts for 56 days starting on the day following their visit to the clinic. Six items were listed (figure 1.4; section 1.10.2) although space was left for inclusion of other symptoms if these predominated. Each symptom was scored daily on a 4-point scale as indicated.

For the analysis, the premenstrual, menstrual and postmenstrual phases were defined as previously described (sections 1.10.1; 2.2.3). Mental

and physical symptom scores for each cycle phase were calculated for each subject taking the mean of the scores for the two individual cycles. The physical score was the mean of the scores for breast discomfort and swelling and the mental symptom score the mean of scores for depression and irritability unless any other mental symptoms were listed. The percentage difference between the premenstrual and postmenstrual symptom scores and between the premenstrual and menstrual scores were calculated as described in section 1.10.1, giving the degree of postmenstrual and menstrual relief of both physical and mental symptoms.

An additional group of 15 subjects were asked to complete visual analogue scales for the initial assessment cycle and then the simple descriptive charts for the second month to enable a direct comparison of the two methods to be made. The postmenstrual mood relief obtained by the two methods was compared by calculation of Spearmann's rank correlation coefficient.

2.6.3 - Results

40 subjects were initially evaluated with the simple descriptive charts, of whom 37 returned charts which were satisfactorily completed. This non-compliance rate of 7.5% is lower than the rate of 16% with the VAS charts (section 2.3.2). In two cases, numerical scores were not used, merely ticks to indicate the presence of symptoms and the third subject 'mislaid' the chart.

In figure 2.7, the 37 women with completed charts are classified on the basis of the degree of postmenstrual and menstrual relief of the

Table 2.7

Postmenstrual and menstrual relief of physical and mental symptoms in 37 women who completed simple descriptive scales each day compared with 100 who completed daily visual analogue scales (VAS)

MENTAL SYMPTOMS

	number (%)	VAS score (%)
Postmenstrual relief		
75% or more	17 (45%)	32%
25% - 74%	10 (27%)	35%
Less than 25%	10 (27%)	31%
Menstrual relief		
Present	19 (51%)	56%
Absent	18 (49%)	44%

PHYSICAL SYMPTOMS

	number (%)	VAS score (%)
Postmenstrual relief		
75% or more	20 (62%)	67%
25% - 74%	8 (25%)	17%
Less than 25%	4 (13%)	16%
Menstrual relief		
Present	21 (66%)	64%
Absent	11 (34%)	36%

mental and physical symptoms. The corresponding figures obtained using visual analogue scales in the larger study (see table 2.3) are given for comparison. Although a higher proportion of the subjects completing the simple scales appeared to have greater than 75% relief of their mental symptoms postmenstrually, the proportions in the three groups do not differ statistically (chi-squared=2.10; 2 degrees of freedom). However, complete (100%) post-menstrual relief of mental symptoms was recorded by 10 (27%) of those completing the simple charts, compared with only 7 (7%) of the VAS group. At the other end of the scale, postmenstrual exacerbation of mental symptoms was recorded by 17% on the simple charts and 14% on the VAS charts. The breakdown of physical symptom relief was remarkably similar in the two groups.

Fourteen of the fifteen subjects asked to complete both types of assessment scale on consecutive cycles did so as instructed. Comments received about the two methods generally favoured the visual analogue scales in terms of greater sensitivity in expression of day to day fluctuations in mood and the women appreciated the space available on the VAS forms for additional remarks. One or two commented that they felt less motivated to complete the simpler charts each day. However others expressed relief that the duration of VAS recordings was limited to only one cycle. The degree of postmenstrual relief of the mental symptoms calculated by the two methods in the two consecutive cycles was found to be significantly correlated ($r=0.629$; $p<0.02$). In this group of subjects, only one of the fourteen recorded 100% relief of mental symptoms postmenstrually on the simple charts and the median

postmenstrual mood relief was no higher (50% with the simple charts compared with 61% with the VAS).

2.6.4 Discussion

The simple descriptive charts were very easy to analyse both visually and quantitatively and were appropriately completed by the majority of the women. When compared with visual analogue scales in the same group of women they appear to yield similar results. A highly significant intercorrelation between visual analogue scales and simple descriptive scales tested during the same cycle has recently been reported by Casper & Powell (1986). This is not altogether surprising when the recordings are being done simultaneously. Testing in consecutive cycles, as in the present study, may result in a greater discrepancy between methods. However highly significant correlations between symptom scores in consecutive cycles were previously found (section 2.3.6) and also reported by others (Chuong, 1985).

The simple charts appear to produce a shift in favour of recording complete postmenstrual symptom relief compared with the visual analogue scales. This may be because the simpler scoring system is liable to result in lack of recording of minor levels of symptomatology. In addition, the subjects may be more aware of cycle phase because of the way in which the chart is set out. Despite this, the two methods detected a similar number of women whose symptoms were clearly not premenstrual. Thus the use of a simple descriptive chart in the context of a general clinic or a general practitioner's surgery seems justified. Their sensitivity appeared to be greater in the group who had first completed the VAS charts for one month, perhaps

reflecting that these women had become accustomed to the practice of daily recording. In the clinical study described in chapter 6 of this thesis, where assessment of symptom response to prolonged therapy with an agonist of LHRH is based on these simple charts, the majority of the subjects had completed the standard VAS charts for two months at some time prior to recruitment.

CHAPTER 3

THE ENDOCRINE BASIS OF CYCLICAL CHANGE AND THE EFFECT OF HORMONE MANIPULATION - LITERATURE REVIEW

3.1 - Introduction

The relationship between premenstrual tension and the luteal phase of the cycle has led to speculation that there is an underlying disorder of ovarian function. Frank (1931) attributed the symptoms in severe cases to an excess of the 'female sex hormone'. He observed favourable results after extreme measures such as venesection, 'elimination' by diuretic agents or laxatives, and, if all else failed, ovarian irradiation! Israel (1938) more specifically considered the cause to be that of progesterone deficiency and found progesterone therapy to be beneficial in five out of seven cases with pituitary ablation therapeutic in another six. Morton (1950) demonstrated a luteal phase deficiency of progesterone in a high proportion of sufferers, based on endometrial biopsy studies and urinary pregnanediol excretion. However all subjects were sampled relatively late in the cycle. He also found that the symptoms could be induced by administration of large doses of oestrogen. On the other hand Gillman (1942) described profound mental symptoms in one subject following intramuscular administration of progesterone and symptoms including irritability, swelling and depression were recognised side effects of therapy with synthetic progestogens (Garcia et al, 1958), suggesting progesterone to be the provoking factor.

More recently several different approaches have been used in an attempt to clarify the relationship between ovarian steroids and the mental and physical symptoms which are associated with the premenstrual phase of the menstrual cycle. These approaches can be summarised as a list of questions:

1. Is there a distinct disorder of ovarian function in women classified as sufferers from premenstrual tension?
2. If so, does this respond to hormonal manipulation with currently available exogenous ovarian steroids?
3. Does the addition of cyclical progestogen provoke adverse physical and mental symptoms in postmenopausal women receiving hormone replacement therapy with oestrogen?
4. Do the combinations of oestrogen and progestogen present in the oral contraceptive pill produce adverse mood and physical changes and if so, is this related to the oestrogenic component, the progestogenic component or the relative proportions of the two?
5. Conversely, does the presence of the more constant plasma ovarian steroid levels associated with oral contraceptive therapy suppress or reduce cyclical symptoms?
6. Do other methods of suppression of ovulation abolish or reduce cyclical symptoms?

In this chapter the literature relevant to these questions will be reviewed in depth, although not necessarily in the order listed above. In addition, other current theories of the cause of premenstrual tension will be briefly discussed where relevant.

3.2 - Circulating ovarian steroids in normal and symptomatic women

There have been a number of studies based on assay of circulating ovarian steroids in small numbers of symptomatic subjects compared with women selected as controls. Most of these studies are open to serious criticism. In particular mood and symptom profiles during the cycle under study have usually not been presented for either the symptomatic or the control group. Some of the studies have been based on women presenting for medical help with their problem and others have recruited volunteers reporting cyclical changes so the populations under study may not be uniform.

Several groups have reported reduced luteal phase plasma progesterone concentrations. Backstrom & Carstensen (1974) found significantly higher oestrogen:progesterone ratios in ten sufferers from premenstrual anxiety and irritability on days 6 to 3 before menstruation, compared with eight healthy non-complainers. Two other women who suffered only from premenstrual headaches had results within the control range. Sampling was only carried out for six days premenstrually but the study was later repeated (Backstrom et al, 1976) when daily sampling was carried out for ten premenstrual days in 15 patients complaining predominantly of premenstrual anxiety and in 17 control subjects. Progesterone concentrations were again significantly lower during the mid-luteal phase in the symptomatic group. Oestradiol concentrations were lower early in the luteal phase but significantly higher in the late luteal phase, the latter preceded by significantly elevated FSH concentrations, although the mechanism of the latter rise is unclear.

The results of Munday et al (1981) were similar to those of Backstrom (1974, 1976). Twenty women diagnosed as suffering from premenstrual tension on the basis of daily symptom recording, were compared with 10 control volunteers by venous blood sampling every 2-3 days. They reported significantly lower progesterone concentrations in the mid-luteal phase with significantly higher oestradiol concentrations in the late luteal phase in patients compared with the control subjects. Smith (1975) studying subjects with premenstrual depression found plasma progesterone concentrations to be significantly lower over the seven premenstrual days compared with control subjects although the concentrations were not related to the symptom severity in any one cycle.

Others have failed to confirm the above findings. Taylor (1979a) could find no significant differences between plasma progesterone or oestradiol or their ratios in 39 young women sampled daily during the premenstrual week and on alternate days for the remainder of the cycle. Presence or absence of cyclical symptoms was determined by daily symptom ratings but as a group these were not women who had presented with premenstrual problems and thus were not truly representative of a pathological group. Interestingly, he found age was positively correlated with plasma progesterone concentration. Andersch et al (1979) also failed to demonstrate any differences in ovarian steroids between 20 women defined as premenstrual tension sufferers and an equal number of healthy volunteers studied over two cycles but subjects were only sampled once during the luteal phase. In contrast, O'Brien et al, (1980) compared 18 symptomatic women with 10 asymptomatic controls and found the symptomatic group to have

significantly higher concentrations of progesterone during the post-ovulatory phase although samples were taken only four times during the cycle and the mean age of the two groups is not stated. In addition, the 'symptomatic' group were selected from a group of volunteers on the basis of a premenstrual symptom rise on daily visual analogue scale recordings and had not originally presented for medical help with their problems.

In a further study, Backstrom et al (1983) were unable to demonstrate any significant differences in plasma oestrogen and progesterone concentrations, sampled at least three times weekly, between symptomatic and asymptomatic women. The subjects were two groups of 18 women drawn both from a clinic population and from a volunteer group. All completed symptom diaries each day throughout the study cycle and were classified on the basis of the results into high mood change and low mood change groups. Thus the methods used may be regarded as superior to those of his earlier studies (Backstrom 1974, 1976).

These above studies may also be criticised on the grounds that no accurate estimation of timing of ovulation was made, making the assumption that it preceded menstruation by exactly 14 days which is not invariably the case (Smith et al, 1984). The subjects of O'Brien et al (1980) kept basal body temperature charts which would not now be regarded as being of sufficient accuracy for timing (Templeton et al, 1982). In a study based on daily overnight 12 hour urine collections, Dennerstein et al (1984) were able to detect the pre-ovulatory oestrogen peak in order to standardise results during the luteal

phase. They found a high incidence (20%) of abnormal cycles among 19 patients, compared with a 4% incidence among 104 normal controls. Abnormalities included anovular cycles and short and deficient luteal phases. Another observation, that of a delayed rise in pregnanediol in patients compared with controls is invalidated by the imbalance of numbers in the two groups. However, they also reported significantly lower luteal phase peak pregnanediol concentrations among the patients compared with selected age-matched controls. The results may be criticised on the grounds that all the control data was based on 24 hour urine collections rather than the 12 hour collections of the patient group although the authors claim that no bias was introduced into the results by the use of the two different methods. These authors, unlike others, were careful to distinguish between patients with clearly defined premenstrual problems, compared with a 'menstrual distress' group (see section 2.4) where no such endocrine abnormalities were apparent.

Watts et al (1985) timed ovulation accurately by assay of plasma LH in 35 women defined as premenstrual tension sufferers on the basis of daily symptom recording compared with 11 control subjects. Apparent differences in luteal phase progesterone and oestradiol profiles between the two groups were largely accounted for by the occurrence of earlier ovulation in 18 of the 35 patients, compared with only 2 of the 11 controls. Follicular ultrasound in a sample of both groups showed the former to ovulate at smaller follicle diameters and lower concentrations of plasma oestradiol than the control group. Some of the patients showed a delayed progesterone fall in the late luteal phase, accounting for delay in onset of menstruation. Interestingly,

plasma cortisol concentrations were uniformly and significantly elevated in the patients compared with the controls, perhaps an indicator of increased stress. The potential importance of environmental stress in the aetiology of menstrual cycle related symptoms is discussed in section 2.4 and chapter 7. The significance of their findings have yet to be clarified, but these results tend to throw doubt on the validity of the earlier studies which failed to accurately time ovulation.

Considering the confusion in the literature about the basic criteria for diagnosis of premenstrual problems (section 1.3) and the heterogeneous group of women who present for help (chapter 2), it is not surprising that the above studies have yielded such discrepant results. As the majority of the above studies are open to criticism om methodological grounds, it is difficult to draw any definite conclusions, other than that as yet no gross abnormality in ovarian steroidogenesis has been demonstrated. Future research should be directed at studying the mechanisms controlling the cycle rather than drawing conclusions from minor differences in circulating ovarian steroids or their urinary metabolites.

3.3 - Other possible mechanisms

Several other theories have been put forward to explain the phenomenon of premenstrual change, either as alternatives to an imbalance of oestrogen/progesterone or in association with such a disorder. The lack of evidence supporting an abnormality of prolactin secretion has been discussed in section 1.8.6. Another popular theory was based on the observation that some cases of depression induced by the combined

oral contraceptive pill (see section 3.5) are due to a relative deficiency of vitamin B6 (pyridoxine). This subject is comprehensively reviewed by Rose (1978). There is some evidence that oestrogens increase the dietary requirement for vitamin B6 by induction of the enzyme tryptophan oxygenase with resulting increased turnover of the pathway of tryptophan metabolism. In addition, oestrogen esters may compete with vitamin B6 for an apoenzyme involved in the conversion of tryptophan to 5-HT (serotonin) in the central nervous system. Impaired synthesis of the latter has been postulated as a cause of depression (Ashcroft et al, 1966). Abnormal tryptophan metabolism, corrected by pyridoxine supplementation in a proportion of women with oral contraceptive pill associated depression was demonstrated by Adams et al (1974) in a placebo-controlled study. However there is no evidence that dietary pyridoxine requirements alter during the course of the normal menstrual cycle (Rose, 1978) and the benefit from its use in women with premenstrual tension was not confirmed in a placebo-controlled study (Stokes & Mendels, 1972). Indeed there is a risk that the consumption of high doses of pyridoxine by some premenstrual tension sufferers may result in toxic side effects (Dalton, 1985).

3.3.1 - Prostaglandins and the use of prostaglandin synthetase inhibitors

Prostaglandins are known to act as local hormone mediators of the actions of ovarian steroids in the uterus and to undergo changes in concentration during the ovulatory menstrual cycle (see section 1.2.3). This has led to theories that abnormalities of prostaglandin metabolism may be causative in premenstrual tension. Many of the

adverse symptoms associated with the latter may be provoked by the systemic administration of various prostaglandins, particularly E_2 and F_{2a} and prostaglandins are also present in gut, kidney, breast and the central nervous system (see reviews by Craig, 1980 and Budoff, 1986). However there is no direct evidence to support such a disorder and studies of plasma concentrations are unhelpful as prostaglandins are cleared rapidly from plasma. Similarly, claims that dietary supplementation with high doses of certain vegetable oils (e.g. evening primrose oil) has a beneficial effect by increasing the synthesis of prostaglandins of the E_1 group relative to the E_2 group (Abraham, 1983; Brush, 1982) remain unsubstantiated.

There have been several studies of the effects of prostaglandin synthetase inhibitors in women with premenstrual complaints. Significant benefit with mefenamic acid relative to placebo was reported by Wood & Jakubowicz (1980) and Jakubowicz et al (1984) in women whose symptoms were present both premenstrually and also during menstruation, with no benefit in the minority of subjects whose symptoms were confined to the premenstrual phase. An association between premenstrual and menstrual complaints was found in a proportion of the subjects described in chapter 2 (sections 2.3.4 & 2.3.5). These results may thus support a possible role of prostaglandins in this sub-group of symptomatic women but not those with symptoms confined to the premenstrual phase of the cycle. Prostaglandin synthetase inhibitors are of proven value in the relief of dysmenorrhoea (see review by Owen, 1984). In the latter condition abnormally high concentrations of prostaglandins in menstrual fluid have been demonstrated (Pickles et al, 1965; Chan et al, 1979; Dawood,

1983). There is also evidence for the involvement of PGE_2 in the aetiology of migraine (Budoff, 1986). It is thus possible that relief of psychological symptoms by prostaglandin synthetase inhibitors is secondary to relief of physical discomfort and headache. In a trial comparing naproxen sodium with placebo, Budoff (1986) found a significant benefit from active therapy for only 4 out of 46 symptoms assessed, one of these being headache. The others were tension, lack of self-control and 'jittery feelings'. None of these studies reported a reduction in breast discomfort, in contrast to that of Rolland et al (1979). The latter group did not however study the effects of prostaglandin synthetase inhibition (with aspirin or indomethacin) on other physical symptoms or on mood.

On the basis of the evidence presented above, no firm conclusions can be reached about the role of prostaglandins in the aetiology of premenstrual symptoms. A lack of consistent response to prostaglandin synthetase inhibitors does not exclude such a role as the doses used may have been insufficient and higher doses would be liable to produce unacceptable side effects.

3.4 - Cycle manipulation with exogenous ovarian steroids

Another approach to the study of the relationship between hormones and mood has been by observation of the effects of administration of exogenous ovarian steroids. The early reports of adverse effects following administration of large doses (section 3.1) have been followed up more recently by studies of the effects of various regimes of hormone replacement therapy in postmenopausal women. Hammarback et al (1985) studied 22 women who were receiving percutaneous oestrogen

replacement, 11 of whom were given oral progestogen supplements during the last 10 days of therapy, while the other half received the oestrogen alone. Analysis of daily visual analogue ratings showed small but significant changes in mood and physical symptoms in the latter part of the cycle in those receiving the progestogen. This study did not include a placebo control but the latter was included in a similar study by Magos et al (1986) involving 58 hysterectomised postmenopausal women receiving hormone replacement with oestradiol and testosterone implants. Compared with placebo, 5 mg of norethisterone given for 7 days out of 28 was associated with a significant increase in negative affect and physical symptoms. A dose of 2.5 mg also resulted in higher scores which did not reach significance but some cyclical changes were seen also with the placebo tablets, illustrating the vital importance of such a control group.

While these results appear to support the theory that premenstrual symptoms are provoked by progesterone, they are based on the administration of synthetic progestogens of the 19-nortestosterone group which may be more liable to produce such effects in low dosage than 'natural' progesterone (Dalton, 1977). Even if they provide an explanation for cyclical changes they still do not explain whether similar mechanisms underlie normal physiological variation in mood and physical symptoms, compared with those which might be regarded as pathological. Neither of these studies involved women who were selected as having previously suffered from cyclical symptoms. A potentially useful model for further study in premenopausal women would be suppression of endogenous ovarian activity by an agonist of LHRH with the addition of varying replacement doses of both 'natural'

and synthetic oestrogens and progestogens. The action and application of LHRH agonists is discussed in greater detail in chapters 5 and 6.

3.5 - Studies based on contraceptive steroids

Greatest experience of the use of oestrogens and progestogens in clinical practice has been in the field of contraception, particularly oral contraception. Adverse effects have been documented but so has improvement in well-being (Bakker & Dightman, 1966; Kane et al, 1967). It was not clear from early studies whether these changes were attributable to the progestogen or oestrogenic component and whether other factors were involved. There have been a few detailed studies of the effects of the oral contraceptive pill on mental and physical well-being and also of its effects on pre-existing cyclical symptoms. The latter is of interest in view of the absence of ovulation and the more constant hormonal environment associated with therapy. The number of detailed studies performed have been few but are of relevance to several areas of this thesis and some of these will be discussed in detail. They are summarised in table 3.1.

3.5.1 - Descriptive studies

Several descriptive studies have been reported, all with the object of determining whether oral contraceptive steroids cause adverse physical and mental changes. The majority also specifically considered effects on pre-existing cyclical symptoms although only two of the studies followed these prospectively, the others relying on retrospective interviews. In these studies, the subjects were either assessed before and during therapy or compared with a control group of women not using oral contraception.

TABLE 3.1 - EFFECT OF ORAL CONTRACEPTIVES ON WELL-BEING AND CYCLICAL SYMPTOMS

Authors	Subject number	Duration	Control group	Formulation	Assessment method	Overall symptoms	Cyclical symptoms
A - Descriptive studies							
Bakker & Dightman (1966)	100	4 years	none	various	retrospective interviews, MMPI depression scale	no overall changes	subjective improvement in PMT
Nillson & Solvell (1967)	126	1 year	none	4 types randomised	monthly interviews	no change in psychological or physical symptoms	significant reduction in PMT during therapy
Herzberg & Coppen (1970)	152	1 year	women not on pill	various	mood and physical symptom scales on four occasions	side effects more frequent in pill group	significant reduction in PMT in pill group
Paige (1971)	102	1 cycle	women not on pill	various	content analysis of speech 4 times during cycle	negative affect unchanged	cyclical changes abolished by pill
Kutner & Brown (1972)	5151	cross-sectional	past & never users	various	single interview, mood scales, MMPI depression scale	moodiness reduced in current pill users	reduced in current pill users
Wilcoxon et al (1976)	33	35 days	no-pill users & males	various	daily MMDQ, MACL, stress inventory	behavioural changes reduced on pill	cyclical changes maintained but reduced on pill

TABLE 3.1 (cont) - EFFECT OF ORAL CONTRACEPTIVES ON WELL-BEING AND CYCLICAL SYMPTOMS

Authors	Subject number	Duration	Control group	Formulation	Assessment method	Overall symptoms	Cyclical symptoms
Sheldrake & Cormack (1976)	3323	cross-sectional	women not on pill	various	single questionnaire check-list	physical symptoms reduced on pill	premenstrual mood changes increased
Andersch & Hahn (1981)	812	cross-sectional	women not on pill	various	single questionnaire, rating scales	pill users less frequently absent from work	age-related reduced prevalence of PMT symptoms
B - Placebo-controlled studies							
Goldzieher et al (1971)	398	6 cycles	placebo cross-over	4 types randomised	monthly interview for nervousness & depression	both reduced by pill, no change on cross-over	not assessed
Silbergeld et al (1971)	8	4 cycles	placebo cross-over	single	daily MMDQ, MACL, interview rating	reduced aggression increased drowsiness	smoothing out but not obliteration of cyclical change
Cullberg (1972)	80	2 cycles	placebo	3 types randomised	monthly interview, MDQ, psychic chang questionnaire	low incidence of adverse reactions	pre-existing PMT largely unchanged
Morris & Udry (1972)	51	1 cycle	placebo	combined & sequential	daily reporting of well-being	no overall differences	premenstrual decline seen in pill groups

Bakker & Dightman (1966) found no increase in tension or depression in 100 women receiving a single agent (Enovid) over 4 years. The women reported an overall improvement in premenstrual tension during therapy. Isolated episodes of depression occurred but were attributed to adverse environmental factors or affected individuals with a pre-pill history of depression. Kutner and Brown (1972b) in a cross sectional study also found current depression to be significantly related to a past history of depression, regardless of contraceptive status. They found that there were significantly fewer reports of premenstrual moodiness and irritability among current pill users compared with past users or women who had never used oral contraception (Kutner and Brown, 1972a). Depression was highest in women taking pills with a lower progestogen content.

However, in a randomised study designed to look at side effects of four different oral contraceptive preparations, Nilsson & Solvell (1967) were unable to demonstrate any differences related to the formulations selected, using monthly interview assessments. Forty percent of their sample of 159 women complained of premenstrual tension prior to starting the oral contraceptive and a statistically significant decrease was reported during the initial 4 months of the study, with a further decline to five percent at 12 months. Unfortunately there was no placebo control.

In another early study in which a group of women commencing the pill were compared with a group starting barrier contraception, Herzberg and Coppen (1970) also reported a significant improvement in

premenstrual mood in the pill group. Assessment was by regular retrospective interviews. However premenstrual and menstrual swelling and headache were unchanged. Physical side effects were commoner in the pill group and although the incidence of psychological side effects was small, depression was reported by more of the pill takers. In keeping with the studies mentioned above, the latter were significantly more likely to have a pre-pill history of depression, compared with the pill takers as a whole. Their pretreatment Maudsley Personality Inventory also showed higher scores for neuroticism and extraversion. No relationship between pill formulation and reported side effects was apparent.

Beneficial effects of oral contraceptives on cyclical symptoms were supported in a more intensive study in which Paige (1971) prospectively studied mood and cyclical changes in 102 married subjects, 52 who took combined oral contraception, 12 on sequential oral contraception and 38 who used non-hormonal methods. Detailed assessment by content of speech analysis was carried out four times during each cycle. This showed cyclical differences in negative affect in the non-pill and sequential pill group which were not present in those on the combined pill.

In another detailed prospective study, Wilcoxon et al (1976) recruited volunteers who were not aware of the true purpose of the study. Detailed daily assessments were carried out on 11 female students not taking oral contraceptives, 11 using the combined pill and 11 male subjects who were arbitrarily assigned 'pseudocycles'. Overall behavioral changes, both positive and negative were lowest in

males and lower in the women receiving the pill than the no-pill group. Negative mood and anxiety showed a peak during menstruation in the no-pill group and premenstrually in the pill group. Physical symptoms peaked both premenstrually and menstrually in both female groups, but scores were highest during menstruation in the no-pill group. However an analysis of co-variance suggested that the negative mood changes were more closely associated with stressful events which occurred premenstrually in both groups, rather than with cycle phase although no such cluster of stressful events was seen in the males. The results support a 'damping down' effect of normal behavioural changes in women on oral contraception with reduction of symptoms during menstruation but not premenstrually. In common with the last study, these subjects had self-selected their contraceptive methods and thus conclusions based on comparisons between the two may not be truly valid.

All the above studies were based on contraceptive formulations containing higher doses of oestrogen than those in current use. One uncontrolled study was based on a single cycle of daily ratings in 12 subjects receiving a combined pill containing 30 mcg of oestrogen. No significant change in anxiety was seen during the course of the cycle although there was a steady increase in the depression score (Forrest, 1979). The author attributed this to a metabolic effect of the pill (see section 3.3). A more recent cross-sectional study (Andersch & Hahn, 1981) can be presumed to have included women on low-dose formulations although this is not actually stated. The authors selected women from five specific age groups, comparing 217 current pill users with 595 women not on the pill. The women were given a

questionnaire which asked specifically about six premenstrual symptoms and their severity. A significantly reduced prevalence of irritability, sadness, anxiety and breast discomfort but not swelling was reported by 25 year old pill users. Similar but non-significant trends were also seen in pill users aged 32, 39 and 46, although these groups were smaller. However, the reverse was true for pill users aged 18, where the prevalence of all the individual symptoms, both physical and psychological, was greater compared with non pill users.

Age may have influenced the results of another, earlier, cross-sectional study of a student population reported by Sheldrake & Cormack (1976). Using a single retrospective questionnaire check-list which asked about both menstrual and premenstrual symptoms, a reduced prevalence of physical symptoms was reported by 756 pill takers, compared with 2543 students not on the pill. However the former group reported an increased prevalence of adverse psychological symptoms during the premenstrual but not the menstrual phase of the cycle. This latter observation is in keeping with those of Wilcoxon et al (1976) in the study discused above which was also based on undergraduate students. The data of Sheldrake & Cormack was not subjected to statistical analysis but does raise the question of an age-related effect which may need to be taken into consideration when interpreting the results of pill studies. Such an effect may however be related to fundamental differences between the individuals who choose to use the pill and non-users.

With the possible exception of women in the younger age groups, the studies discussed above did not reveal any overall adverse

psychological effects from oral contraceptives, except in women with a past history of such problems. Indeed the majority reported an improvement in cyclical symptoms. Ideally such studies should be randomised and a placebo group included. Clearly this raises problems when the object of the therapy is to prevent conception. Preconditioning and expectation are likely to play an important role in an individual's response to therapy. An interesting study which could never now be repeated was reported by Aznar-Ramos (1969) from Mexico. One hundred and forty seven young married women were given placebo tablets and told they were an oral contraceptive. A remarkably high incidence of 'steroid-like' side effects were reported. Bakker & Dightman (1966) categorised the adverse effects of oral contraception into 3 groups; those actually attributable to the steroids themselves, those where the pill might be regarded as a 'scapegoat' eg weight gain and those which are suggestion-induced, for example by hearing about adverse effects from other sources. It is thus apparent that only limited conclusions may be drawn from these uncontrolled studies.

3.5.2 - Placebo-controlled studies

One early study, in contrast to the others discussed here, was based on women receiving depot medroxyprogesterone acetate for contraception (Seymour & Powell, 1970). One common side effect of this preparation is irregular bleeding and amenorrhoea (Fraser & Weisberg, 1981) for which cyclical oestrogen was given to half the 752 subjects, with placebo to the other half in a double blind manner. Side effects during the period of supplementation were documented and found to be

identical in the two groups, with the exception of amenorrhoea which was higher in the placebo group.

Four placebo-controlled studies of the effects of the oral contraceptive pill have been reported, all using rather different designs and methodology. The largest was described by Goldzieher et al, 1971a & b) who studied 398 subjects over 1523 cycles, comparing the side effects of different contraceptive formulations with each other and with placebo. Assessments were made by monthly interviews with no attempt to study cyclical patterns. After preliminary pretreatment assessment, the subjects were randomly assigned to several groups. All received a single therapy for four cycles after which those on placebo crossed over to either low oestrogen (50 mcg) or no oestrogen (progestogen-only) formulations. The high oestrogen groups crossed over to no oestrogen and vice versa. Results showed all physical and mental symptoms normally associated with the menstrual cycle or with contraceptive steroid therapy to be reduced during treatment, with the exception of nausea. A significant fall in reports of depression were seen in all groups during therapy with no significant differences between groups although there was a trend towards higher reporting in the groups taking high oestrogen preparations. However after the cross-over there was no significant deterioration in the group switching to high oestrogen. Nervousness showed significantly less reduction during the first treatment cycle among women taking high oestrogen preparations compared with the placebo group. This however did not persist beyond cycle 1 and no increase in nervousness was apparent when the oestrogen free group switched to high oestrogen.

An overall low incidence of adverse reactions to contraceptive steroids was also reported by Cullberg (1972), although in this study reactions were least in the placebo group. Four groups of 80 women were randomised between therapy with placebo or with one of three combined oral contraceptives containing 50 mcg of ethinyloestradiol and 1.0, 0.5 and 0.06 mg of norgestrel respectively. Assessments were made by interview and questionnaires before and after two months of therapy. The group taking the oestrogen-dominated preparation were rated significantly higher for irritability and depression than the other three groups but prior assessment of personality had shown the adverse reactors of this group to be emotionally more labile and more neurotic. An association between adverse reactions to oral contraceptives and neuroticism had also been reported by Herzberg & Coppen, 1970 (see section 3.5.1 above). Women with a previous history of premenstrual irritability were more likely to experience relief on the high progestogen preparation and exacerbation with the high oestrogen formulation. However among women without a previous history of emotional upset, there were more adverse reactions to the high progestogen preparation.

Two detailed placebo-controlled studies assessed symptoms on a daily basis and, in contrast to most of the other studies reported above, found cyclical patterns to persist during oral contraceptive therapy. Morris & Udry (1972) randomised 51 women to therapy with a combined preparation, a sequential preparation or placebo over one cycle. They did not study specific symptoms but each subject recorded her overall feeling of 'well-being' each day. There were no overall significant

differences between the groups but those on placebo felt least well during menstruation and both pill groups felt worst premenstrually. Silbergeld et al (1971) performed a cross-over study in 8 women, comparing two cycles on active therapy with two cycles on placebo. The pill reduced physical discomfort and irritability but increased nausea, breast discomfort, swelling and drowsiness. Significant cycle phase effects were seen irrespective of therapy for pelvic discomfort, breast tenderness, irritability, tension and aggression but not depression. All these symptoms peaked either premenstrually or during menstruation. However the oral contraceptive did appear to reduce the magnitude of these changes.

3.5.3 - Conclusions from contraceptive studies

Overall, these studies do not demonstrate an excess of adverse reactions to oral contraceptive steroids, regardless of formulation. However the majority included relatively high doses of ethinyl-oestradiol (50 mcg), higher than that in current use and the conclusions cannot necessarily be applied to lower dose preparations. The results support a 'damping down' but not obliteration of cyclical symptoms in women who experienced such problems prior to therapy.

It is relevant that all three studies which showed persistence of cyclical symptoms were based on daily recordings. The presence of such changes does not necessarily imply that they were distressing to the individual or would have been reported in an interview. However, the presence of a premenstrual symptom peak is difficult to explain on the basis of hormonal changes. Endogenous ovarian steroids remain suppressed throughout therapy with little fluctuation even in the

pill-free week and the exogenous steroids are fairly constant except on withdrawal (Elstein et al, 1976; Brenner et al, 1977). Persistence of premenstrual symptoms under these circumstances does suggest that other factors such as conditioning (see section 1.7) are involved.

There is some evidence that oestrogen-dominated preparations evoke more adverse reactions than other preparations, particularly in individual predisposed to such problems. Several of the studies found a relationship between past psychological problems and 'pill-induced' mood changes. This implies either that these women are more sensitive to the effects of exogenous steroids or that the pill was being 'blamed' for the symptoms. Only one of the studies (Cullberg, 1972) reported greater adverse effects from a progestogen dominated pill, in this case women previously free of psychological problems or cyclical symptoms.

3.6 - Progesterone and progestogens in the management of premenstrual tension

While the results of these oral contraceptive studies are of interest in relation to the effects of exogenous ovarian steroids on mood, the subjects were not selected for study because of pre-existing cyclical problems and to date there have been no reported controlled trials of the therapeutic use of the pill in premenstrual tension. There have been a number of treatment trials (see below) investigating the use of progesterone and progestogens in the management of premenstrual tension. The results are a source of further information about the relationship between progesterone and progestogens and mental and physical well-being.

3.6.1 - Progesterone

The use of supplementary progesterone during the second half of the cycle was first advocated by Dalton (1977), based on the assumption, then and still unproven (see section 3.2), that the syndrome was attributable to a progesterone deficiency. She claimed considerable success from therapy (Dalton, 1977) but performed no controlled trials. Some of her patients required very large doses for relief (up to 1200mg/day) which results in plasma concentrations greatly in excess of those seen physiologically. Urinary pregnanediol concentrations five to ten-fold higher than those present in the mid-luteal phase of the normal cycle were observed in two patients managed personally who had increased their daily dose of intravaginal progesterone to 1200mg/day. Doses of between 200 and 500 mg have been reported to induce rapid hypnosis when administered as an intravenous bolus (Merryman et al, 1954). It is thus very probable that these large rectal/vaginal doses are having a direct pharmacological sedative action.

Two placebo controlled studies failed to support Dalton's results. Smith (1975) showed no benefit from 50 mg of progesterone given intramuscularly on alternate days from day 19 of the cycle in patients with premenstrual depression. In a double blind cross-over study, Sampson (1979) compared progesterone 200mg twice daily with placebo, given for 12 days premenstrually over one cycle. Symptoms were self assessed daily with the Moos Menstrual Distress questionnaire. Thirty five out of 39 subjects completed the study but no significant benefit was seen. Twenty four of the subjects were then treated with

progesterone 400 mg bd compared with placebo. Here there was a worsening of symptoms with the active therapy, perhaps unexpected in view of the above observations made by Dalton.

A third cross-over controlled study investigating the use of progesterone did show a positive benefit over placebo (Dennerstein et al, 1985). This differed from the earlier trials in the use of an orally active form of progesterone (micronised progesterone which is not currently available for routine use). This was given at a dose of 300 mg daily, starting approximately 3 days after ovulation. Two active and two placebo cycles were studied in 24 subjects, only one of whom subsequently withdrew. Assessments were made by monthly interviews, affective tests and daily symptom records. Overall changes were in favour of the progesterone, but of a large number of parameters assessed by interviews and psychometric tests, only fluid retention, control, stress and anxiety were significantly improved with active therapy during the first treatment month. Only 'fluid retention', assessed subjectively, showed significant improvement over both treatment cycles. The daily symptom records (10 symptoms) showed a significantly better response to active therapy for depression and swelling during the first month. Hot flushes as well as swelling were significantly improved over both cycles. The greater response to the active therapy during the first rather than the second treatment month does question whether the effect would have been sustained for much longer. The positive effect of progesterone demonstrated by this study appears to be restricted largely to physical symptoms and does not convincingly support the theories that premenstrual symptoms are a consequence of progesterone deficiency. However the effects on 'fluid

retention' would be worthy of confirmation in a further study which incorporated more detailed assessment of fluid and electrolyte balance and daily weighing (see section 1.8.2).

3.6.2 - Progestogens

The need to administer progesterone by intramuscular injection or by the rectal or vaginal route led to investigation of the use of oral synthetic progestogens as an alternative. This was again based on the assumption that the underlying problem was one of progesterone deficiency. An early placebo-controlled study was reported by Swyer (1955), who compared the effects of ethisterone, mephenesin (a muscle relaxant) and placebo taken from days 15-25 of the cycle. No significant differences emerged although mephenesin brought relief more often than ethisterone. Jordheim (1972) compared medroxyprogesterone acetate (MPA) 7.5 mg for 10 days premenstrually with MPA combined with a thiazide diuretic in a double blind cross-over study of 35 patients. Unfortunately there was no placebo group although he did compare the combined therapy with placebo in a group of student nurse volunteers. No significant differences emerged, although the premenstrual symptoms did not appear to be exacerbated by the progestogen.

More recently there has been considerable enthusiasm for the use of dydrogesterone (Duphaston - Duphar). It was selected because of its closer structural resemblance to progesterone than other synthetic progestogens, although it has less progestogenic potency (Swyer & Little (1962). The chosen regimen has been 10 mg twice daily from days 12-26, i.e. commencing in the late follicular phase or around the

time of the mid-cycle surge. The reason for the choice of this regimen has not been stated. The widescale current use of the therapy was based on a single-blind study by Kerr et al (1980), who recruited 103 patients for treatment over 6 cycles, but encountered a drop out rate of 35%. All patients were initially assessed over one cycle and described as 'symptom free' 2 days after the onset of menstruation. After an initial placebo cycle, active therapy was given for 3 cycles, followed by 2 further placebo cycles. The results are reported in terms of the gynaecologist's assessment by interviews conducted prior to each change over and at the beginning and end of the study. The results of daily diary charts completed by the subjects were not described. A 43% response to the initial placebo cycle was reported with an overall improvement in depression, irritability, and abdominal swelling but no reduction in breast discomfort. 21% of the subjects improved only on the active therapy.

Clearly the single-blind design of the last study is open to criticism and a large multi-centre study was set up in four European countries, based on general practitioner populations of women. This was not a cross-over study but involved treatment over 3 cycles with either Duphaston or placebo, after an initial control month. Simple diary cards were used to record the presence and severity of 6 psychological and 7 physical symptoms on a daily basis, and the subjects were interviewed and their symptoms rated each month. A preliminary report of the Dutch part of the study involving 150 women, of whom 123 completed the treatment, showed significant differences between the two groups (Haspels et al, 1981). Overall symptoms scores at the end of therapy demonstrated that 73% of the subjects had improved on

active therapy and 53% on placebo. This difference was statistically significant. However, the only individual symptoms to show a significant improvement were depression and breast discomfort. The full study was reported by Williams et al (1983). Data from only 300 of the 421 subjects recruited was analysed, the remainder being excluded prior to analysis for various reasons. Drop out during therapy was low in both groups, at 14.3% from active and 12.1% from placebo therapy. Results were again expressed in terms of the results of the monthly interviews and data from the daily record cards was not presented, perhaps because insufficient numbers had been completed or handed back. There were no significant differences between the two groups for any individual symptoms although trends favoured the Duphaston for depression, aggression, backache and swelling. They favoured placebo for nausea. However 'global' assessment of efficacy made by both the subjects and the physicians at each visit significantly favoured active therapy at the end of three but not two months.

In view of doubts regarding the methodology of these studies and the rather equivocal results, further double blind placebo-controlled studies have also been conducted by Sampson and colleagues and Dennerstein and colleagues, crossing over two months of active therapy with two months of placebo. Using identical methods of assessment to those used in their double blind study of oral progesterone, Dennerstein et al (1986) failed to find any significant differences between active therapy and placebo, although the maximum benefit from both was present during the initial two treatment cycles. A

preliminary report by Sampson et al (1983) also failed to demonstrate a significant benefit from active therapy.

Overall these results do not convincingly support any positive effect from Duphaston although it is still possible that the benefit reported by Williams et al (1983) from more prolonged therapy reflected a gradual decline of the placebo effect over the 3 months of the study. One interesting result to emerge from the study of Kerr et al (1980) was that luteal phase progesterone concentrations were significantly reduced during active therapy. This suggests that any benefit from the Duphaston is exerted through interference with ovulation rather than by 'boosting' progesterone levels. Past studies of the effect of cyclical dydrogesterone therapy on ovulation have yielded conflicting results; some reporting lack of inhibition (Bishop et al, 1962) at a dose of 10 mg bd from days 5 to 26. However, ovulation suppression with the same dose regime has also been reported but in a much smaller number of subjects (Jaffe et al, 1969). A recent study by Lenton (1984) of six subjects who commenced therapy in the mid-follicular phase has demonstrated absence of a mid-cycle gonadotrophin surge but with subsequent luteinisation. It is thus probable that commencement of therapy prior to this surge modifies later events in the cycle with consequent effects on cyclical symptoms. This suggests that an alternative approach to treatment may be by suppressing ovulation.

3.7 - Studies involving inhibition of ovulation

Studies investigating the effect of inhibition of ovulation with cyclical progestogens and with LHRH analogues are the basis of chapters 4, 5 and 6 of this thesis. Recently there have been several

published reports of alternative approaches to ovulation suppression. One involved administration of an implant of oestradiol (100 mg) to suppress ovarian activity, accompanied by regular oral progestogens to induce withdrawal bleeds. This was compared with an identical placebo regime (Magos et al, 1986). The study did not incorporate a cross-over and the placebo response was initially extremely high at 93%, possibly because of the 'surgical' nature of the treatment. However as the placebo effect declined with time, the active therapy became significantly more effective. Although the success of this therapy is attributable to suppression of ovulation, a direct steroid effect cannot be excluded. Serum oestradiol concentrations were considerably elevated 3 months after administration of a 100 mg depot of oestradiol (Thom et al, 1981) and gradually rising concentrations have been documented over 36 months in postmenopausal women receiving 50 mg depots for hormone replacement therapy (Barlow et al, 1986). Thus it is possible that supranormal oestrogen levels are being achieved, equivalent to those around mid-cycle, which has been associated with an increased sense of well-being and a peak of positive mood (Sanders et al, 1983). Anecdotal evidence is available from one patient managed personally who was treated in this way while resident in London and who continued therapy for almost 3 years. On stopping therapy, her serum oestradiol remained over 1000 pmol/l for over 18 months from the time of the last implant with resulting irregular bleeding and endometrial hyperplasia. This raises concern about the long term safety of such therapy in young women particularly with regard to the risk of endometrial carcinoma.

Another way of suppressing ovulation is with the antigonadotrophin danazol. Gilmore et al (1985) conducted an elaborate double-blind cross-over study of danazol 400 mg daily compared with placebo, each over three cycles. Only 20 of the 39 subjects recruited completed both phases of the study but among those who did, significant improvements in physical and mental symptoms were seen. In a second report (Watts et al, 1987), 27 out of 40 women completed a study comparing three different doses of danazol with placebo over three cycles but not incorporating a cross-over. Twelve of the thirteen drop-outs were from active therapy and related to side effects. Nevertheless, in those completing the study, significant symptomatic improvement was documented by daily records. A 200 mg daily dosage was better tolerated but was not invariably associated with suppression of menstruation. Whether or not ovulation was suppressed was not reported. However the 400 mg dose was associated with amenorrhoea in the majority of the subjects and the benefit of therapy may be related to loss of awareness of impending menstruation. A better model for ovulation suppression would involve maintenance of menstrual cyclicity, such as occurs with the combined oral contraceptive pill or with cyclical norethisterone (see chapter 4).

One theoretical concern about the long term use of danazol is its metabolic effects. Danazol has androgenic, anabolic and antioestrogenic properties (Luciano et al, 1981). Presumably because of these androgenic effects (Heller et al, 1983), it has been shown to produce significant alterations in lipoproteins, with consistent and significant falls in high density lipoprotein-cholesterol (HDL-C) to around 40% of pre-treatment levels (Malkonen et al, 1980; Allen &

Fraser, 1981; Fahraeus et al, 1984). The dose used in these studies was 400-800 mg/day but similar changes have been reported with daily doses as low as 200 mg/day (Luciano et al, 1983). Significant rises in low density lipoprotein-cholesterol were found in some of these studies (Malkonin et al, 1980; Allen & Fraser, 1981; Fahraeus et al, 1984). Both an elevation of LDL-C and, in particular, a fall in circulating HDL-C are regarded as strong risk factors for the development of coronary heart disease (Gordon et al, 1977; Kannel et al, 1979). The above studies all demonstrated a rapid reversal of the abnormal lipoprotein profiles to normal 1-2 months after cessation of therapy. This is reassuring in relation to the management of endometriosis where therapy rarely exceeds 6-9 months in duration but is of considerable concern if danazol is to be used widely in the management of premenstrual tension where therapy may be continued for a number of years.

3.8 - Conclusions

Despite this extensive literature, it is difficult to draw firm conclusions about the relationship between endogenous and exogenous ovarian steroids and mood and physical change. In answer to the questions posed at the beginning of this chapter (section 3.1), a number of comments can be made.

1. There is no good evidence to support a disorder of ovarian steroidogenesis in women with premenstrual problems although conclusions are limited by differences in the populations selected for study and methodological deficiencies.

2. The approach to therapy most widely used to date, namely based on 'boosting' luteal phase progesterone concentrations, has on the whole been unsuccessful and is probably ill-founded, although further studies of oral progesterone are indicated.

3. Progestogens given cyclically to women receiving oestrogen alone for hormone replacement therapy can produce mild symptoms similar to those present premenstrually in normal women, but so also can placebo.

4. There is little evidence that any combined oral contraceptive formulations provoke adverse mental symptoms in normal women although they may exacerbate pre-existing problems in susceptible individuals.

5. Hormonal manipulation of the cycle by contraceptive steroids does appear to reduce cyclical symptoms, although this conclusion is based on populations of 'normal' women rather than those presenting with adverse symptoms.

6. Although therapies which involve ovulation suppression appear to reduce the intensity of cyclical symptoms, there may be other mechanisms involved in their action.

The next sections of this thesis explore alternative methods of ovulation suppression in the management of premenstrual problems.

CHAPTER 4

SUPPRESSION OF OVULATION WITH CYCLICAL ORAL PROGESTOGENS - THE EFFICACY OF MEDROXYPROGESTERONE ACETATE AND NORETHISTERONE COMPARED WITH PLACEBO

4.1 - Introduction

As already discussed (section 3.2), there is no convincing evidence for any gross endocrine abnormality in the aetiology of premenstrual tension. The relationship between the symptoms and the luteal phase of the cycle does however suggest that suppression of ovulation would be a logical approach to management. There is a surprising lack of studies which use this approach in the literature. The effect of the oral contraceptive pill on mood and cyclical change has been evaluated in the past and results have on the whole supported a damping down of cyclical problems with its use (section 3.5). However the subjects of such studies had been receiving therapy for contraceptive purposes, not for management of cyclical problems and thus represent a different population of women. The age and reproductive status of our population of premenstrual tension sufferers (see section 2.3.1) makes the use of the combined pill inappropriate as a therapy as surgical sterilisation was the most frequent method of contraception and half the women were aged 35 years or more. Progestogens used alone will inhibit ovulation in adequate doses (Garcia et al, 1958; Taymor, 1964) when commenced in the follicular phase or used continuously but have never been previously evaluated in this way for the management of cyclical symptoms. The object of the following study was to investigate the effect of suppression of ovulation with

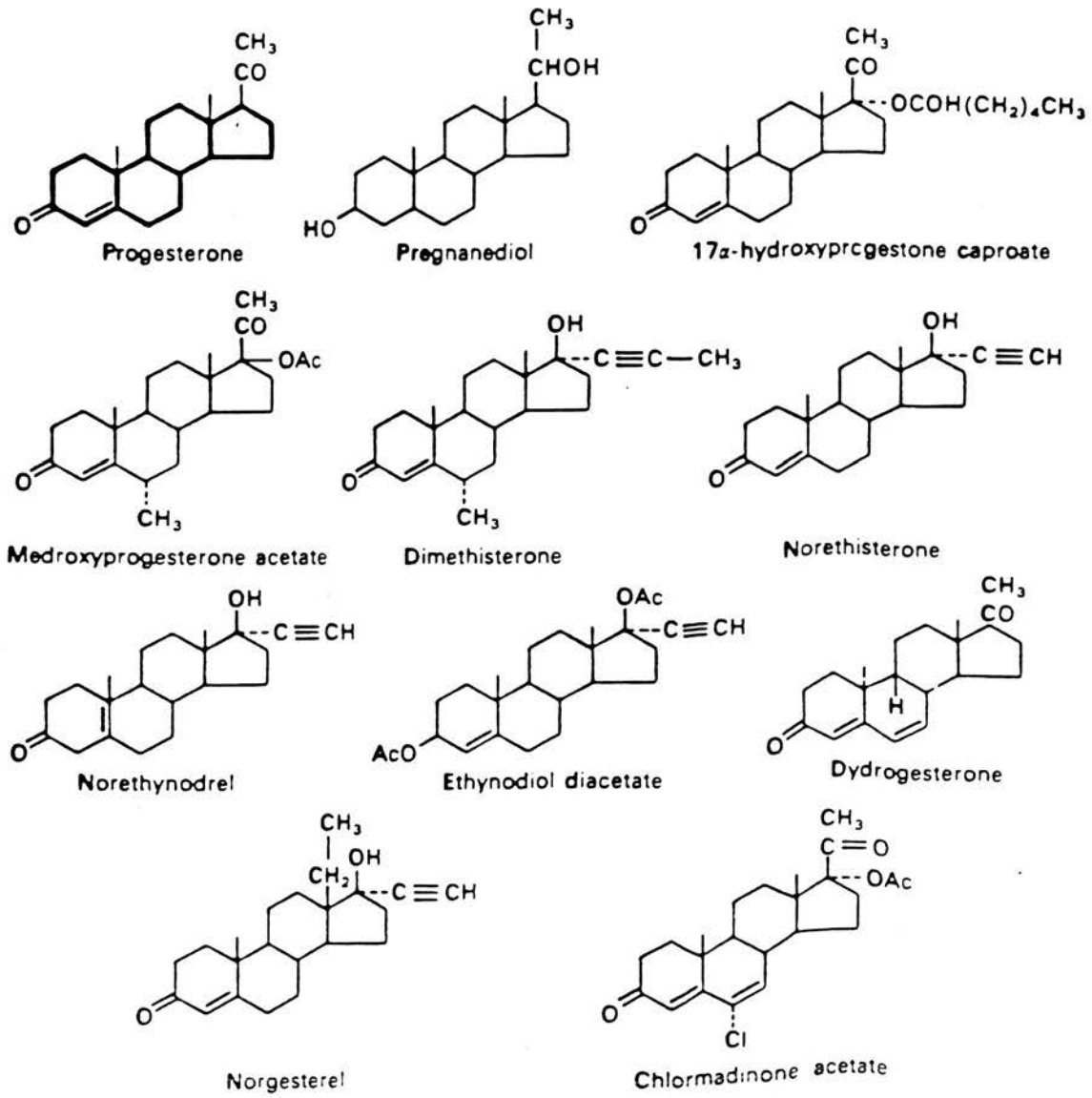
two commonly used progestogens on the symptoms of premenstrual tension. A small uncontrolled pilot study had already been conducted on 9 women attending the clinic, with promising results (Backstrom, 1979 - unpublished observations). It used the dose regime and schedule which was adopted in the present study.

The two progestogens selected were norethisterone (Primolut-N - Schering Pharmaceuticals) and medroxyprogesterone acetate (Provera - Upjohn Ltd). Their structures are shown in figure 4.1. Norethisterone (NET) is a derivative of 19-nortestosterone (Pincus, 1956), and is used extensively in oral contraceptives as well as in the management of other gynaecological conditions (Bishop & de Almeida, 1960; Rock et al, 1960) although its use in gynaecological practice has not been subjected to controlled clinical trial. At a dose of at least 10 mg daily from days 5-26 of the cycle it was shown to suppress ovulation (Garcia et al, 1958; Brown et al, 1962) with associated relief of dysmenorrhoea (Bishop, 1962).

Medroxyprogesterone acetate (MPA), a derivative of 17a-hydroxy-progesterone, was first described by Wied & Davis (1959) and was available in a parenteral as well as an oral form from an early stage. Its lack of androgenicity led to its early use in the management of threatened and recurrent abortion (Goldzieher, 1964). The prolonged ovulation inhibiting effect of the depot form was initially regarded as an unfortunate side effect of therapy (Rubin, 1964), before its potential as an injectable contraceptive was further investigated (Coutinho, 1966). The oral form was investigated as a contraceptive in combination with oestrogen (Eichner, 1963) although it never became

Figure 4.1

Structure of progesterone and synthetic progestogens



established as a component of the combined pill because of a single report of an association with benign breast tumours in beagle bitches (Finkel & Berliner, 1973). Later literature on this subject has been reassuring (Fraser & Weisberg, 1981). As a single agent, suppression of ovulation with oral therapy was reported at a dose of 10 mg/day from day 5 of the cycle (Eichner, 1963). Its use in the management of premenstrual tension was anecdotally mentioned in the same report although not subsequently investigated any further.

4.2 - SUBJECTS AND METHODS

4.2.1 - Subjects

All the women recruited into the study had been fully evaluated over at least one and usually two control cycles to establish the relationship of their symptoms to menstruation (see section 2.2.2). However the results of this preliminary evaluation were not always available at the time of recruitment. In light of the results presented in chapter 2, only data from those whose premenstrual mental symptoms were relieved by at least 25 percent during the postmenstrual phase was considered suitable for analysis. None of the subjects received any other form of medication during the course of the study and were all free of significant medical conditions. A normal menstrual interval not exceeding 26-32 days was also necessary for inclusion. All the subjects felt that their symptoms were sufficiently disabling to wish active therapy and all gave informed consent to participate in the study, for which prior ethical committee approval had been obtained. They were not routinely informed that one

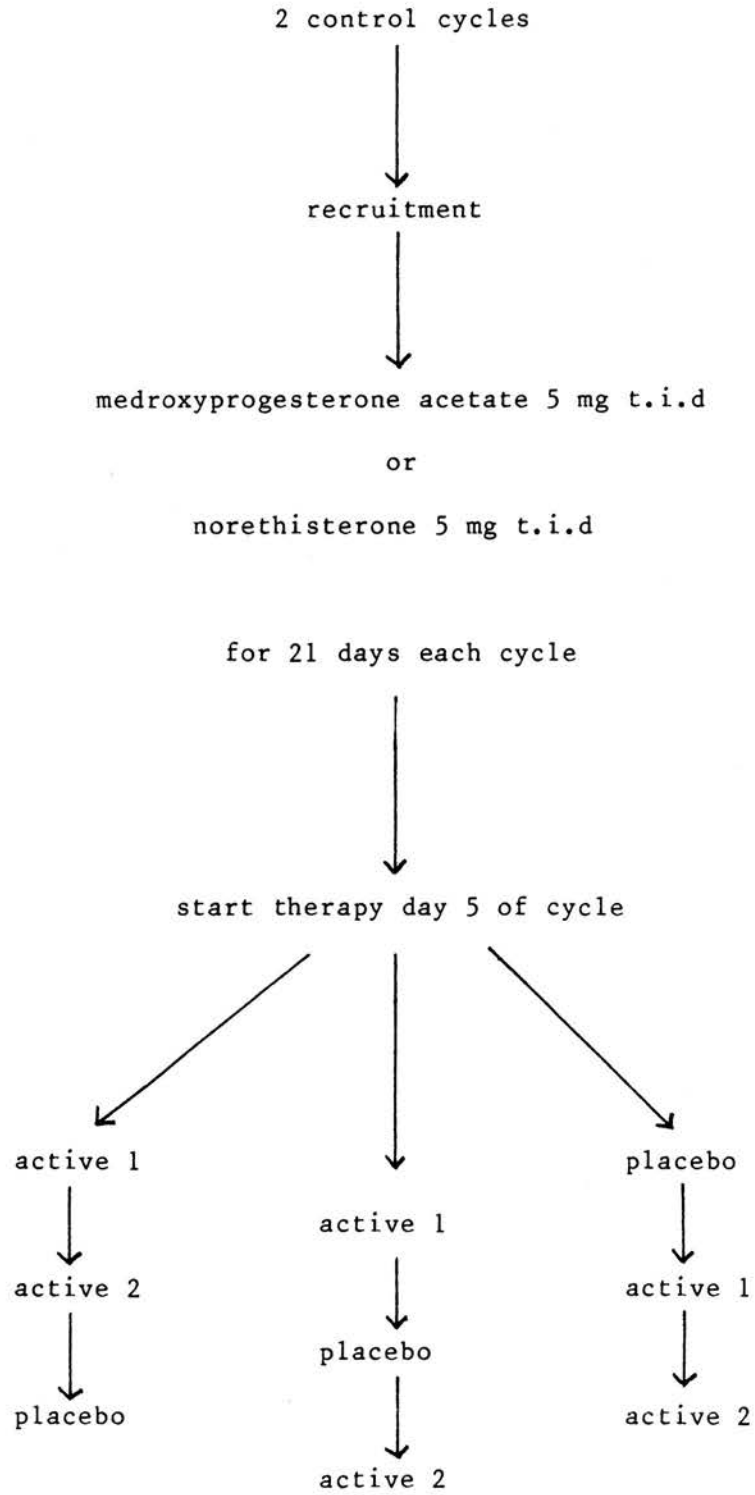
of the bottles contained placebo, nor that two were identical. They were told that the object of the study was to study the effect of hormonal treatment and that the dose of therapy would alter during the course of the study. Only one subject asked if a placebo was being used and she later withdrew because of acute symptoms of anxiety during the second treatment cycle.

4.2.2 - Therapy and design

Originally, a randomised double-blind study comparing both progestogens with placebo was planned but it was not possible to obtain identical preparations of both active agents within a reasonable interval of time. It was therefore decided to run two separate studies, one following the other, allowing a period of approximately 2 years for recruitment to each. The medroxyprogesterone acetate study started in 1981; the norethisterone study at the end of 1983. Both were of identical design, incorporating 3 study cycles randomised between 2 active treatment cycles and one placebo cycle. The studies were entirely double-blind with the placebo cycle falling before, in between or after the two active cycles (see figure 4.2). The dose of both progestogens was 5 mg three times daily, taken for 21 days each cycle. Treatment was initiated on day 5 of menstruation for study cycle 1. Thereafter subjects were instructed to break the therapy for 7 days before recommencing and to continue for the full 21 days regardless of bleeding as some cycle irregularities were anticipated during active therapy.

Figure 4.2

PROGESTOGEN STUDY - PROTOCOL



4.2.3 - Assessment of symptoms

Mood and physical symptoms were recorded daily throughout the study using visual analogue scales as previously described (section 1.10.1) and the subjects were asked to continue recordings for at least 14 days after completion of the third bottle. This instruction was not initially given leading to loss of data from cycle 3 in three subjects, one where menstruation was delayed in a placebo cycle and in two who commenced recordings prior to the onset of the study and subsequently ran out of forms before completion of cycle 3. There was space on the charts for comments and for recording of side effects. The subjects were given a contact phone number in case of problems or queries relating to therapy. All were seen routinely at the end of the three months or sooner if requested.

4.2.4 - Endocrine monitoring

The majority of the subjects were asked to collect samples of early morning urine on a weekly basis for assay of total oestrogens and pregnanediol (see section 2.2.5) in order to determine whether ovulation was being suppressed during active therapy and to ensure that the control cycles were ovulatory. These were stored in the subjects' own domestic freezers and delivered to the laboratory every four weeks.

4.2.5 - Data analysis

The data obtained from therapy with the two progestogens and their matched placebos was analysed separately and will be presented in different sections. The completed visual analogue scales (VAS) were initially analysed cycle by cycle without breaking the code. For each

cycle, three phases were defined, and a mean score calculated for each symptom in each subject for each cycle phase. These phases were the seven premenstrual days, days 1-5 of menstruation inclusive and seven 'postmenstrual' days, usually days 6-12 inclusive. Where withdrawal bleeding did not occur, the first 5 days off therapy were analysed as the menstrual phase, unless there had been a previous bleed when the latter was taken as menstruation. The high incidence of breakthrough bleeding made division of the cycle into phases difficult in some cases. Sometimes it was necessary to make a distinction between 'spotting' and onset of more normal flow, the latter then being regarded as menstruation. This was later verified (see section 4.3.3). All the subjects clearly documented the nature of the bleeding which greatly facilitated the analysis.

Mean individual symptom scores for each cycle phase and for each subject were then computed and analysed with the help of 'Minitab Data Analysis Software' on an IBM PC-compatible microcomputer system. The overall differences between the three treatment cycles (active 1, active 2 and placebo) for individual mental and physical symptoms were then analysed by cycle phase for the group as a whole. Statistical significance was tested using analysis of variance. Parametric statistical methods were only used for within-subject comparisons as discussed earlier (section 1.9.7). Where any inter-subject comparisons were made, non-parametric tests were used and are individually described in the text.

For the endocrine data, results of urinary pregnanediol:creatinine and total oestrogen:creatinine excretion were plotted out for each subject

through each individual cycle, standardising the cycles as described in section 4.3.7. For pregnanediol, mean concentrations were calculated at regular intervals of 3-5 days to enable comparisons to be made between the different treatment cycles. In the case of total oestrogen excretion, such detailed information was not required and overall mean concentrations for each individual treatment cycle were calculated. Statistical comparisons were made using the Mann-Whitney test.

4.3 - RESULTS

4.3.1 - Compliance

Details of the 56 subjects who entered the studies are shown in table 4.1. The proportion with complete and analysable data was 59% of those given medroxyprogesterone acetate (MPA) and 66% of those given norethisterone (NET). However the proportions who withdrew because of adverse effects were almost identical at 19% and 17% respectively. Eight of the ten with side effects complained of worsening of their premenstrual symptoms or their occurrence earlier than anticipated in the cycle. In one, an acute depressive illness was precipitated during what turned out to be a placebo cycle. The side effects in the other two subjects were leg pains (MPA) and abdominal pain and flatulence (NET). The latter was not relieved on stopping therapy and the former had been present prior to its onset. Of those in the MPA group who failed to provide a complete set of data, two had completed the charts for the placebo cycle and one active treatment cycle, but their results were not included in the analysis. It was not necessary to exclude any subjects from analysis on the grounds that

TABLE 4.1. - RECRUITMENT TO PROGESTOGEN THERAPY STUDIES

4.1.1 - Medroxyprogesterone acetate

Entered	32	
Completed & data analysed		19 (59%)
Data incomplete		4
Failed to return charts		2
Lost to follow up		1
Withdrew from side effects		6 (19%)

4.1.2 - Norethisterone

Entered	24	
Completed and data analysed		16 (67%)
Data incomplete		2
Failed to return charts		1
Therapy not commenced		1
Withdrew from side effects		4 (17%)

the degree of postmenstrual relief was less than 25% in the control cycles. However, some of those who withdrew from the study fell into this category (see below).

4.3.2 - Subjects who completed the studies

The characteristics of the subjects in the two groups who completed the study and the severity of their presenting symptoms are summarised in table 4.2. The only significant difference between the two treatment groups was the severity of the mental symptoms during menstruation, the median score being higher in the group receiving MPA (W=181.5; P=0.0052 (Mann Whitney test). However there was a greater proportion of single women in the MPA group compared with the NET group where more of the subjects were divorced or separated.

Details of the 18 women who withdrew or failed to provide a completed set of visual analogue scale charts are given in table 4.3, which combines those who withdrew from both studies. Their general characteristics were similar to those who completed the studies apart from a significantly greater number with a past history of psychiatric therapy. The severity of their premenstrual symptoms was no different but the median mood score during the menstrual phase of the cycle was significantly higher. Although the median postmenstrual mood score did not significantly differ from the group who completed the study, review of the individual cases showed that 7 out of the 18 women who withdrew would have been excluded from the subsequent analysis on the basis that their premenstrual symptoms were relieved by less than 25 percent postmenstrually.

TABLE 4.2

CHARACTERISTICS OF PATIENTS WHO COMPLETED THE STUDY (median & range)

	MPA	NET
Age at recruitment	34 (28-45)	34 (30-42)
Parity	2 (0-3)	2 (1-3)
Marital status:		
-married	15	13
-single	4	0
-div/sep	0	3
Psychiatric history	6	4
Occupation:		
-clerical	5	5
-domestic	3	1
-professional	5	5
-housewife	6	5

Pretreatment mood scores (mean + SD)

Premenstrual	4.4 $\pm$ 2.0	3.5 $\pm$ 1.2
Menstrual	3.3 $\pm$ 1.9	1.7 $\pm$ 1.5
Postmenstrual	1.7 $\pm$ 1.4	1.0 $\pm$ 1.1

TABLE 4.3

CHARACTERISTICS OF THE 18 SUBJECTS WHO FAILED TO COMPLETE THE STUDY

Marital status:			
-married	12		
-single	1		
-div/sep	5		
Occupation:			
-clerical	5		
-domestic	3		
-professional	3		
-housewife	6		
	median	range	
Age at recruitment	34	(25-45)	
Parity	2	(0-3)	
Psychiatric history	11		*
	mean	SD	
Premenstrual mood score	4.3	1.7	
Menstrual mood score	4.6	2.7	*
Postmenstrual mood score	2.4	2.1	

* significantly different from subjects who completed ($p<0.05$)

4.3.3 - Effect of therapy on mood and physical symptoms

4.3.3a - Medroxyprogesterone acetate

The effect of both cycles of active therapy and of the placebo is compared in figures 4.3.1 - 4.3.3. The P values indicate where the results of analysis of variance showed an overall significant difference between the three treatment cycles. The data is given in greater detail in tables 4.4.1 to 4.4.3. The only significant differences between active treatment and placebo was in the reduction of premenstrual breast discomfort (figure 4.3.1; table 4.4.1). The crude data is given in table 4.4.4. Further analysis, using Dunnett's T-test, to determine the source of the variance showed significant differences ($P<0.01$) between each individual active treatment cycle and the placebo. The results from each cycle phase showed no exacerbation of physical or psychological symptoms during active therapy. There appear to be non-significant trends in favour of reduction of premenstrual symptom intensity during active therapy, compared with placebo.

As shown later (section 4.3.6), active therapy with MPA caused considerable disruption of the normal bleeding pattern with frequent onset of bleeding early in the cycle. To ensure that the results were not being biased by basing the analysis around the onset of atypical menstruation, the data was reanalysed by calculating the mean score for each symptom for the last 14 days of the cycle (the latter 9 days of therapy and the initial 5 days off therapy). Analysis of variance showed significant benefit from active therapy only for the symptom of breast discomfort (table 4.4.5), with no significant improvement of

Figures 4.3.1 - 4.3.3

Effect of medroxyprogesterone acetate (MPA) and placebo therapy on individual mean symptom scores during each phase of the menstrual cycle.

Key to cycles:

Statistical analysis is by repeated measures analysis of variance

Figure 4.3.1 - Effect of MPA v placebo on premenstrual symptoms

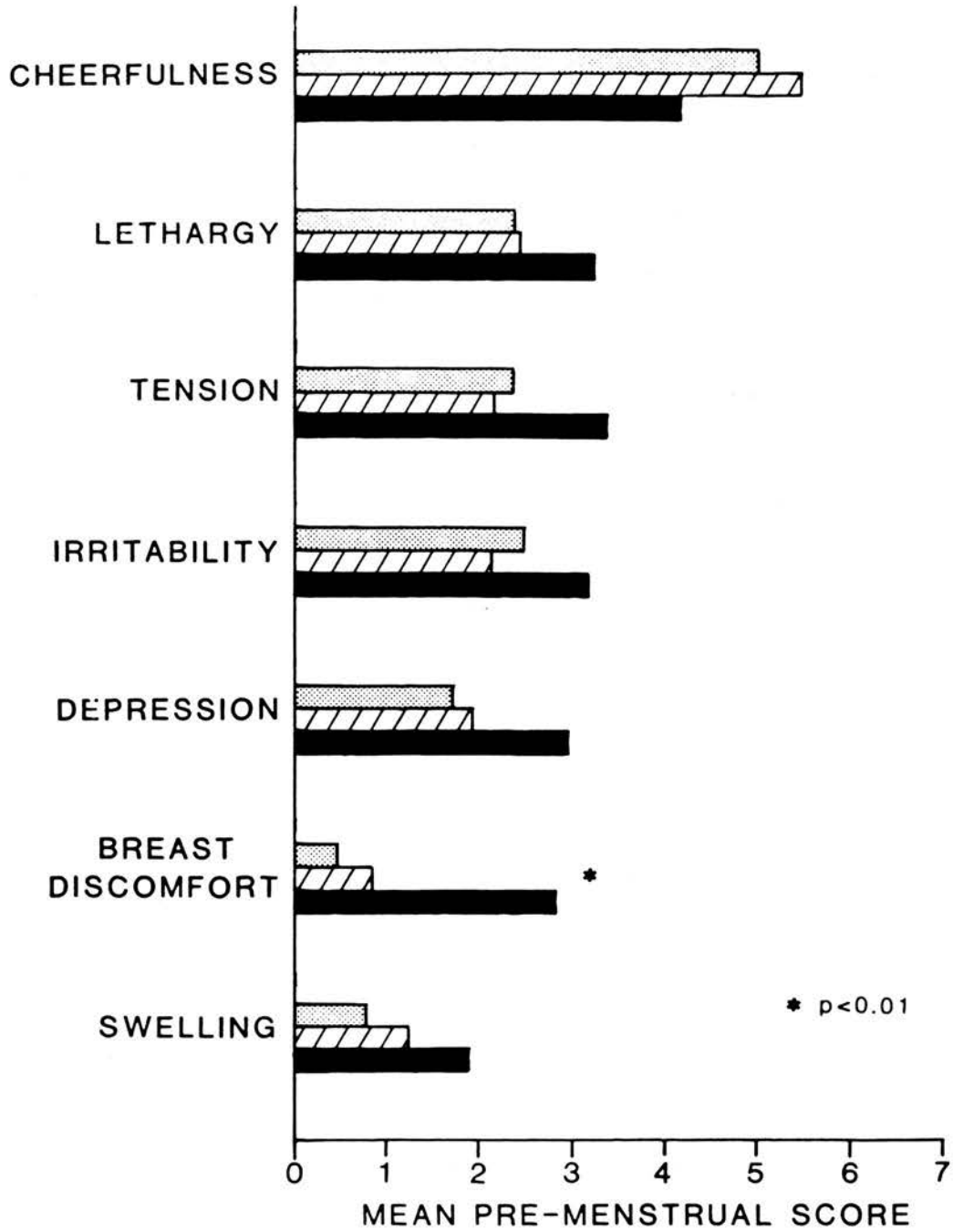


TABLE 4.4.1

PREMENSTRUAL SYMPTOM SCORES (MEAN & SD)
Medroxyprogesterone acetate v placebo

Symptom	Active 1	Active 2	Placebo	F *	P
Cheerfulness	5.04 (2.50)	5.48 (2.45)	4.18 (2.98)	1.10	NS
Lethargy	2.40 (2.01)	2.44 (2.35)	3.28 (2.54)	0.87	NS
Tension	2.36 (2.32)	2.17 (2.56)	3.38 (2.77)	1.24	NS
Irritability	2.47 (1.97)	2.15 2.39	3.20 (2.69)	0.98	NS
Depression	1.72 (1.94)	1.92 (2.72)	2.96 (2.58)	1.43	NS
Breast pain	0.46 (0.92)	0.82 1.58)	2.83 2.80)	8.32	<0.01
Swelling	0.76 (1.04)	1.23 (1.95)	1.89 (1.88)	2.16	NS

* Degrees of freedom 2 & 54

Figure 4.3.2 - Effect of MPA v placebo on menstrual symptoms

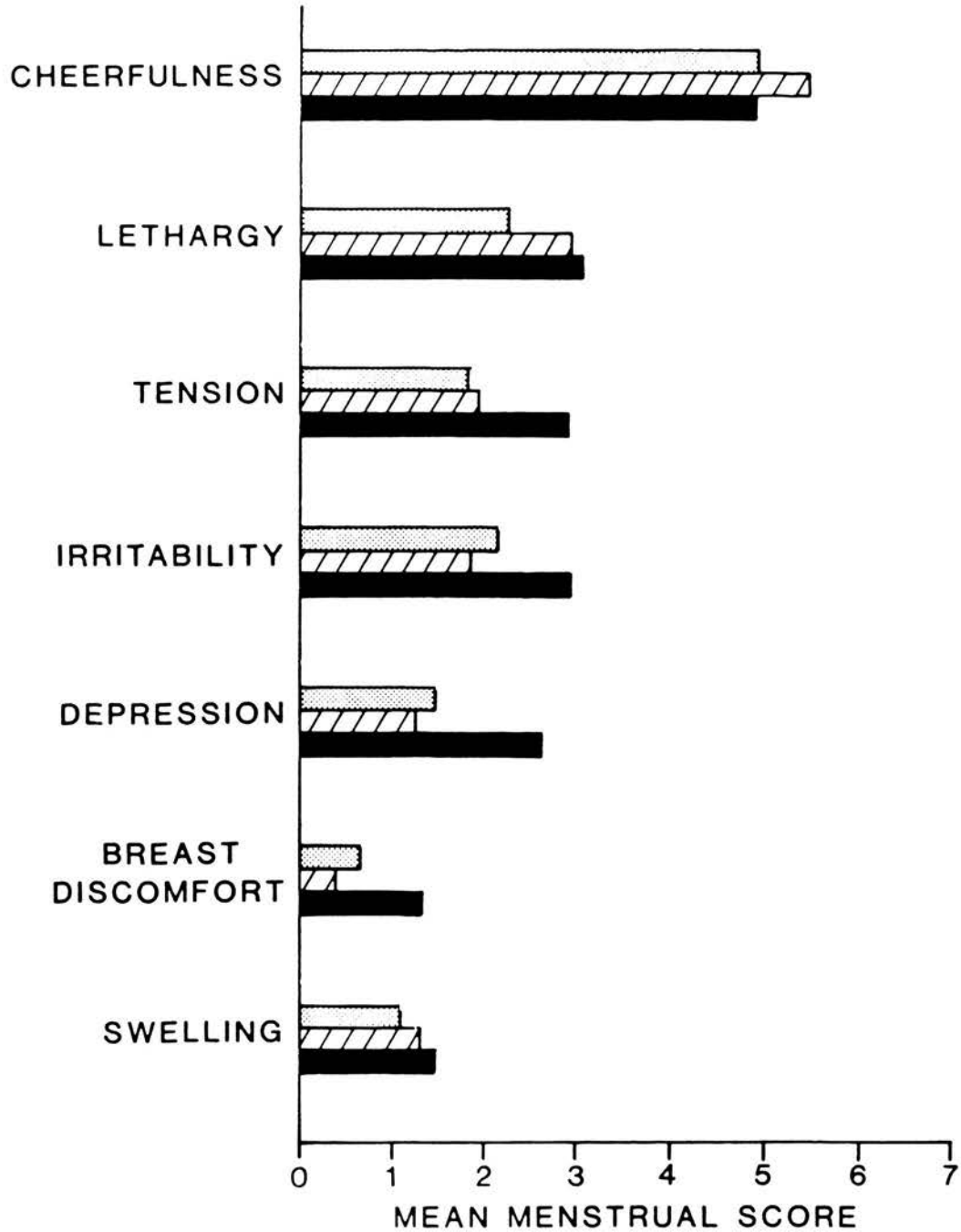


TABLE 4.4.2

MENSTRUAL SYMPTOM SCORES (MEAN & SD)
Medroxyprogesterone acetate v placebo

Symptom	Active 1	Active 2	Placebo	F *	P
Cheerfulness	4.98 (2.21)	5.51 (1.96)	4.94 (2.32)	0.36	NS
Lethargy	2.28 (1.83)	2.96 (2.49)	3.09 (2.64)	0.62	NS
Tension	1.84 (2.03)	1.93 (2.07)	2.91 2.87)	1.13	NS
Irritability	2.17 (1.78)	1.86 (1.92)	2.92 (2.67)	1.15	NS
Depression	1.47 (1.64)	1.25 (1.71)	2.64 (2.85)	1.74	NS
Breast pain	0.67 (1.48)	0.39 (1.24)	1.33 (1.42)	2.22	NS
Swelling	1.10 (1.70)	1.31 (2.24)	1.46 (1.66)	0.16	NS

* Degrees of freedom 2 & 54

Figure 4.3.3 - Effect of MPA v placebo on postmenstrual symptoms

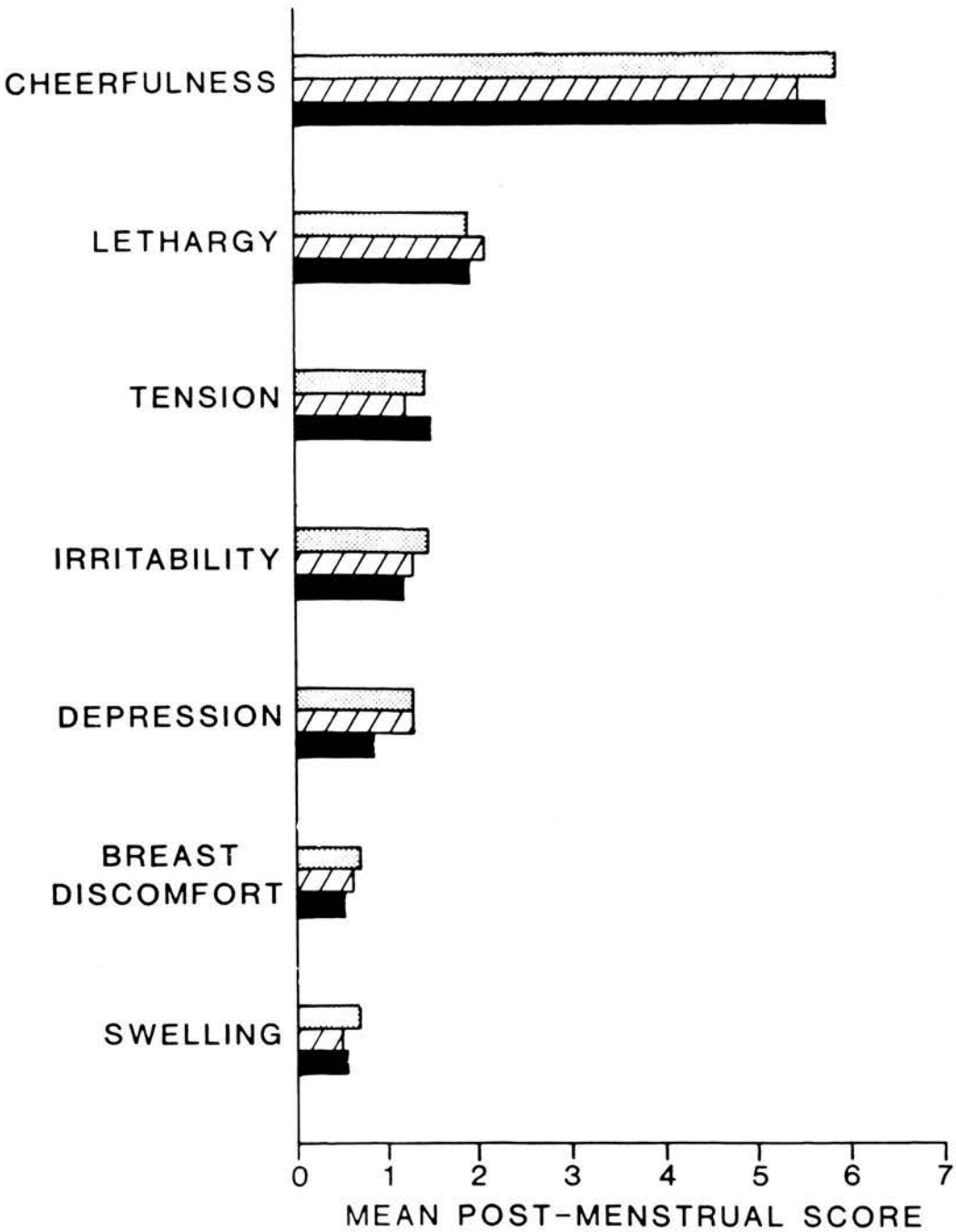


TABLE 4.4.3

POSTMENSTRUAL SYMPTOM SCORES (MEAN & SD)
Medroxyprogesterone acetate v placebo

Symptom	Active 1	Active 2	Placebo	F *	P
Cheerfulness	5.89 (2.12)	5.50 (2.33)	5.58 (3.06)	0.14	NS
Lethargy	1.91 (2.09)	2.10 (2.11)	1.96 (1.77)	0.04	NS
Tension	1.41 (1.77)	1.21 (1.76)	1.49 (1.57)	0.14	NS
Irritability	1.46 (1.51)	1.29 (1.70)	1.18 (1.20)	0.17	NS
Depression	1.29 (1.76)	1.29 (2.08)	0.84 (1.23)	0.43	NS
Breast pain	0.70 (1.23)	0.61 (1.19)	0.51 0.87)	0.14	NS
Swelling	0.69 (0.88)	0.50 (1.07)	0.56 (1.03)	0.18	NS

* Degrees of freedom 2 & 54

TABLE 4.4.4

PREMENSTRUAL BREAST DISCOMFORT - INDIVIDUAL DATA
Medroxyprogesterone acetate v placebo

SUBJECT	Active 1	Active 2	Placebo	Order
JB	0.14	2.29	2.14	AAP
PB	0.14	1.86	5.43	PAA
CB	0.00	0.00	9.71	AAP
RC	0.00	0.00	5.00	APA
IC	4.00	6.29	3.86	APA
WC	0.00	0.00	2.29	AAP
MD	0.43	0.14	0.00	PAA
BG	0.00	0.00	0.00	PAA
AG	0.29	0.00	0.86	APA
HH	0.43	2.43	1.71	AAP
MI	0.00	0.00	6.00	PAA
HK	1.14	1.00	3.43	AAP
JL	0.57	0.00	7.71	PAA
FM	0.14	1.57	1.71	AAP
PP	0.00	0.00	1.57	APA
MT	0.14	1.57	1.71	AAP
ST	0.43	0.00	0.00	APA
MU	0.00	0.00	0.86	PAA
AW	0.00	0.00	0.00	AAP
Mean	0.46	0.82	2.83	
SD	0.92	1.58	2.80	

TABLE 4.4.5

SYMPTOM SCORES DURING SECOND HALF OF CYCLE (MEAN & SD)
Medroxyprogesterone acetate v placebo

Symptom	Active 1	Active 2	Placebo	F *	P
Cheerfulness	5.21 (2.26)	5.42 (2.00)	4.39 (2.42)	1.08	NS
Lethargy	2.22 (1.77)	2.82 (2.14)	2.84 (2.05)	0.56	NS
Tension	1.85 (1.78)	2.03 (2.02)	2.79 (2.32)	1.11	NS
Irritability	2.12 (1.70)	1.73 (1.45)	2.91 (2.28)	2.00	NS
Depression	1.52 (1.76)	1.37 (1.65)	2.66 (1.95)	2.98	NS
Breast pain	0.65 (1.19)	0.64 (1.28)	1.80 (2.22)	3.21	<0.05
Swelling	1.07	1.14	1.36	0.19	NS

* Degrees of freedom 2 & 54

the psychological symptoms. These results are consistent with those obtained by the other method of analysis described above.

4.3.3b - Norethisterone

The results of treatment in all three cycle phases and for each individual symptom are summarised in figures 4.4.1 - 4.4.3 and given in more detail in tables 4.5.1 - 4.5.3. No significant differences between the treatment cycles were seen during any of the three cycle phases. Here trends were towards higher symptom scores during the initial active cycle, with the exception of premenstrual breast discomfort where scores were highest with placebo (figure 4.4.1; table 4.5.1).

4.3.4 - Influence of pretreatment mental symptom profiles

4.3.4a - Medroxyprogesterone acetate

The potential importance of defining women with premenstrual complaints in relation to the degree to which their symptoms are relieved postmenstrually has been discussed in chapter 2. The lack of response to active treatment might be related to inclusion of a proporton of subjects whose symptoms were not clearly related to the premenstrual phase of the cycle. The 19 subjects who completed the MPA study were therefore subdivided into two groups according to the degree of postmenstrual relief of their mental symptoms in the control cycles. There were 9 women with pre-treatment postmenstrual mood relief below 75% ('low' relief) and 10 with mood relief greater than 75% ('high' relief). Comparison of the effects of active treatment and placebo on the mean premenstrual psychological symptom scores for

Figures 4.4.1 - 4.4.3

Effect of norethisterone (NET) and placebo therapy on individual mean symptom scores during each phase of the menstrual cycle

Key to cycles:

Statistical analysis is by repeated measures analysis of variance

Figure 4.4.1 - Effect of NET v placebo on premenstrual symptoms

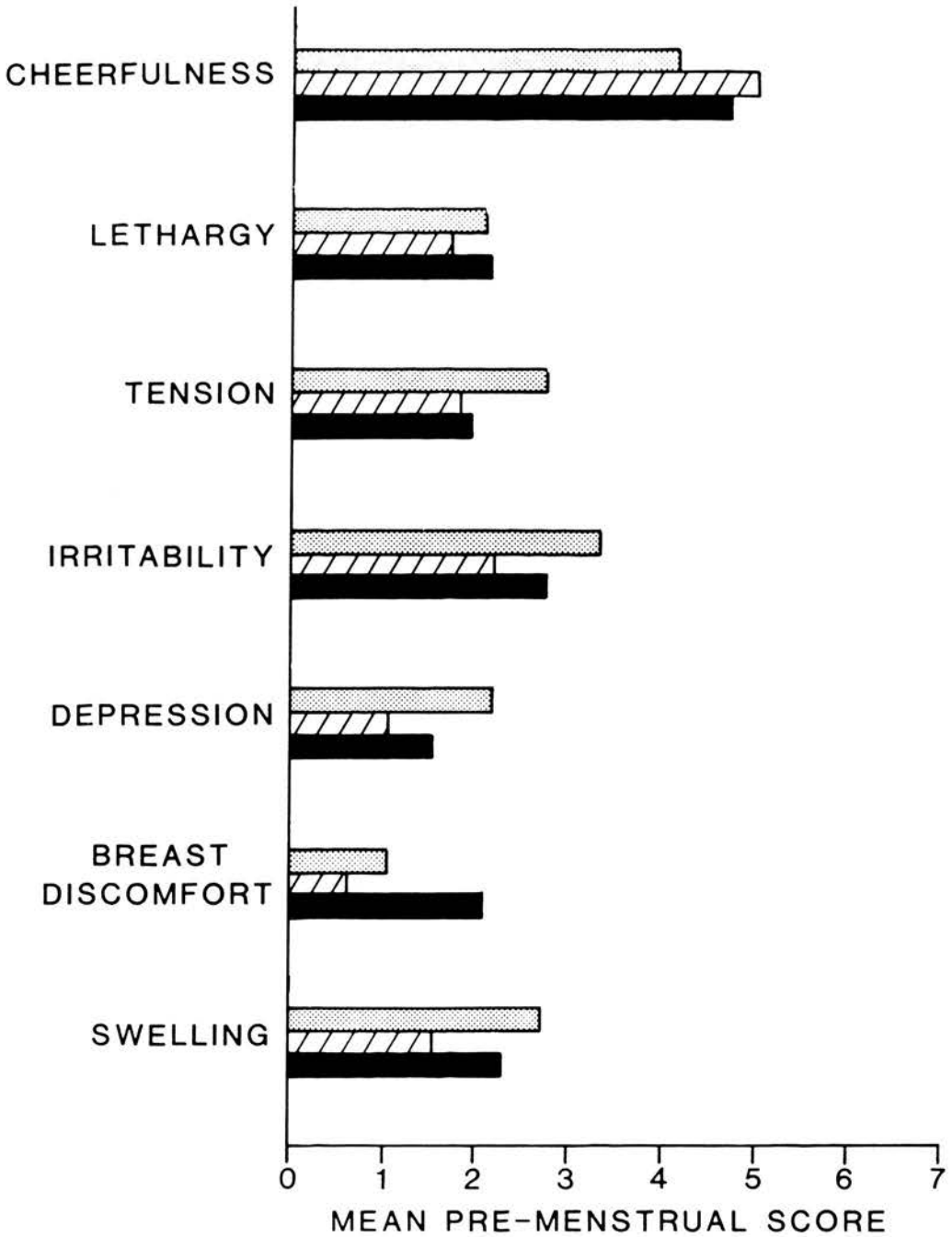


TABLE 4.5.1

PREMENSTRUAL SYMPTOM SCORES (MEAN & SD)
Norethisterone v placebo

Symptom	Active 1	Active 2	Placebo	F *	P
Cheerfulness	4.15 (1.80)	5.01 (1.60)	4.70 (2.56)	0.51	NS
Lethargy	2.10 (2.00)	1.75 (1.86)	2.16 (2.08)	0.16	NS
Tension	2.76 (2.66)	1.84 (2.11)	1.95 (2.33)	0.79	NS
Irritability	3.35 (2.71)	2.20 (2.06)	2.53 (2.36)	0.88	NS
Depression	2.17 (2.21)	1.04 (1.95)	1.54 (2.30)	0.96	NS
Breast pain	1.05 (1.92)	0.63 (0.99)	2.09 (2.44)	2.47	NS
Swelling	2.70 (2.34)	1.52 (2.02)	2.23 (2.25)	1.11	NS

* Degrees of freedom 2 & 44

Figure 4.4.2 - Effect of NET v placebo on menstrual symptoms

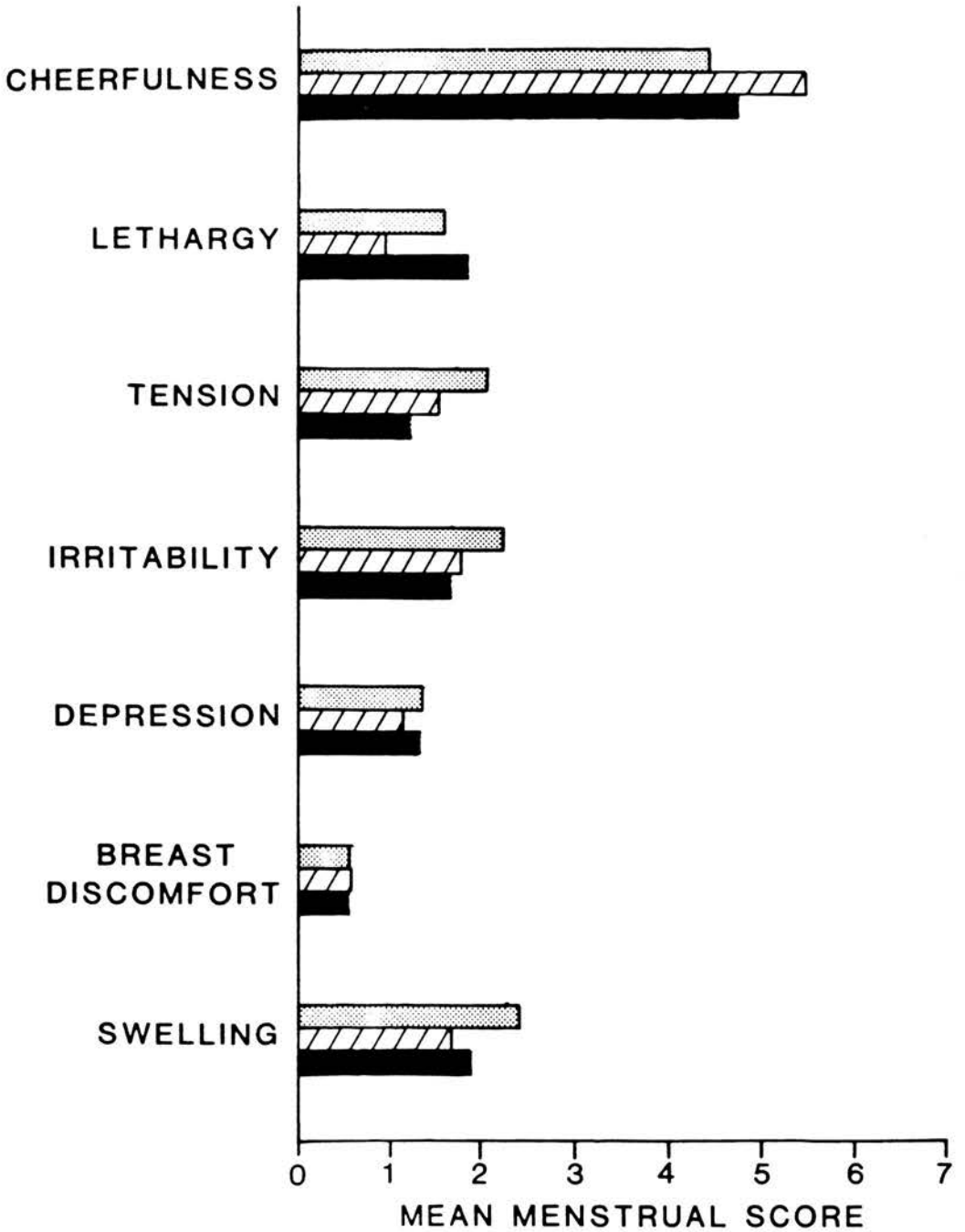


TABLE 4.5.2

MENSTRUAL SYMPTOM SCORES (MEAN & SD)
Norethisterone v placebo

Symptom	Active 1	Active 2	Placebo	F *	P
Cheerfulness	4.51 (2.63)	5.53 (2.01)	4.79 (2.53)	0.60	NS
Lethargy	1.65 (1.90)	1.00 (1.43)	1.91 (1.87)	0.88	NS
Tension	2.12 (2.27)	1.55 (2.01)	1.26 (2.03)	0.60	NS
Irritability	2.28 (1.96)	1.83 (1.79)	1.71 (1.70)	0.44	NS
Depression	1.38 (2.08)	1.16 (1.96)	1.34 (1.75)	0.07	NS
Breast pain	0.56 (1.09)	0.59 (0.96)	0.55 (0.86)	0.01	NS
Swelling	2.43 (2.35)	1.68 (1.90)	1.90 (2.40)	0.47	NS

* Degrees of freedom 2 & 44

Figure 4.4.3 - Effect of NET v placebo on postmenstrual symptoms

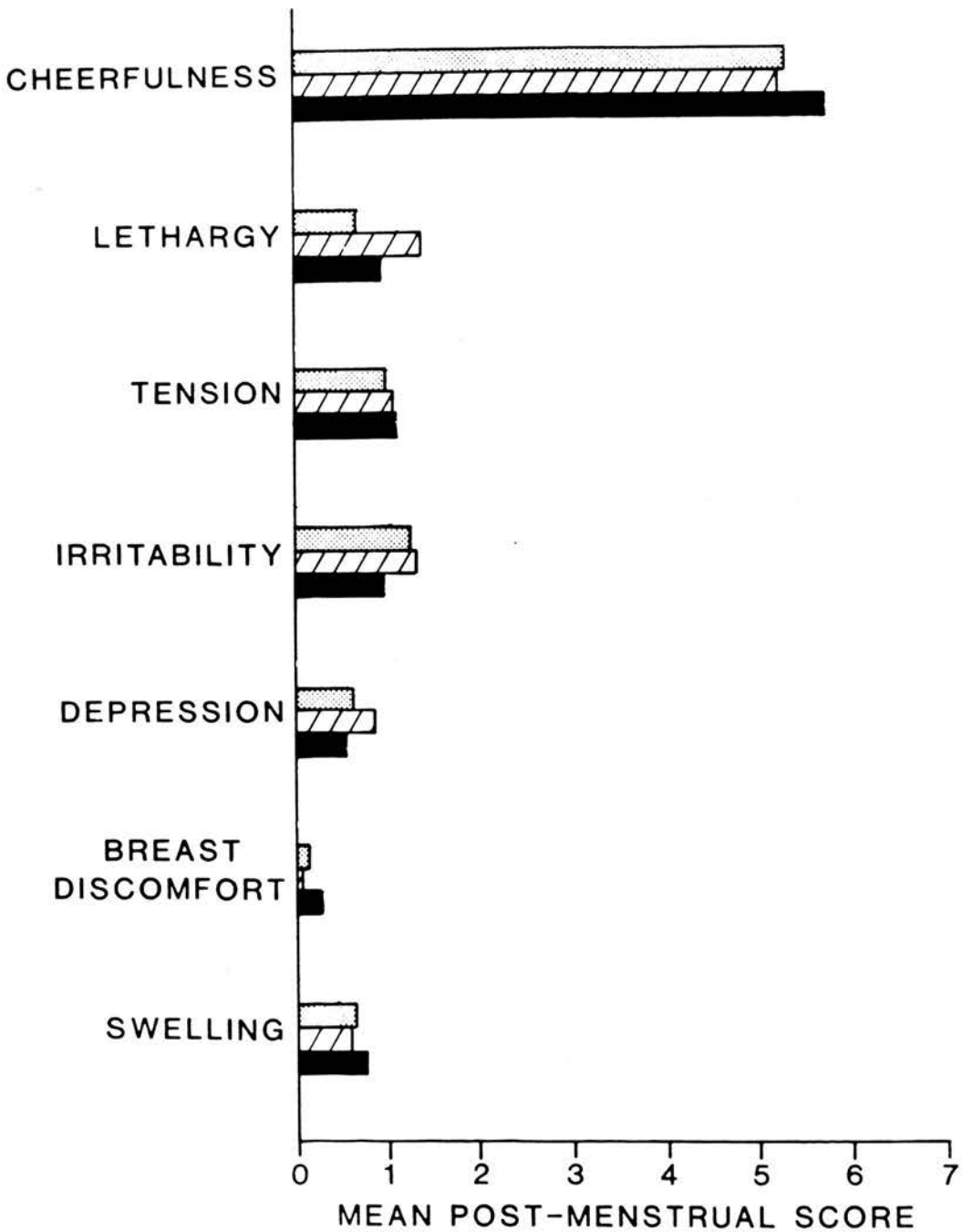


TABLE 4.5.3

POSTMENSTRUAL SYMPTOM SCORES (MEAN & SD)
Norethisterone v placebo

Symptom	Active 1	Active 2	Placebo	F *	P
Cheerfulness	5.37 (2.03)	5.29 (1.78)	5.78 (1.69)	0.26	NS
Lethargy	0.71 (1.26)	1.40 (1.83)	0.98 (1.14)	0.73	NS
Tension	1.02 (1.91)	1.11 (1.74)	1.15 (2.17)	0.06	NS
Irritability	1.25 (1.24)	1.34 (1.54)	0.97 (1.60)	0.18	NS
Depression	0.63 (1.19)	0.88 (1.29)	0.55 (1.12)	0.31	NS
Breast pain	0.11 (0.33)	0.05 (0.14)	0.28 (0.67)	1.17	NS
Swelling	0.64 (1.44)	0.61 (1.06)	0.76 (1.60)	0.05	NS

* Degrees of freedom 2 & 44

the individual subjects (table 4.6) showed a greater placebo effect in the group with low postmenstrual mood relief prior to therapy. However the differences between active treatment and placebo in the group with high pretreatment relief still failed to reach significance. Among the individual subjects, 7 out of the 10 with high pretreatment mood relief recorded least benefit from placebo treatment, compared with the two active cycles. This compared with 2 out of the 9 with low pretreatment relief (table 4.6). Again, this just fell short of statistical significance (P=0.051 by Fisher's exact test).

4.3.4b - Norethisterone

Analysis of mean psychological symptom scores (not illustrated) failed to demonstrate any influence of pretreatment mood profiles in the response to NET or placebo.

4.3.5 - The placebo effect

In the presentation of the above results, there is no indication of the order in which active and placebo treatments were administered. The numbers of subjects receiving the placebo first, second or third are shown in table 4.7.1. Further analysis was carried out in an attempt to determine whether the order in which the placebo was given in relation to the active treatment affected the results. The premenstrual symptom scores for tension, depression and irritability during each of the three treatment cycles were ranked in descending order of severity for the individual subjects, adding the ranks for the three symptoms to give an overall rank total for each cycle in each subject. A rank of 1 indicated maximum severity so that a low

TABLE 4.6

EFFECT OF PRE-TREATMENT POSTMENSTRUAL RELIEF OF MENTAL SYMPTOMS
Medroxyprogesterone acetate v placebo
Mean premenstrual mood scores for individual subjects

SUBJECT	Active 1	Active 2	Placebo	F
A - POSTMENSTRUAL RELIEF BELOW 75%				
CB	0.36	0.57	1.06 +	
IC	6.14	5.75	4.90	
WC	1.36	0.00	1.32	
MD	1.36	1.68	1.00	
BG	0.57	0.36	0.29	
AG	1.57	1.00	1.14	
HH	5.65	3.32	3.36	
FM	5.43	0.39	3.32	
ST	2.22	2.04	4.04 +	
Mean	2.74	1.68	2.27	0.66
SD	2.32	1.85	1.64	(NS)
B - POSTMENSTRUAL RELIEF ABOVE 75%				
JB	1.25	1.39	0.89	
PB	1.61	1.32	2.39 +	
RC	1.40	0.54	0.00	
MI	2.32	0.46	5.39 +	
HK	0.75	0.72	5.36 +	
JL	2.22	2.54	2.90 +	
PP	0.68	0.79	4.00 +	
MT	2.90	3.36	4.04 +	
MU	3.39	6.68	9.14 +	
AW	1.34	8.14	6.15	
Mean	1.79	2.59	4.04	2.51
SD	0.90	2.72	2.67	(NS)

+ indicates subjects who responded least well to placebo

rank total score for the placebo cycle indicated little effect from the placebo. The rank total scores for the placebo cycles were then analysed by the order of therapy, namely according to whether the placebo had been given first, second or last. Any significant differences were determined by use of the Kruskal-Wallis non-parametric test. The results for each progestogen are shown in table 4.7.2 and do not identify a significant order effect although it is apparent from 4.7.1 that the MPA was biased towards more placebo cycles placed third in order, with fewest placebo cycles placed third in the NET group. In view of this the results were pooled and reanalysed but again no significant differences emerged (table 4.7.2.)

4.3.6 - Cycle control during active and placebo therapy

4.3.6a - Medroxyprogesterone acetate

During active treatment cycles, there was considerable disruption of normal menstrual cyclicity, as illustrated in table 4.8.1. Only one quarter of the cycles were entirely normal and prolonged bleeding of normal or lighter than normal flow was recorded in 17 (42.5%) of the cycles. The placebo treatment cycles were entirely normal in 16 cases but menstruation was delayed beyond 7 days of stopping therapy in two cycles (to 11 and 12 days respectively). In two, menstruation occurred early in the cycle (8 and 10 days before stopping the tablets) and in both cases was preceded by ovulation. All four abnormal cycles occurred where placebo therapy was third. In a fifth, where placebo therapy was the middle cycle, there was complete

TABLE 4.7 - PLACEBO CYCLES - EFFECT OF ORDER

4.7.1 - Placebo cycle order - number in each category

Placebo order	MPA	NET	BOTH
Cycle 1	6	6	12
Cycle 2	5	6	11
Cycle 3	8	4	12

4.7.2 - Analysis of placebo rank totals by treatment order

	median rank total		
Placebo order	MPA	NET	BOTH
Cycle 1	4.25	6.25	4.75
Cycle 2	6.00	6.00	6.00
Cycle 3	5.75	5.50	5.75
H*	2.11	0.37	1.70
P	NS	NS	NS

*Kruskal Wallis test

amenorrhoea but ovulation was not assessed. None of the monitored cycles were anovular (see below).

4.3.6b - Norethisterone

By comparison with MPA, satisfactory cycle control was achieved with NET, 25 (78%) of cycles being entirely normal with prolonged bleeding in only 4 (12.5%) (table 4.8.2). The placebo cycles were normal in 14 of the 16 subjects. Menstruation was delayed beyond one week of stopping the tablets (9 days) in one subject who received the placebo tablets after both active cycles. In one case, where placebo came in the middle, the cycle appears to have been anovular because of absence of menstruation but this was not confirmed by endocrine monitoring.

4.3.7 - Results of endocrine monitoring

4.3.7a - Medroxyprogesterone acetate

Measurement of weekly urinary pregnanediol:creatinine in 28 of the cycles indicated ovulatory levels in only one sample from a single cycle where it coincided with the treatment-free week. Complete sets of results of weekly monitoring throughout each treatment cycle were available from 13 of the subjects. Mean pregnanediol:creatinine concentrations calculated for 5 day intervals from days 1-10 and 3 day intervals thereafter are given in table 4.9.1. For this, it was necessary to standardise each cycle to 28 days, taking the start and finish of tablet taking as days 5 & 26 respectively for active treatment cycles. Placebo cycles were standardised around day 1 of menstruation. Data from control cycles in the same individuals is given for comparison. Results from the active treatment cycles

TABLE 4.8 - CYCLE CONTROL DURING ACTIVE PROGESTOGEN THERAPY

4.8.1 - Medroxyprogesterone acetate

Normal cycle (24 days or longer)	10
Normal cycle with BTB (7 days or less)	4
No withdrawal bleed, BTB less than 10 days	8
Amenorrhoea	1
Prolonged bleeding (10 days or more)	17
(median 14, range 10-19 days)	---
TOTAL	40

4.8.2 - Norethisterone

Normal cycle (24 days or longer)	25
Normal cycle with BTB (7 days or less)	3
Amenorrhoea	0
Prolonged bleeding (10 days or more)	4
(median 16, range 12-20)	---
TOTAL	32

(BTB - break through bleeding)

confirmed inhibition of ovulation. No significant differences in luteal phase characteristics between the placebo and control cycles were apparent.

The results of urinary total oestrogen:creatinine are given in table 4.10. The results are expressed as mean concentrations for each individual cycle. Significant suppression of urinary oestrogen excretion occurred during active treatment, compared with placebo. However results during placebo treatment were significantly higher than during pretreatment control cycles. This may be a rebound effect in those cycles which followed or fell between active therapy.

4.3.7b - Norethisterone

During active treament, one ovulatory urinary pregnanediol result was detected although this cycle was associated with a short luteal phase. Complete weekly urinary steroid excretion data was available from 13 women and the results are shown in tables 4.9.2 and 4.10, with data from control cycles for comparison. The pregnanediol results indicate ovulation inhibition during active therapy and there was also significant suppression of urinary total oestrogen:creatinine excretion. Results from the placebo cycles show no significant differences from control cycles. There appeared to be greater suppression of oestrogen excretion by NET, compared with results obtained from the women treated with MPA (table 4.10), although statistically significant differences were seen only during active cycle 2.

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Table 4.9

RESULTS OF URINARY PREGNANEDIOL:CREATININE EXCRETION (MEAN ± SD)

Days	Active 1	Active 2	Placebo	Control
4.9.1 - MEDROXYPROGESTERONE ACETATE				
1-5	0.36 ± 0.12	0.29 ± 0.24	0.23 ± 0.09	0.37 ± 0.22
6-10	0.45 ± 0.25	0.29 ± 0.11	0.38 ± 0.09	0.44 ± 0.22
11-13	0.37 ± 0.17	0.37 ± 0.27	0.30 ± 0.09	0.49 ± 0.47
14-16	0.44 ± 0.22	0.24 ± 0.14	1.13 ± 0.96	0.66 ± 0.25
17-19	0.30 ± 0.29	0.32 ± 0.18	1.56 ± 0.25	1.39 ± 0.29
20-22	0.39 ± 0.07	0.35 ± 0.14	2.64 ± 0.98	2.80 ± 1.80
23-25	0.33 ± 0.20	0.53 ± 0.39	2.24 ± 1.31	2.18 ± 0.77
26-28	0.43 ± 0.74	0.36 ± 0.15	1.01 ± 0.32	1.96 ± 1.09
4.9.2 - NORETHISTERONE				
1.5	0.50 ± 0.26	0.38 ± 0.25	0.29 ± 0.24	0.48 ± 0.26
6-10	0.40 ± 0.21	0.27 ± 0.15	0.30 ± 0.19	0.45 ± 0.22
11-13	0.39 ± 0.21	0.34 ± 0.24	0.39 ± 0.32	0.35 ± 0.30
14-16	0.29 ± 0.15	0.35 ± 0.19	0.52 ± 0.46	0.81 ± 0.45
17-19	0.39 ± 0.27	0.35 ± 0.22	1.32 ± 0.57	1.81 ± 1.15
20-22	1.03 ± 1.93	0.12 ± 0.11	2.34 ± 1.38	3.25 ± 1.51
23-25	0.35 ± 0.27	0.21 ± 0.16	4.24 ± 2.26	4.06 ± 1.76
26-28	0.30 ± 0.21	0.22 ± 0.12	1.24 ± 1.08	1.90 ± 0.88

TABLE 4.10

RESULTS OF URINARY TOTAL OESTROGEN:CREATININE EXCRETION

Expressed as mean ± SD for each complete treatment cycle

	Active 1	Active 2	Placebo	Control
MPA	10.1 ± 5.9	10.1 ± 5.1	16.3 ± 8.8	14.0 ± 10.5
P *	0.005	0.0002		
NET	8.0 ± 4.0	6.5 ± 3.4	11.6 ± 7.4	12.7 ± 8.1
P *	0.013	0.0002		

* Mann-Whitney test comparing active cycles with placebo

Comparison between treatment cycles with MPA and NET:

Active 1	Not significant
Active 2	P = 0.0003
Placebo	P = 0.0045
(Control	Not significant)

4.3.8 - Outcome of therapy

At the end of the three study cycles, the women were given the option of continuing on active therapy if they felt that they had benefited during at least two of the treatment months. Nine of the 16 (56%) who had completed NET opted to continue and 6 (37.5%) found a sustained benefit over a period of at least 6 months. Fifteen of the 21 completing MPA (71%) opted to continue and 9 (43%) are known to have completed 6 months on therapy, with 7 continuing to date. Only three of the group stopped specifically because of the bleeding problems and in those who continued the problem has lessened considerably. Three of the women have achieved a more satisfactory benefit from an alternative therapy, in two cases danazol and in the third an LHRH agonist. All three were women whose symptoms on initial assessment were considerably relieved postmenstrually. The remaining subjects have coped without active therapy.

4.4 - DISCUSSION

These results fail to demonstrate any significant relief of the adverse psychological symptoms during active therapy with medroxyprogesterone acetate or norethisterone in women complaining of premenstrual problems. However MPA did significantly relieve the symptom of breast discomfort, compared with placebo treatment. Both progestogens suppressed ovulation and thus the results do not support the hypothesis that inhibition of ovulation will eradicate premenstrual symptoms. In contrast to the results of some of the studies discussed earlier (section 3.4), there was no indication that either progestogen actually provoked PMT-like symptoms. With the exception of the few subjects who withdrew from therapy, mood scores were no worse during active therapy than during placebo treatment. These results therefore throw doubt upon the relationship between adverse mood and both exogenous and endogenous ovarian steroids.

The only significant benefit of therapy with either progestogen was the reduction of breast discomfort during active therapy with MPA. There was also a trend towards improvement of breast discomfort with NET. Breast discomfort is one symptom which has been consistently related to the premenstrual phase of the cycle in normal subjects as well as in women who present for help with premenstrual problems (see chapters 1 & 2). Although the mechanisms underlying the symptom are unclear, well documented morphological changes are seen in the breast as a consequence of cyclical hormonal action (see section 1.8.7). Thus the benefit from progestogen therapy is likely to be a result of endocrine suppression. Neither progestogen significantly relieved the sensation of 'swelling', although the basis for the latter symptom

is poorly understood (see chapter 1). There were trends towards improvement rather than worsening of this symptom.

A direct comparison between the effects of the two different progestogens is not possible because the two groups were not randomised. Both appeared to effectively inhibit ovulation although suppression of follicular activity, as measured by urinary oestrogen excretion, was greater with NET. There was a trend towards improvement of the psychological symptoms with MPA but not with NET. This improvement in mood may have been secondary to relief of breast pain but it is also tempting to postulate that the improvement was related to the cycle disruption which occurred in such a high proportion of the MPA treated cycles. Early onset of menstruation or of break-through bleeding may remove anticipation of later menstruation. A similar observation was made by Sampson (1981) who reported relief of cyclical symptoms when progesterone was given in sufficient dosage to disrupt the cycle. This question might be clarified by comparing the dose of MPA used in the present study with a higher dose which gave better cycle control.

In chapter 2, the importance of quantifying the degree to which the mental symptoms are relieved postmenstrually has been stressed. Low levels of postmenstrual relief are indicative of underlying problems which are present throughout the cycle and thus unlikely to be helped by hormonal manipulation. Those women in the MPA group with low postmenstrual mood relief during the pre-treatment cycle showed a greater response to the placebo than did the women with high postmenstrual mental relief prior to therapy. Had the study been

confined to the latter group, with increased numbers, the differences between active and placebo therapy might have achieved significance. However no similar trends were seen with NET.

Of the subjects recruited to both studies, only two thirds or less completed them satisfactorily and yielded analysable data. Many published studies have not stated compliance rates but there are others in which drop outs are high (Williams et al, 1983; Sampson, 1983; Kerr et al, 1980; Gilmore et al, 1985; Watts et al, 1987). All these studies took place over at least three cycles and two of them over six (Williams et al, 1983; Gilmore et al, 1985), involving daily recordings which are demanding for the subjects. Indeed published results of the studies by Kerr (1980) and Williams et al (1983) did not give a breakdown of the daily symptom ratings, basing their published results only on interviews and it is possible that this was because of the incompleteness of their data. The subjects in the present study were not seen monthly. More frequent visits to hospital might have encouraged better record-keeping and yielded more complete data from those who finished the study.

In terms of its design, this study is open to a number of criticisms. It would have been better to have included at least two, preferably three, placebo and active cycles with cross-over midway. This would allow for a changing placebo response as the latter is known to be greatest in the initial treatment cycle (Sampson, 1979) and decline thereafter (Magos et al, 1986; Watts et al, 1987). It would also control for any carry-over effects of hormonal suppression at the cross-over and may have yielded more conclusive results. However such

a regimen may have resulted in even poorer compliance and incomplete data collection as the method of recording was already relatively demanding for the subjects; particularly in view of the high drop out rate from the other studies discussed above. In the present study, there was little evidence for carry-over effects of hormonal suppression as endocrine monitoring showed that the placebo cycles did not differ significantly from control cycles. Two active cycles were ovulatory which may have reduced the response. On the other hand, the delay in ovulation and menstruation seen in some placebo cycles when these followed two active treatment cycles may have caused bias because the premenstrual week then fell outwith the phase of tablet-taking.

The problems encountered with irregular bleeding and poor cycle control illustrate the difficulties of conducting a double-blind study of this nature and may explain the lack of any other similar studies in the literature. Where active treatment is likely to cause easily identifiable physical changes or endocrine based carry-over effects, an alternative design would be to eliminate the cross-over and randomise active and placebo treatment between two groups of symptomatic women. Much larger numbers of subjects would be needed with the latter design to enable statistical comparisons to be made and it would be difficult to control for all possible variables in the randomisation process. However it would permit the assessment of the effects of both placebo and active therapy over a more prolonged interval of time. The effect of passage of time is likely to be important in this condition and ideally the design of any treatment trial should include a tablet-free interval. This has not been built

into any of the other published treatment studies and there is little information in the literature about long-term follow-up of women with premenstrual complaints.

The differences encountered in cycle control with the two progestogens were not altogether unexpected. Early studies demonstrated the very excellent cycle control with NET (Garcia et al, 1958) which was attributed in part to its oestrogenicity (Paulsen et al, 1962). On the other hand, cyclical oral MPA which has no intrinsic oestrogenic activity, is associated with breakthrough bleeding, even in combination with oestrogen (Eichner, 1963). Despite the apparently similar doses of the two required to suppress ovulation, marked differences in their ability to delay menstruation have been demonstrated (Swyer & Little, 1962). The differences seen in the above studies may simply be related to the lesser degree of follicular suppression seen with the MPA. However, higher incidences of bleeding abnormalities have been reported with the contraceptive depot medroxyprogesterone acetate compared with its norethisterone related counterpart, norethisterone oenanthate (WHO task force, 1983), although endocrine suppression and endometrial changes are very similar (Mishell et al, 1968; Chaudhuri et al, 1985). The differences in the effect of the two progestogens on the endometrium may reflect differences elsewhere, in particular the breast and central nervous system. While this may offer an explanation for some of the observations of the present study, these can only be speculative because the two groups were not randomly selected.

The numbers of subjects completing the study were small and this may have contributed to the negative results. Because of the trends favouring treatment with MPA compared with placebo, further studies would appear to be justified, in particular using a higher dose regimen and with better subject selection. It is relevant to consider safety apects of progestogen therapy, particularly in view of the recent epidemiological evidence that the dose of the progestogenic component of the oral contraceptive pill is associated with atherosclerotic cardiovascular disease (Meade et al, 1980). Progestogens of the 19-nortestosterone group have been shown to lower high-density lipoprotein cholesterol (HDL-C), (Gustafson & Svanborg, 1972; Malkonen et al, 1980; Howard et al, 1982) although the effect is less marked than that of danazol (see section 3.7). A comparative study of different oral progestogens failed to show any such effect with medroxyprogesterone acetate (Silverstolpe et al, 1979) which is non-androgenic. However long term therapy with depot MPA has been shown to produce a fall in HDL-C (Kremer et al, 1980), perhaps as a result of lowered circulating oestrogens (Mishell et al, 1972). Fortunately this problem does not appear to be associated with oral administration (Bradley et al, 1978), presumably because the degree of oestrogen suppression is less complete. In view of their widespread and long-term use in fertility control, both depot MPA and the depot form of NET, norethisterone oenanthate, have been subjected to extensive scrutiny to establish their safety with respect to factors such as blood coagulation, liver function, glucose tolerance, blood pressure and carcinogenesis. The results have been reassuring (Fraser & Weisberg, 1981; Howard et al, 1982).

4.5 - Conclusions

In the doses and regimes selected for study, both medroxyprogesterone acetate and norethisterone suppressed ovulation although follicular activity was more effectively suppressed with the norethisterone and with considerably better cycle control. MPA significantly improved the physical symptom of breast discomfort in comparison with placebo but neither therapy significantly improved the psychological symptoms. Small but similar numbers from both groups were unable to tolerate therapy due to adverse psychological effects. In the case of MPA, but not NET, there were trends towards greater relief of the psychological symptoms with active therapy. With MPA the placebo response appeared to be greater in those women whose showed low levels of postmenstrual relief of their symptoms during control cycles, although these observations just fell short of statistical significance.

Suppression of ovulation with norethisterone with preservation of normal menstrual cyclicity is in theory a good model for testing the effect of ovulation suppression. Its lack of benefit does put into question the relationship between menstrual cycle symptomatology and the endocrine events of the cycle. There may be other explanations for the lack of effect of NET but the results obtained with MPA are suggestive of a benefit related to disruption of menstrual cyclicity rather than to inhibition of ovulation. The studies described above are subject to a number of criticisms but despite these, failed to demonstrate a significant benefit from ovulation suppression in women with premenstrual tension.

CHAPTER 5

PITUITARY-OVARIAN SUPPRESSION WITH ZOLADEX DEPOT (GOSERELIN) - AN AGONIST ANALOGUE OF LHRH

5.1 - Introduction

Suppression of ovarian function is normally achieved by administration of exogenous ovarian steroids, usually a combination of an oestrogen and a progestogen in a dose regimen designed to maintain control and regular shedding of the endometrium. High dose progestogens or danazol are alternatives in certain situations where maintenance of a regular menstrual pattern is not essential. As discussed earlier (chapters 3 and 4), such steroids may provoke adverse mental or physical side effects and are in certain situations contraindicated on medical grounds. This section of the thesis is concerned with a new class of therapeutic agents which inhibit ovarian cyclicity by pituitary suppression. These are the synthetic agonist analogues of luteinising hormone-releasing hormone (LHRH). Because they are free of any oestrogenic or progestogenic actions and suppress production of endogenous ovarian steroids, their administration should also inhibit physical and mental symptoms which are secondary to these steroids.

In this chapter, the endocrine and clinical effects of a newly available depot preparation of an LHRH agonist are described. The subjects of the study are 20 premenopausal women, of whom a subgroup presented with uterine fibroids and the remainder with premenstrual problems. The response of the uterive fibroids to therapy will also be presented in this chapter. The effects of ovarian suppression on

cyclical mental and physical symptoms are described in detail in the next chapter (chapter 6).

5.1.1 - LHRH and its agonists

Ovarian function is controlled by specific glycopeptide hormones secreted by the anterior lobe of the pituitary, follicle stimulating hormone (FSH) and luteinising hormone (LH) (see section 1.2.1). In turn, synthesis and secretion of these pituitary gonadotrophins is modulated by a hypothalamic decapeptide, luteinising hormone-releasing hormone (also called gonadotrophic hormone-releasing hormone).
The structure of LHRH was first described by Schally and co-workers in 1971. Ability to synthesise it opened up many new possibilities for therapeutic uses, particularly for ovulation induction. However the very short half life of the natural peptide led to development of synthetic agonist analogues, obtained by substitution of various amino acids to obtain derivatives which were more potent and longer acting. A single dose of one of these superactive agonists stimulates release of LH and to a lesser extent FSH from the anterior pituitary, but repeated administration results in pituitary desensitisation and inhibition of gonadotrophin release (Sandow, 1983).

LHRH and its analogues cannot be administered orally but are absorbed when given intranasally or subcutaneously. A number of analogues are available for use in humans and are the subject of current or published clinical studies. Their structures are shown in table 5.1.

Table 5.1 - Structures of LHRH agonists currently under clinical investigation.

Compound	International non-proprietary name or trade name
D-Ala^{6}, Pro^{9}-Ethylamide/LHRH	-
D-Leu^{6}, Pro^{9}-Ethylamide/LHRH	Leuprolide
D-Trp^{6}, Pro^{9}-Ethylamide/LHRH	-
D-Trp^{6},/LHRH	Decapeptyl
D-Trp^{6}, N-MeLeu^{6}, Pro^{9}-Ethylamide/LHRH	Letrelin
D-Ser(tBu)^{6} Aza-Gly^{10}/LHRH	Goserelin (Zoladex)
D-His(Bzl)^{6}, Pro^{9}-Ethylamide/LHRH	Histrelin
D-Nal(2)^{6}/LHRH	Nafarelin

5.1.2 - Endocrine and clinical effects of LHRH agonists during prolonged administration

Prior to the commencement of this study of the new depot preparation (Zoladex), there were only a few published reports of the effects of administration of LHRH agonists to premenopausal women although the literature on the subject is now rapidly growing. Initial interest was in their potential use for the control of fertility. Two groups have published data on the effects of chronic intranasal administration of the agonist buserelin, using single daily doses of 400 or 600 mcg (Schmidt-Gollwitzer et al, 1981; Bergquist et al, 1982). Inhibition of ovulation was observed in over 90% of cycles studied but variable effects on oestradiol were seen, with concentrations in some subjects intermittently approaching the preovulatory range, although there was a trend towards greater suppression with more prolonged therapy. Approximately one third of subjects developed amenorrhoea but irregular bleeding episodes were a problem in some cases and one of the groups found evidence of endometrial hyperplasia in 8 out of 31 biopsies (Schmidt-Gollwitzer & Hardt, 1981), indicating an unopposed oestrogen effect. Ovulatory ovarian activity recurred rapidly on discontinuation of the agonist.

Intranasal administration of another agonist, nafarelin, has been investigated more recently for its contraceptive efficacy at daily doses of 125 and 250 mcg. Inhibition of ovulation in 261 out of 262 treatment months was reported by Gudmundsson et al (1986) with suppression of oestradiol to early follicular phase concentrations after 4 weeks. The majority (77%) of the subjects became amenorrhoeic after the initial 3 months of therapy, particularly those on the

higher dose and hot flushes were the main reason for withdrawal from therapy (9/47 subjects). In contrast, Brenner et al (1985) reported 12 ovulations in 114 treatment cycles, two of these at the higher dosage, with poor suppression of oestradiol and a high incidence of irregular bleeding. The reason for the discrepancy between these two reports is unclear unless there were problems with compliance in the latter study.

Similar variability of response to intranasal buserelin was seen in 5 women with endometriosis treated with a dose of 200 mcg three times daily for 6 months (Shaw et al, 1983) although 3 of the 5 remained suppressed and no ovulations were seen. Increasing the dose of therapy results in greater ovarian suppression (Hardt & Schmidt-Gollwitzer, 1983) although even at daily doses of 800-1200 mcg, 4 out of 9 subjects showed marked intermittent fluctuations in serum oestradiol. Another problem with intranasal administration is the duration of the initial stimulatory phase, the acute response of LH to individual doses being maintained, although attenuated, for over 2 weeks (Lemay et al, 1985; Hardt & Schmidt-Gollwitzer, 1983), with more rapid loss of acute FSH response. The stimulatory phase of oestradiol secretion lasted between 1 and 5 weeks in the same group of subjects. Similar findings were reported with nafarelin when women with endometriosis were treated with a daily dose of 1000 mcg although more reproducible ovarian suppression was obtained once the initial stimulation had resolved (Schriock et al, 1985).

This prolonged initial stimulatory effect is avoided by subcutaneous administration of the agonist. Lemay et al (1984) gave 200mcg of

buserelin twice daily by the subcutaneous route for the first week of therapy in 10 women with endometriosis and found that marked gonadotrophin stimulation was seen only with the first injection and abolished thereafter. FSH was suppressed to baseline levels within 48 hours although a more progressive decline in LH was seen. The same group (Maheux et al, 1985) treated women with uterine fibroids with subcutaneous bolus therapy over six months and found that oestradiol stabilised at early follicular phase levels after three weeks with failure of suppression in only one out of 10 subjects. Serum LH declined only slowly over 3 months.

In an attempt to achieve more constant plasma levels of agonist, Healey et al (1986) treated 5 women with uterine fibroids with a subcutaneous infusion of buserelin. They started therapy in the mid-luteal phase of the cycle, in contrast to the other groups quoted above, where therapy was initiated in the early follicular phase. The rationale for this was based on observations of Fraser & Sandow (1985) who found that oestrogen stimulation did not occur when subcutaneous infusions of the agonist were commenced in the late luteal phase in stump tailed macaque monkeys. This lack of initial oestrogen stimulation was confirmed in the clinical study.

5.1.3 - Administration by subcutaneous depot

The greater and more predictable suppression achieved with subcutaneous administration of the agonist is outweighed by the lack of acceptability of frequent subcutaneous bolus injections or an infusion pump. Constant and sustained plasma levels of agonist are best obtained with a subcutaneous depot and recent efforts on behalf

of the pharmaceutical companies have been directed towards development of the latter (Hutchison & Furr, 1987). Zoladex depot (goserelin) is manufactured by ICI Pharmaceuticals, Macclesfield, UK. The analogue (D-ser(tBu)^{6},Aza-Gly^{10}-LHRH) is dispersed in a biodegradable lactide-glycolide copolymer rod which is prepacked in a special syringe applicator. The 3.6mg depot releases the agonist continuously at an average rate of 120 mcg/day over approximately 30 days. Preliminary studies in males with advanced prostatic carcinoma showed this dose to be effective in inducing reversible suppression of gonadotrophins and testosterone (Williams et al, 1984; Ahmed et al, 1985). In addition, limited experience of treatment of women with disseminated breast cancer demonstrated pituitary-ovarian suppression (Millstead, 1984 - personal communication) although no previous studies had been performed on women with benign conditions.

The object of the present study was to investigate the endocrine and clinical effects of goserelin (Zoladex depot) 3.6mg in premenopausal women treated for up to 6 months. A secondary objective was to establish the time taken following cessation of therapy for return of ovulatory menstruation and also to determine the optimum time in the cycle for initial commencement of treatment. Two groups of women were selected for study, a group complaining of premenstrual mental and physical symptoms and a group with symptomatic uterine fibroids. Some of the subjects had both problems. Initial approval was given for recruitment of 12 subjects, all of whom would commence therapy in the luteal phase of the cycle and another 6 who would start in the early follicular phase. Any who defaulted at an early stage could be replaced by another recruit who fitted the criteria for inclusion. In

this chapter the endocrine results will be presented in detail, together with a summary of the effect on uterine fibroids. The effects on cyclical symptoms will be presented and discussed in the next chapter.

5.2 - SUBJECTS AND METHODS

5.2.1 - Subjects

A total of 20 women were recruited to the study, of whom 17 completed 6 months therapy. All were premenopausal, with regular menstrual cycles (range 26-32 days). A condition for recruitment was that they had been surgically sterilised (the company had not received approval at that stage for clinical studies in potentially fertile women) and thus all were parous. They ranged in age from 31 to 48 years (mean 40.8 years) with a mean parity of 2 (range 1-5). Mean weight was 62.3 kg (range 52.0-82.0 kg) prior to therapy and 60.7 kg (range 52.2-81.5 kg) at its completion. Seven of the women had initially presented with premenstrual problems and the other 13 had uterine fibroids diagnosed clinically and confirmed by ultrasound. All were medically fit and receiving no additional form of hormonal therapy or any other medication which might interfere with interpretation of the results. The nature and objectives of the study were explained in detail to each of the subjects who gave written consent to participate. Full details of the protocols had been submitted in advance to the local ethical committee for approval.

5.2.2.- Therapy

The depot injections were administered at 28 day intervals, starting between days 20-25 of the cycle (14 subjects) or days 1-6 (6 subjects). Therapy was continued for a maximum of 6 months. Zoladex depot was injected into the subcutaneous tissues of the anterior abdominal wall, using the pre-packed sterile syringe applicator. Initially, infiltration of the skin with 2% lignocaine was performed routinely but after modification of the design of the needle by the manufacturers this was no longer found to be necessary.

5.2.3 - Endocrine monitoring

Each subject was asked to collect early morning samples of urine (20 mls) twice weekly for (i) at least one complete cycle prior to commencement of therapy, (ii) for its duration and (iii) after its cessation until the return of menstruation. Some subjects were asked to continue collections until the third post treatment menstruation. Between visits, the samples were stored by the subjects in their own domestic freezers. The samples were assayed for oestrone glucuronide, pregnanediol and creatinine. Results were expressed as the steroid:creatinine ratios. Venous blood was withdrawn immediately prior to administration of each depot and 1 and 3 months post-therapy for estimation of LH, FSH, oestradiol and progesterone. In addition, more detailed endocrinology was performed on a sub-group of 7 women commencing therapy in the luteal phase, who had additional samples withdrawn on days 1,2,3,7,14,21 of the first treatment cycle and day 14 of cycle 2 (taking day of administration of depot as day 0 regardless of actual menstrual cycle day). These 7 subjects also had monthly venous blood samples assayed for testosterone, androstenedione

and sex hormone binding globulin (SHBG). The laboratory methods are described in section 5.2.7.

5.2.4 - Other laboratory measurements

Venous blood was also taken monthly for measurement of full blood count, platelets, urea, bilirubin, alkaline phosphatase, alanine aminotransferase, calcium, phosphorus, total proteins and albumin. Six subjects had a short Synacthen test performed prior to therapy and during the last treatment cycle.

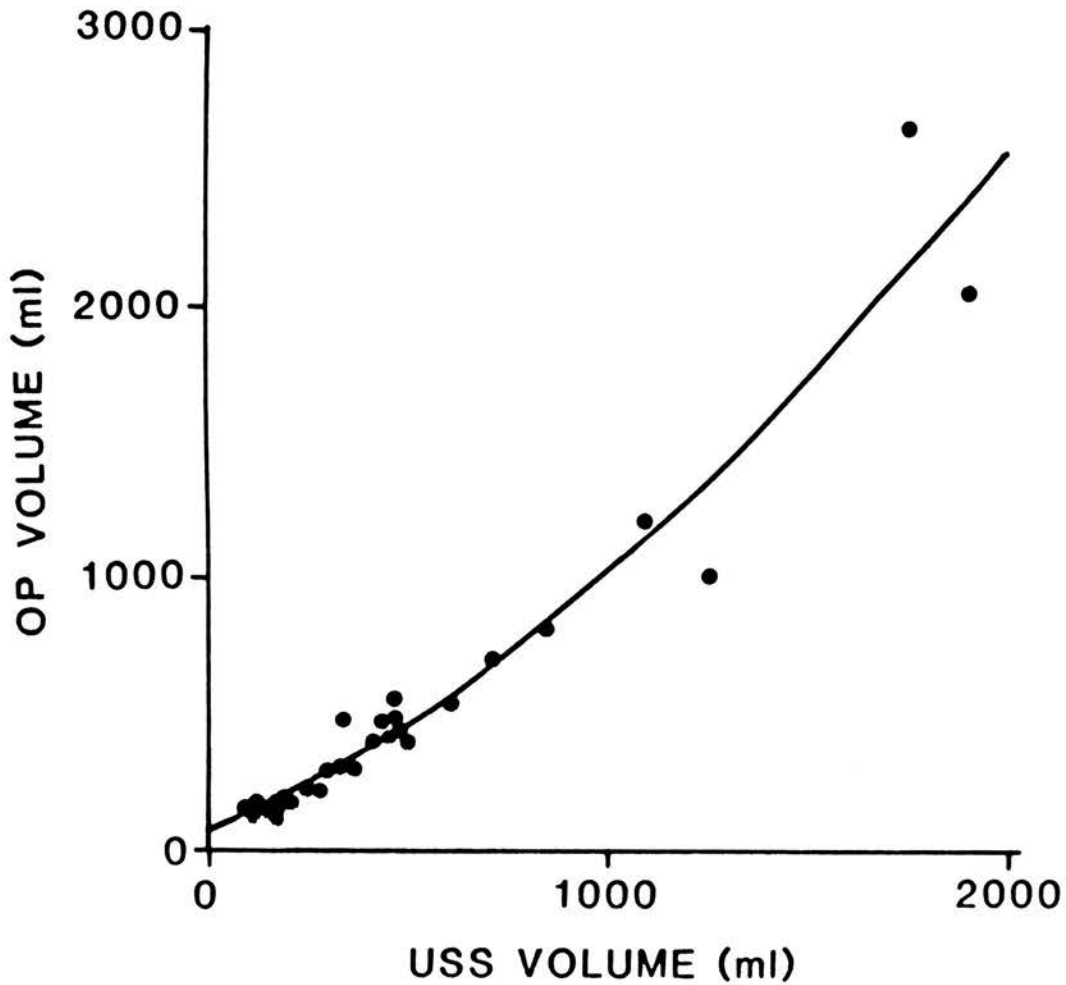
5.2.5 - Clinical assessment

The subjects were interviewed monthly and asked specifically about changes in presenting symptoms and any side effects attributable to therapy. In particular, they were questioned specifically about the occurrence of hot flushes, night sweats, vaginal dryness and sexual problems. Symptoms were rated by the interviewer on a four-point scale. All subjects kept a menstrual calendar and those with cyclical symptoms completed a daily symptom diary chart (see section 6.2.3).

5.2.6 - Assessment of uterine volume

At diagnosis, an initial ultrasound scan was performed to confirm the presence of fibroids and to exclude any coincidental ovarian pathology. Volume measurements were performed immediately prior to the initial depot, monthly during therapy and three months after its completion. Total uterine volume was measured by ultrasound using a real-time linear array machine (Picker LS 700). The maximum length (excluding the cervix) and the widest transverse diameters in 2 planes at right angles were taken and the volume calculated using the formula

Figure 5.1
Correlation between ultrasound measurement of uterine volume and measurement by water displacement.



$4/3\pi r^3$ which approximates to the product of the three diameters multiplied by 0.523. This method of assessment had been previously validated by comparing ultrasound measurements prior to hysterectomy with direct measurement of the unfixed operative specimen. A highly significant correlation between the two methods was obtained (r=0.96; figure 5.1).

5.2.7 - Laboratory methods

Plasma was stored at -20 degrees before radioimmunoassay (RIA) of LH, FSH, oestradiol, progesterone, testosterone, androstenedione and SHBG. Plasma LH and FSH were measured by double antibody RIA (Hunter & Bennie, 1979) and the results expressed in terms of standards obtained from the National Institute of Biological Standards and Control, Holly Hill, London (LH 64/80, 77 U/ampoule, FSH 69/104, 10 U/ampoule). The intra-assay coefficients of variation were 10% and 9% respectively for LH and FSH, while the interassay coefficients of variation were 16% and 15% respectively. Limits of sensitivity were 0.2 U/l and 0.1 U/l for LH and FSH respectively. Oestradiol and progesterone were measured by RIA (Scaramuzzi et al, 1975; Backstrom et al, 1982). Sensitivities were 10 pg/ml for oestradiol and 200 pg/ml for progesterone. Intra- and inter-assay coefficients of variation were 9% and 13% respectively for oestradiol and 8% and 15% for progesterone.

Androstenedione and testosterone were measured in duplicate by specific RIA (McNatty et al, 1976; Baird et al, 1974, 1981). Following extraction with hexane:ether (4:1), androstenedione and testosterone were separated by alumina chromatography before assay.

The interassay coefficients of variation for androstenedione and testosterone were 12% and 11.5% respectively and the limits of sensitivity 50 and 10 pg/ml. The SHBG assay was a modification of the method of Rosner (1982) described by Anderson et al (1976) using both unlabelled and [3H]-dihydrotestosterone (DHT). The method measures total binding capacity of plasma in the form of the mass of 5a-dihydrotestosterone required to saturate the available binding sites. The SHBG-DHT complex is precipitated with ammonium sulphate and the radioactivity in the supernatant used to assess the SHBG binding capacity.

The aliquots of early morning urine were assayed for oestrone-3-glucuronide by direct RIA after 100-fold dilution using specific antisera supplied by P. Samarajeewa, Courtauld Institute, Middlesex Hospital (Baker et al, 1979). Sensitivity was 6 ng/ml and intra- and inter-assay coefficients of variation 7.9% and 15.8% respectively. Pregnanediol was determined by gas-liquid chromatography (Chamberlain & Contractor, 1968). Creatinine was measured by autoanalyser using the Jaffe reaction and the results expressed as the steroid:creatinine ratios.

5.3 - RESULTS

5.3.1 - Patient compliance

Of the 20 women who commenced therapy, only 3 failed to complete the full 6 months. Two of these had presented with cyclical symptoms and dropped out after 3 and 5 months respectively. Further details are given in section 6.3.1. Only one subject with fibroids withdrew prior

to completion. She presented one week after the administration of depot 2 with continuous heavy bleeding accompanied by cramp-like pelvic pain. This was followed by prolapse of a degenerating submucous fibroid which was removed under general anaesthesia. She elected to undergo hysterectomy which was performed 2 weeks later. At operation the uterus contained a large infarcted intramural fibroid.

5.3.2 - Endocrine response

5.3.2a - Plasma ovarian steroids and gonadotrophins

The gonadotrophin, oestradiol and progesterone assay results from the 7 subjects who underwent more frequent sampling during the initial treatment cycle are shown in figure 5.2 and the results of monthly sampling from the 17 subjects who completed 6 months therapy in table 5.2. One way analysis of variance for repeated measures was used to test for overall significant differences. Results show an initial marked rise in the concentration of LH to reach a peak within 24 hours of the initial depot, accompanied by lesser stimulation of FSH (figure 5.2a). Rapid return to basal levels occurred over the next 48 hours. Thereafter concentrations of FSH remained within the pretreatment range. In contrast, plasma LH showed a significant and sustained suppression for the duration of therapy ($F=4.22$; $p<0.01$ by analysis of variance). Plasma oestradiol (figure 5.2b) fell to early follicular phase levels (normal range of 55 ± 20 pg/ml - mean$\pm$SD) within 14 days and was maintained in or below that range for the duration of therapy.

Figure 5.2.
Plasma LH, FSH, oestradiol and progesterone (mean ± SEM) during therapy with Zoladex depot 3.6mg, starting in the mid-luteal phase of the first treatment cycle. Results are from 7 subjects sampled on days 0,1,2,3,7,14,21 of the initial treatment cycle, days 0,14 of cycle 2 and monthly thereafter.

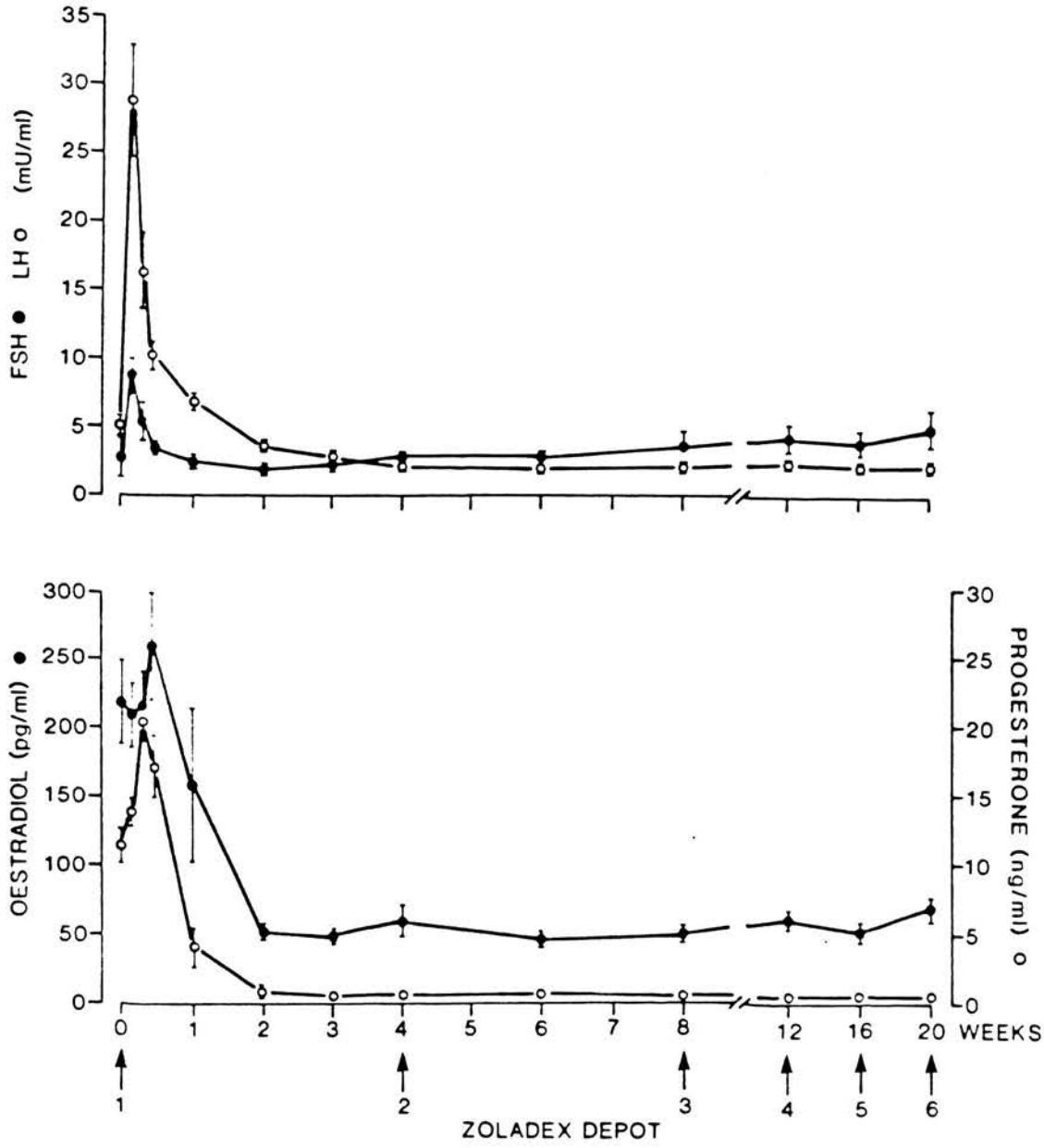


Table 5.2

Changes in plasma oestradiol and gonadotrophins (mean + SEM) during therapy with Zoladex depot (n=17)

CYCLE	OE2 (pg/ml)	LH (mu/ml)	FSH (mu/ml)
Pre	248.7 ± 48.2	6.6 ± 0.9	4.4 ± 0.7
1	51.3 ± 5.6	2.2 ± 0.4	3.1 ± 0.3
2	47.6 ± 3.0	2.1 ± 0.3	4.1 ± 0.4
3	50.7 ± 3.3	2.4 ± 0.3	5.0 ± 0.5
4	53.3 ± 3.3	2.2 ± 0.5	4.7 ± 0.4
5	56.3 ± 3.9	2.3 ± 0.4	5.8 ± 0.6
6	55.5 ± 3.5	1.2 ± 0.3	5.2 ± 0.7

Figure 5.3
Plasma testosterone and androstenedione (mean ± SEM) prior to and during the initial 4 months of therapy with Zoladex depot 3.6 mg.

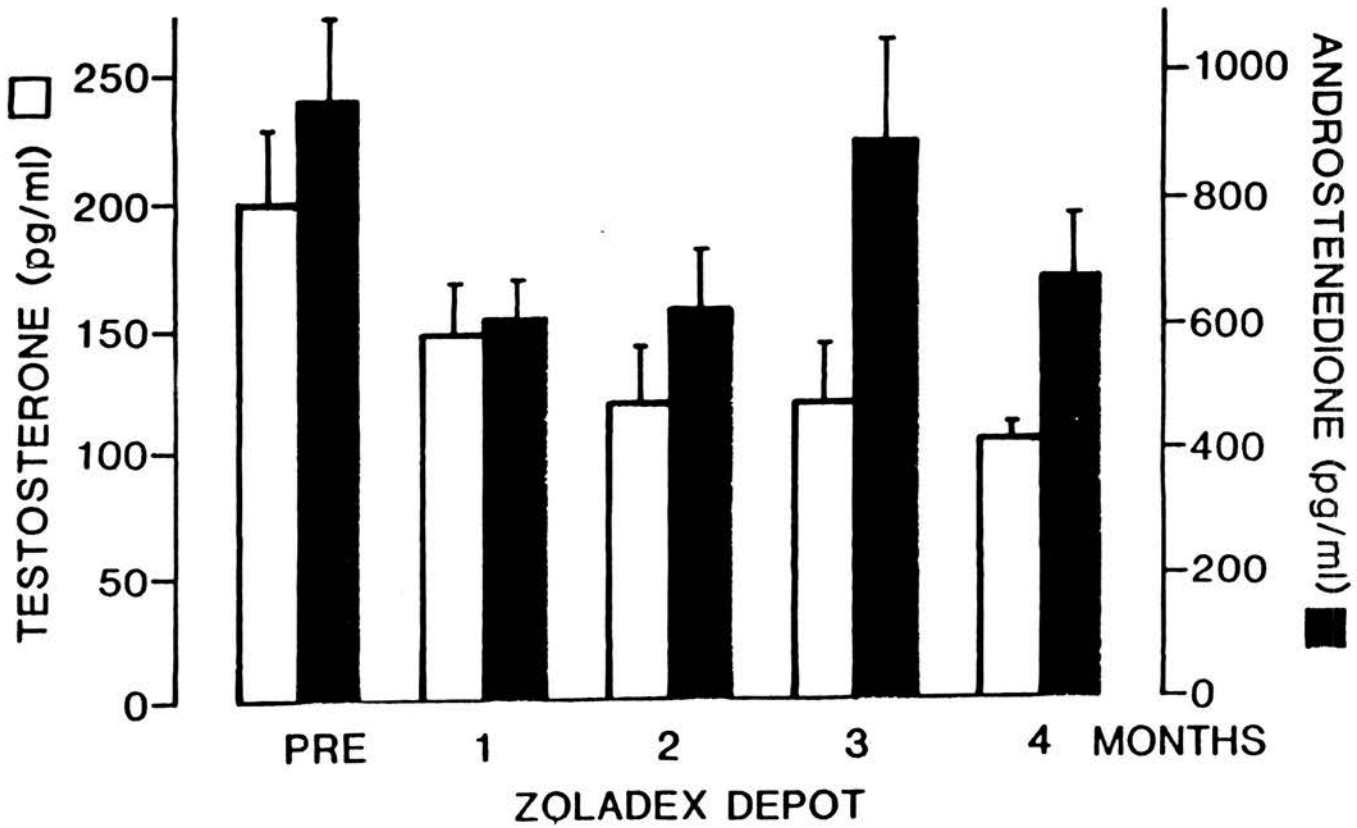


Table 5.3

Changes in plasma androgens and sex hormone binding globulin (SHBG) (mean±SEM) during therapy with Zoladex depot (n=7)

CYCLE	Androstenedione (pg/ml)	Testosterone (pg/ml)	SHBG (nmol/l)
Pre	978 ± 129	205 ± 26	68.0 ± 10.8
1	627 ± 66	147 ± 19	60.0 ± 9.7
2	634 ± 90	120 ± 17	59.0 ± 8.5
3	879 ± 162	119 ± 17	60.8 ± 8.5
4	673 ± 90	104 ± 5.9	69.3 ± 11.0
5	878 ± 212	120 ± 10	63.8 ± 11.3

5.3.2b - Androgens and SHBG

Mean plasma testosterone concentrations were also significantly reduced during therapy ($F=3.33$; $P<0.05$ - figure 5.3; table 5.3). However an initial fall in plasma androstenedione was not sustained beyond the third treatment cycle and did not reach statistical significance ($F=1.17$). Plasma SHBG showed a small but non-significant reduction ($F=0.62$ - table 5.3).

5.3.2c - Urinary ovarian steroid metabolites

Mean values of urinary ovarian steroid metabolites were calculated for each 3-4 day interval before, during and after completion of therapy in those 12 subjects who commenced Zoladex treatment in the mid-luteal phase of the cycle (figure 5.4.1). The post-treatment results are standardised around day 1 of the initial menstruation. Ovulation, assessed by twice weekly urinary pregnanediol, was inhibited in all the subjects throughout treatment. The mean urinary oestrone glucuronide:creatinine ratio remained within or just below the early follicular phase range of the pretreatment cycle. Differences in ovarian steroid profiles during the initial treatment cycle were seen between those women who commenced therapy in the mid luteal phase of the cycle (median day 23), as illustrated in figure 5.4.1 and those 6 subjects who commenced in the early follicular phase (median day 4), shown in figure 5.4.2. When the initial depot was given in the luteal phase, suppression of urinary oestrogen was apparent after 14 days in all the subjects. A more variable response was seen in the group where therapy was initiated in the follicular phase, 3 of the subjects showing marked oestrogen stimulation lasting between 14 and 21 days (eg figure 5.5.1a) while stimulation was mild and transient in the

Figure 5.4.1
Urinary steroid metabolites (mean ± SD) for each half week period before, during and after 6 months therapy with Zoladex depot in 12 subjects who commenced treatment in the mid-luteal phase of the cycle. Post treatment results are standardised around day 1 of first menstruation.

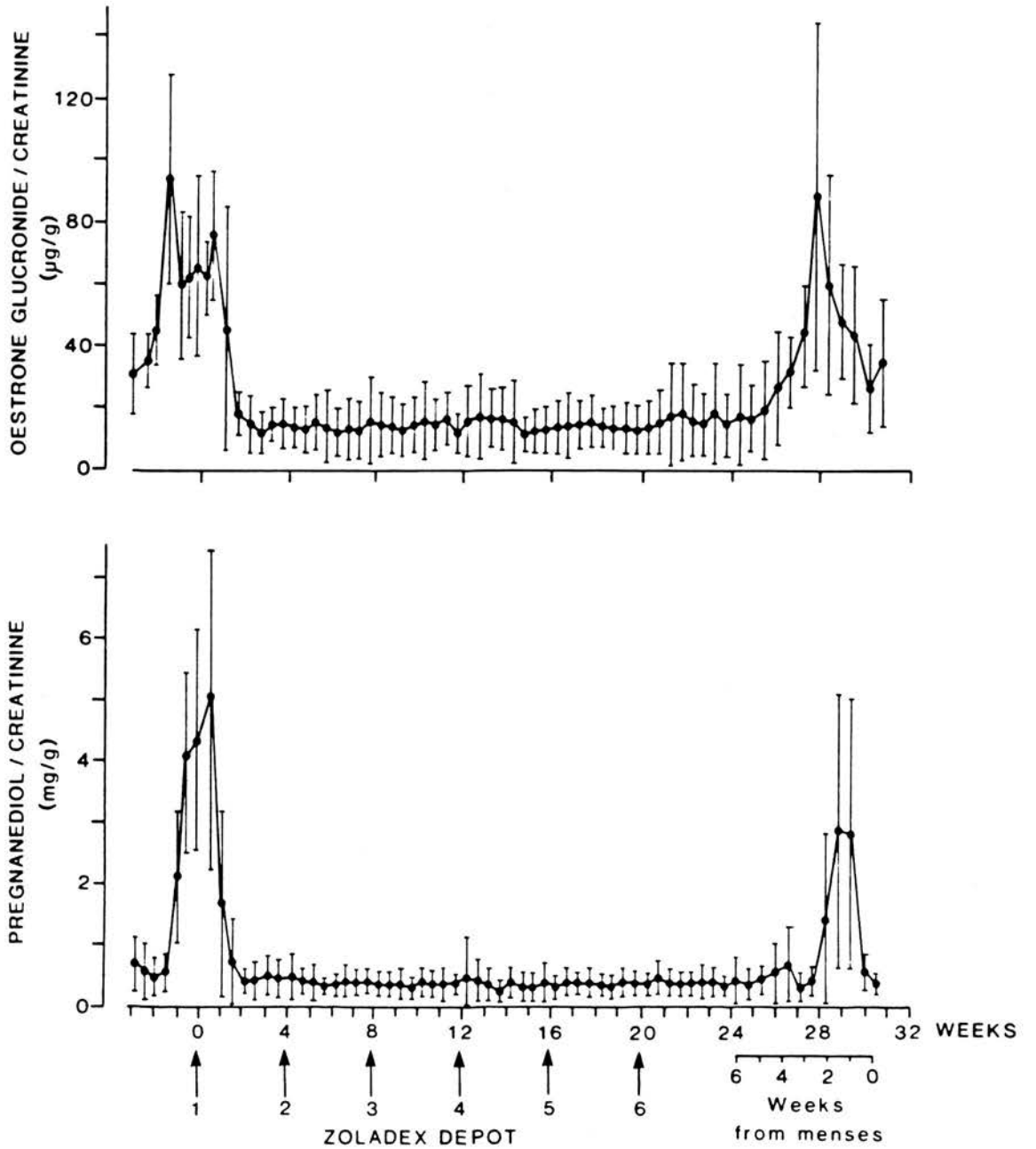
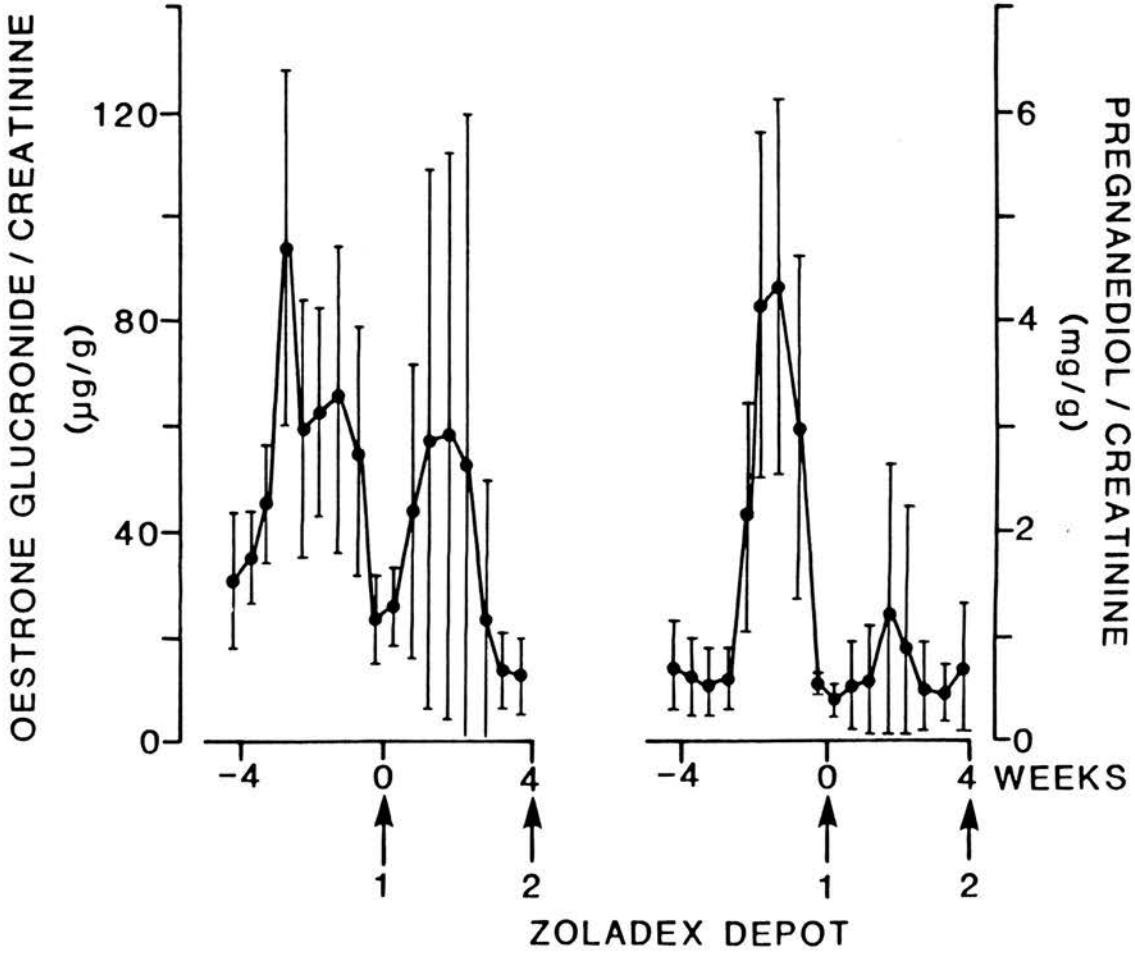


Figure 5.4.2
Urinary ovarian steroid metabolites (mean ± SD) during the pretreatment cycle and treatment cycle 1 in 6 subjects who commenced therapy in the early follicular phase of the cycle.



other 3 subjects (eg figure 5.5.1b). For the remainder of therapy, mean urinary ovarian steroid metabolites in those starting therapy in the follicular phase did not differ from those who started in the luteal phase (figure 5.4.1) and are thus not plotted out in full. One subject who inadvertently commenced therapy around mid-cycle showed marked oestrogen stimulation although this was not associated with any adverse clinical effects. Individual differences in ovarian steroid profiles during therapy are discussed below and in section 5.3.5 and illustrated in figures 5.5.1 - 5.5.3.

Following the administration of the last depot, 15 of the 17 women who completed 6 months therapy resumed menstruation within 80 days (median 72 days, range 62-80 days), with a delay to 95 days in one subject and 5 months in another aged 44 years who subsequently developed post-menopausal levels of gonadotrophins and became amenorrhoeic. The two stopping after 3 and 5 months resumed ovulatory menstruation within 65 days. Recovery of ovarian activity following the administration of depot 6 is shown for 4 individual subjects in figure 5.6 and for the group as a whole in figure 5.4.1. In the latter, results have been standardised around day 1 of menstruation. Two of the women recorded episodes of spotting 32 and 36 days respectively after depot 6 and in one there was a transient rise in urinary pregnanediol. The first post-treatment menstruation was anovular in one case and preceded by a short luteal phase in 2 others. Some of these individual differences are illustrated in figures 5.5 - 5.6.

Figure 5.5.1
Ovarian steroid metabolites, uterine volume and menstrual bleeding in two subjects who commenced therapy in the early follicular phase of the cycle, showing differences in steroid profiles during the initial treatment cycle.

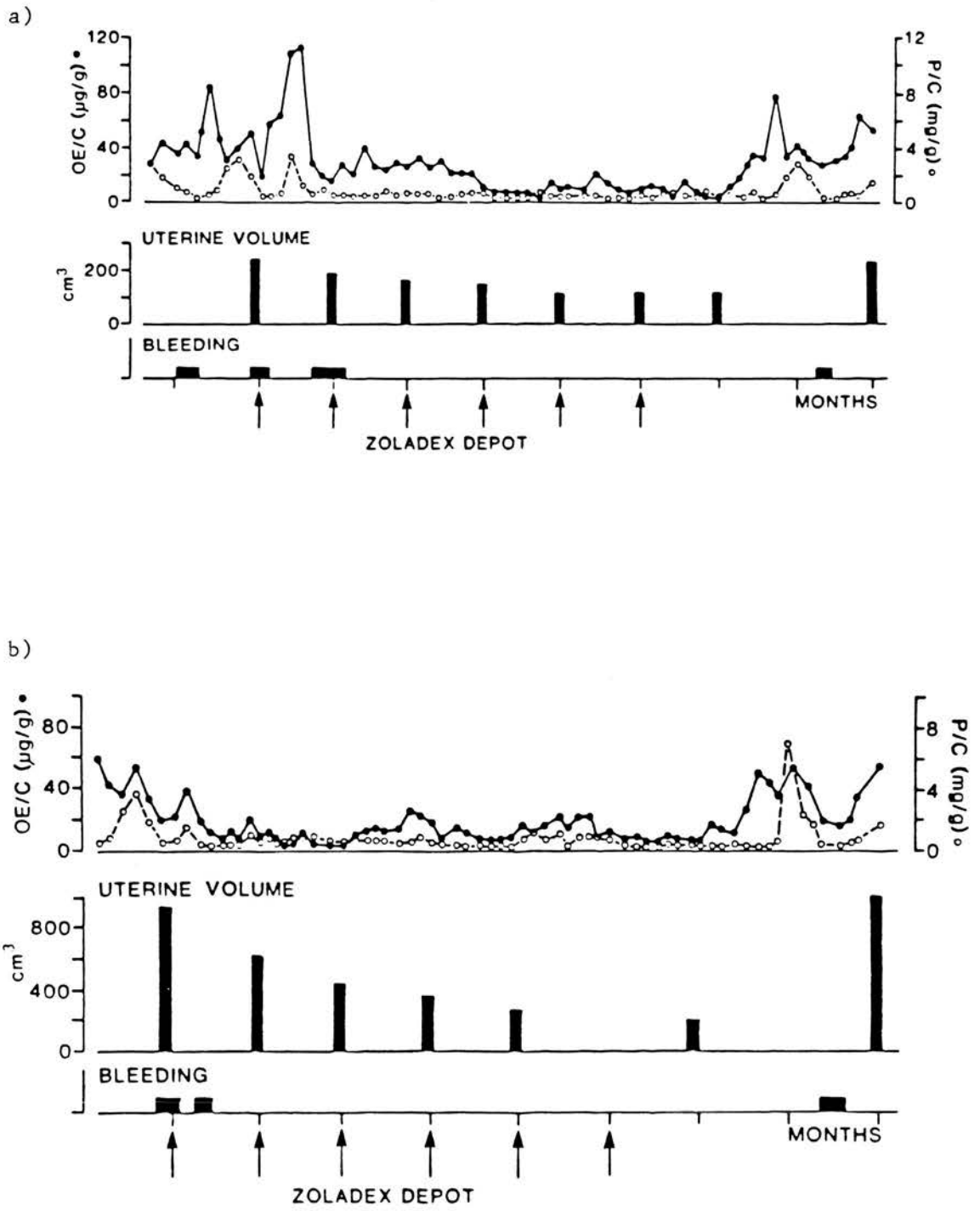


Figure 5.5.2
Ovarian steroid metabolites, uterine volume and menstrual bleeding in two subjects who commenced therapy in the luteal phase of the pretreatment cycle, showing marked differences in oestrogen suppression and fibroid response.

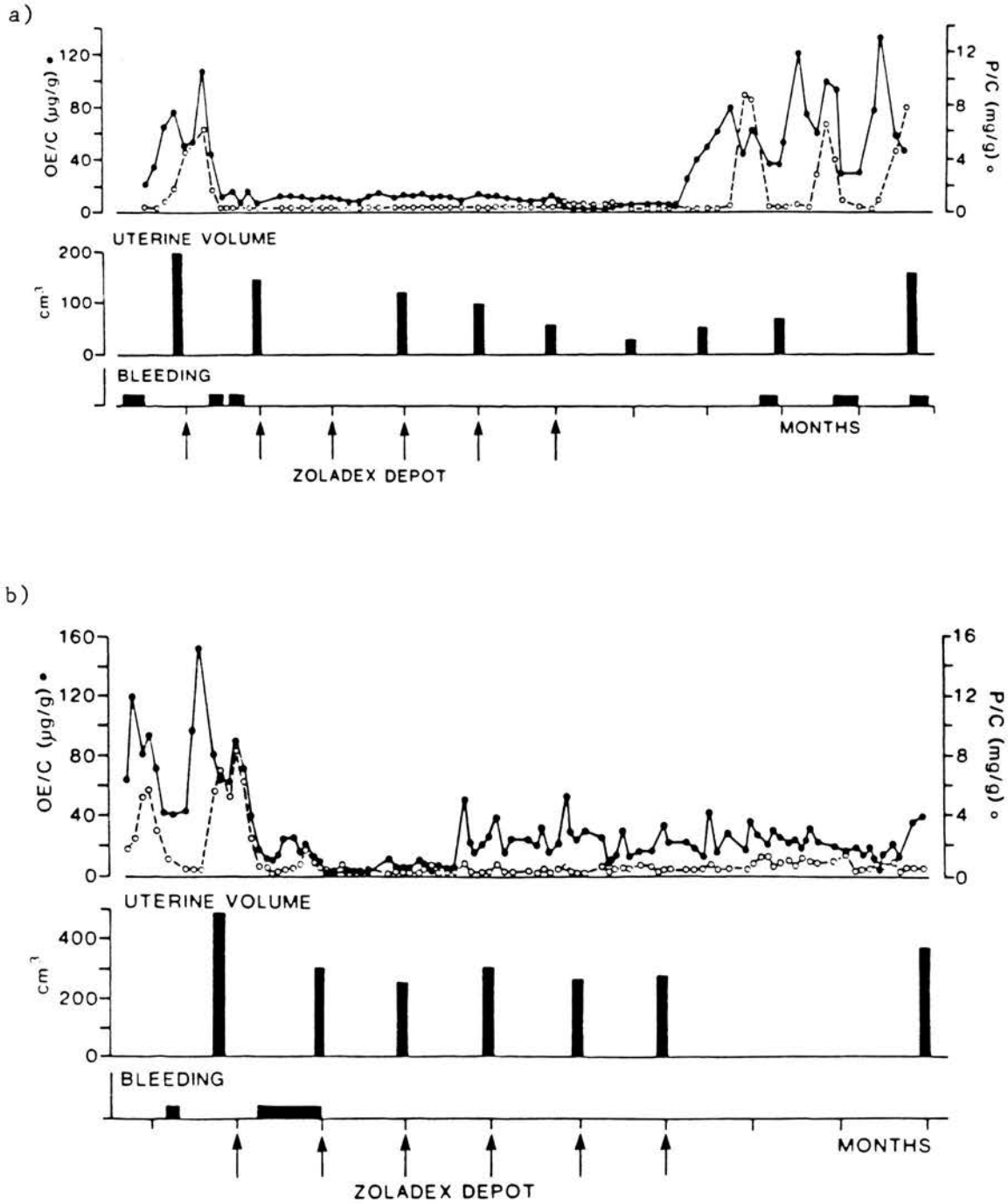


Figure 5.5.3
Urinary steroid metabolites, uterine volume and menstrual bleeding in one subject who failed to show suppression of plasma LH during therapy, with irregular bleeding and a poor fibroid response.

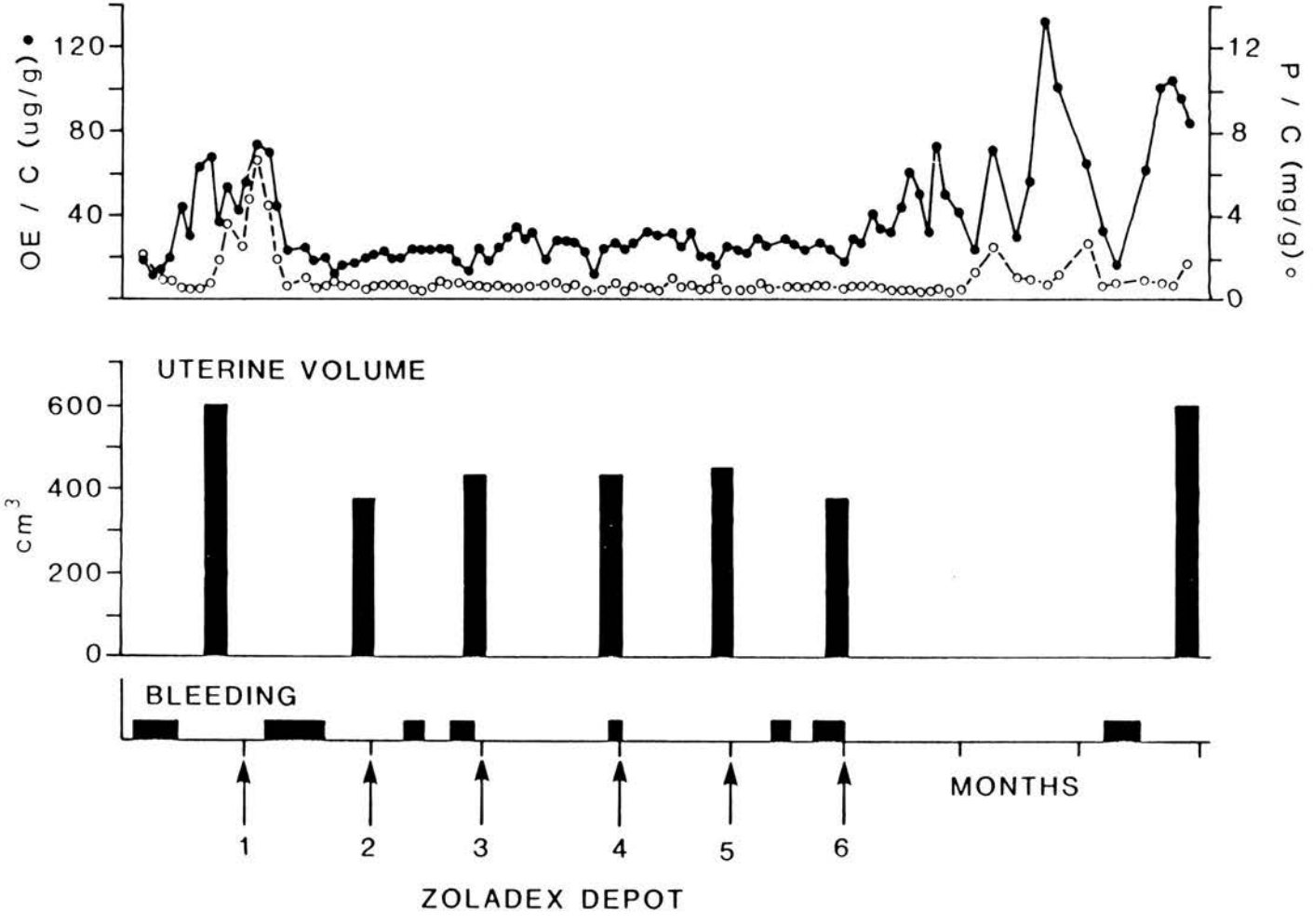
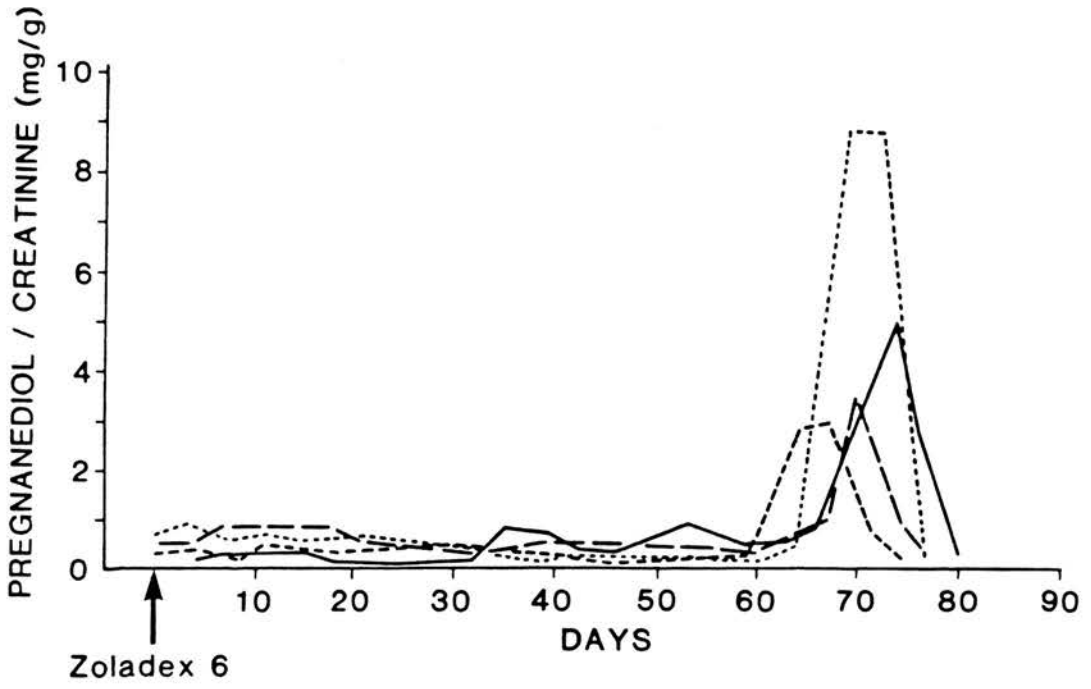
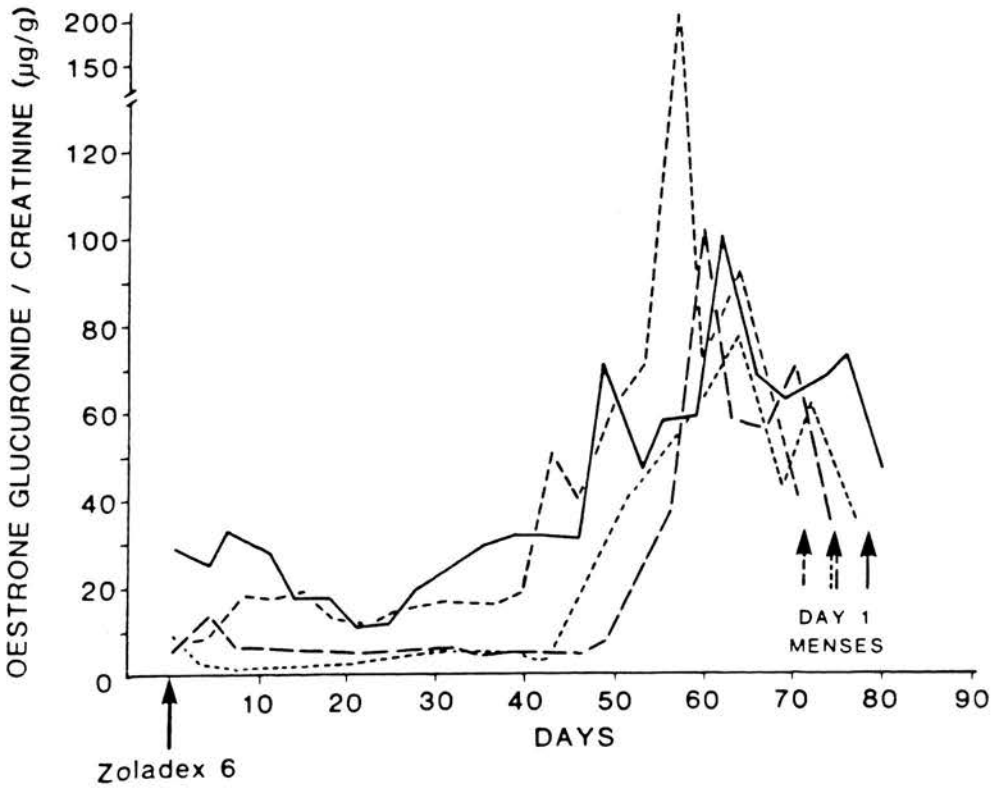


Figure 5.6
Recovery of urinary ovarian steroid metabolites and return of menstruation after administration of depot 6 in 4 subjects. In one (— —) a short luteal phase is seen.





5.3.3 - Biochemical and haematological results

No changes in biochemical and haematological parameters were seen during therapy and the cortisol response to Synacthen was not impaired at the end of treatment. Beneficial effects on haemoglobin were seen in two subjects who were mildly anaemic at its commencement. The unfortunate subject with prolapse of a submucous fibroid required transfusion because of an acute fall in haemoglobin concentration secondary to haemorrhage.

5.3.4 - Clinical response to therapy

Menstrual pain and pressure symptoms secondary to the presence of uterine fibroids were relieved completely during therapy. Bleeding during treatment cycle 1 was more prolonged than normal although with a normal or less than normal flow. In those subjects starting therapy during the luteal phase, bleeding occurred around or just after the time of expected menstruation (figure 5.5.2). When therapy was initiated in the early follicular phase, further bleeding occurred 3-21 days after the depot and corresponded to oestrogen withdrawal although there was evidence of luteinisation in some cases (figure 5.4.2; 5.5.1). The duration of first cycle bleeding was not significantly different, regardless of whether the treatment had been started in the luteal (median 11.5 days, range 4-24 days) or the follicular phase (median 8.5 days, range 5-26 days). There were 7 episodes of bleeding in 4 subjects after the completion of treatment cycle 1. Four of these episodes were very scant, lasting 3 days or less and were not associated with any changes in oestrogen excretion (see table 5.5). The fifth subject had three episodes of bleeding lasting 9, 4 and 11 days respectively, associated with

oestrogen excretion in the mid-follicular phase range. This subject showed lack of LH suppression during therapy and a poor fibroid response (figure 5.5.3).

5.3.5 - Fibroid response

All the subjects with fibroids showed reduction of uterine volume during therapy (figure 5.7). The individual response varied between 84% and 38% reduction at the end of therapy, with an overall reduction of 55%. The reduction was statistically significant ($p<0.01$ by repeated measure analysis of variance). The greatest reduction occurred during the first treatment cycle (table 5.4), lessening towards the end of therapy, although there was considerable individual variation. In the subject illustrated in figure 5.5.2a, suppression of oestrogen excretion into the castrate range was accompanied by an 84% reduction of uterine volume while the subject in figure 5.5.2b showed resumption of ovarian follicular activity accompanied by loss of fibroid response after depot 3. The subject described above who showed an overall poor response to therapy is illustrated in figure 5.5.3. There was no significant difference in fibroid response during the first cycle between those subjects where therapy was initiated in the early follicular phase and those who had started in the mid luteal phase. In the subject illustrated in figure 5.5.1a a 22% reduction in uterine volume had occurred in the first cycle despite marked initial oestrogen stimulation. Excluding the first treatment cycle, there was a highly significant inverse correlation between the percentage reduction in uterine volume and mean urinary oestrone glucuronide:creatinine ratio ($r=0.882$; $p<0.001$, Spearmann's rank correlation coefficient).

Figure 5.7
Serial ultrasound measurements of uterine volume in individual subjects before, during and after completion of 6 months therapy with Zoladex depot 3.6 mg.

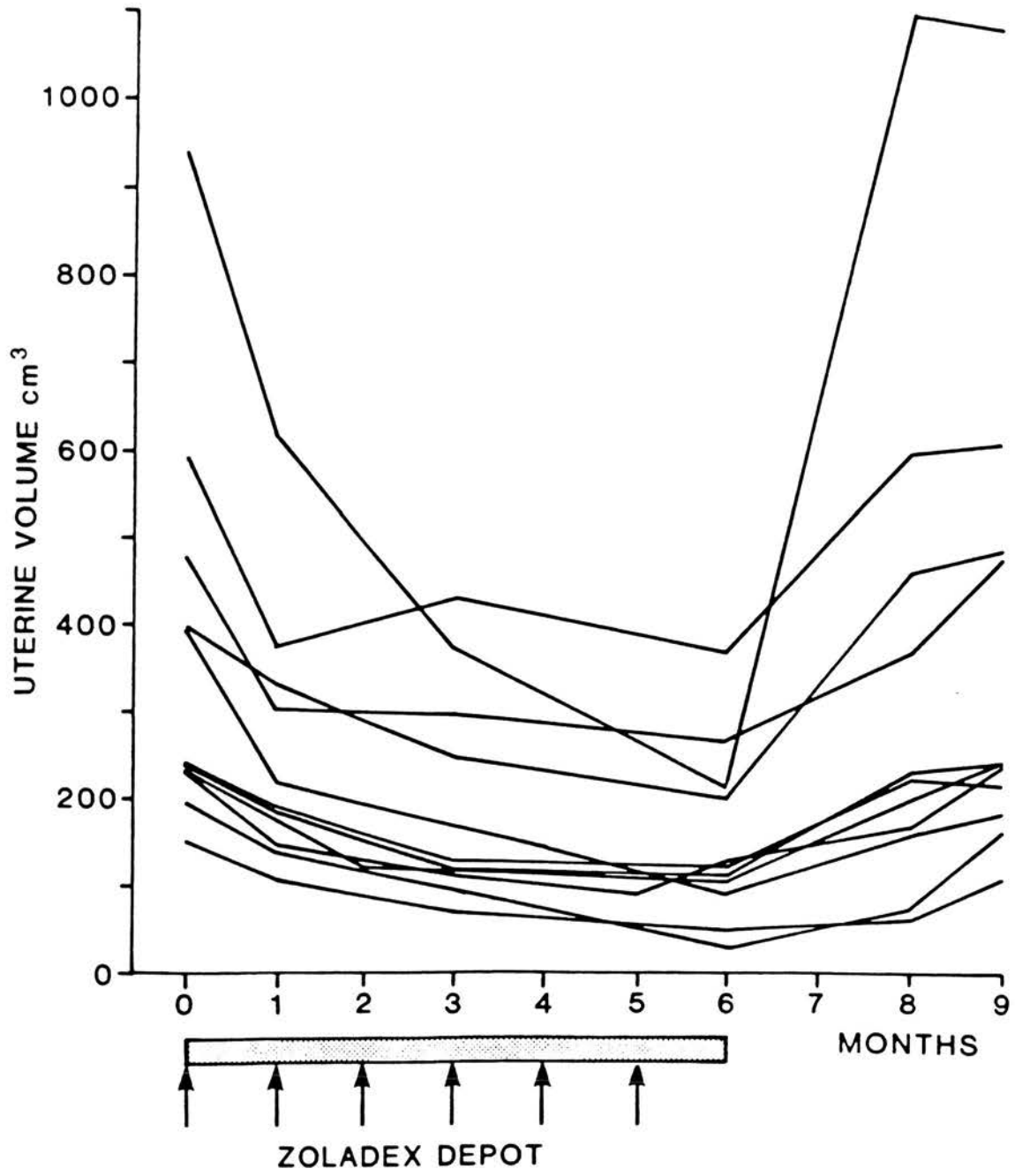


Table 5.4

Changes in uterine volume during and 3 months after therapy with Zoladex depot (n=12)

CYCLE	volume (cm3) (mean ± SD)	% reduction per cycle	% pretreatment volume
Pre	360 ± 225	---	100
1	253 ± 146	30.0	70
2	220 ± 126	13.0	61
3	199 ± 120	10.0	55
4	167 ± 115	16.0	47
5	154 ± 102	8.1	43
6	162 ± 100	-5.8	45
Post	367 ± 100	---	102

Three months after the cessation of therapy, fibroid volume had returned to pretreatment values (figure 5.7; table 5.4). Some regrowth was seen even in those subjects where ovulatory menstruation had not yet resumed (figure 5.5.2b).

5.3.6 - Other effects and side effects of therapy

The effect of therapy with Zoladex depot on menstrual bleeding has been outlined in section 5.3.4. The occurrence of dysfunctional bleeding and side effects associated with oestrogen suppression, namely vasomotor symptoms and vaginal dryness is summarised in table 5.5. Here the incidence and severity of these problems is shown for all treatment cycles with the exclusion of treatment cycles 1.

All but two of the subjects reported hot flushes on direct questioning although the degree of associated distress was variable. There was a significant negative correlation ($r=-0.545$, $p<0.03$) between mean urinary oestrogen level (cycles 2-6) and overall severity of flushes for the corresponding treatment cycles. Eight subjects reported vaginal dryness at some time during therapy and in two of these there was associated dyspareunia which in both cases was transient. The vaginal symptoms tended to peak during treatment cycles 2, 3 and 4 and resolve towards the end of therapy. Only one of the subjects complained of lack of libido and she later withdrew from therapy prior to its completion, although not primarily because of this problem (see section 6.3.3). All were questioned monthly about the occurrence of headaches but only in one case did these appear to be more frequently present than prior to therapy. None of the subjects gained weight

Table 5.5

SIDE EFFECTS OF THERAPY WITH ZOLADEX DEPOT

Treatment cycles excluding cycle 1 (n=90)

Dysfunctional bleeding:	
Amenorrhoea	83 (92%)
Scanty 3 days or less	4 (4%)
Longer (range 4-11 days)	3 (3%)
Hot flushes:	
None	12 (13%)
Present not distressing	44 (49%)
Distressing	34 (38%)
Vaginal dryness:	
Absent	70 (78%)
Mild	16 (18%)
Associated dyspareunia	4 (4%)

during therapy and no problems were encountered with the injection sites.

Four subjects reported onset of symptoms of depression and/or anxiety soon after the commencement of therapy (see section 6.3.3). All four had reported cyclical mood changes prior to therapy although only one presented with these as her primary complaint and she later withdrew from the study. In the other three, who had presented with fibroids, the problem gradually resolved and no other adverse mental symptoms were reported.

5.4 - DISCUSSION

The administration of Zoladex depot resulted in sustained suppression of pituitary-ovarian function in these 19 premenopausal subjects. The subcutaneous depot produces a more reproducible response than that seen with the intranasal route of administration (Hardt & Schmidt-Gollwitzer, 1983; Lemay et al, 1984) and is more convenient than frequent subcutaneous bolus administration (Maheux et al, 1985) or a subcutaneous infusion (Healey et al, 1986). Inadequate endocrine response was seen in only one subject although oestrogens did not usually reach the castrate range. Some of the individual differences in urinary oestrogen excretion may be attributable to oestrogen derived from peripheral conversion of adrenal androgens. The latter pathway is not affected by pituitary-ovarian suppression (Couzinet et al, 1986) and this oestrogen contributes to the urinary metabolite measured by our assay.

Our finding that mean oestrogen levels remain within the early follicular phase range are in contrast with the results of some other groups, where suppression to post-menopausal levels or to the castrate range have been reported (eg. Meldrum et al, 1982; Muse et al, 1984; Coddington et al, 1986; Walker et al, 1986). The urinary results include oestrogens derived from adrenal sources but we also found that mean plasma oestradiol concentrations were maintained within or just below those obtained in the early follicular phase of the cycle. It is possible that the constant plasma levels of the agonist obtained with a depot preparation enabled this less than complete degree of suppression to be maintained while intermittent dosage regimes must exert a more profound suppression for the effect to be sustained. As

yet there is limited data from other groups on the effects of depot administration. The only other published report of the use of Zoladex in premenopausal women, in this case women with advanced breast cancer (Walker et al, 1986), did show greater ovarian suppression than that observed in the present study.

A dissociation between the effect of therapy on LH and FSH was seen, with prolonged suppression of LH while FSH returned to the pre-treatment range. This is the reverse of the dissociation of response reported during short term therapy, where sustained elevation of LH was observed with an acute rise following individual bolus doses (Meldrum et al, 1982; Lemay et al, 1985), while suppression of FSH and loss of acute response occurred at an early stage. There was no relationship between the degree of oestrogen suppression and FSH levels and the mechanism of this dissociation of gonadotrophin response is unclear. However a similar observation was made by Walker et al (1986) using Zoladex depot.

Marked differences in endocrine profiles were seen when therapy was commenced in the luteal phase of the cycle, compared with its initiation in the early follicular phase as has been the usual practice in the majority of published studies. The latter timing has the advantage of convenience, particular if cycles are irregular and avoids the possibility of commencing therapy during early pregnancy in potentially fertile women. However ovarian stimulation lasting up to 4 weeks or longer has been reported in these other studies (eg Hardt & Schmidt-Gollwitzer, 1983; Shaw et al, 1983; Muse et al, 1984). Our results showed a variable effect when therapy was initiated in the

early follicular phase, with prolonged stimulation in about half the subjects and minimal stimulation in the others. A more consistent response was seen where therapy was initiated in the luteal phase with the advantage of no additional menstruation after the expected bleed, although the latter was invariably prolonged. However the duration of first cycle bleeding did not significantly differ between the two groups. It was also interesting that fibroid response during the first cycle did not differ between the groups starting treatment in the two cycle phases. In practice then, the luteal phase start would not seem to confer any particular advantages despite the more uniform endocrine response. Timing of initiation of therapy in relation to other symptoms is discussed in the next chapter.

Ovarian function recovered rapidly after cessation of therapy, allowing for the fact that the duration of action of each depot is at least 30 days. The more prolonged recovery seen in two subjects may be attributable to their age. The median delay of 72 days to onset of first menses, when corrected to 42 days (by subtracting 30 days), is equivalent to the mean of 47 days following intranasal nafarelin for treatment of endometriosis (Schriock et al, 1985) and 43 days when used for contraception (Gudmundsson et al, 1986). However shorter recovery intervals have been reported by others using buserelin (Bergquist et al, 1982; Lemay et al, 1984). Recovery was shorter following a single depot of Zoladex (Thomas et al, 1986), where menses returned between 61 and 71 days after administration. Thus, in women wishing to preserve childbearing potential, the depot route of administration appears entirely reversible.

The reversibility of the effect of the agonist is seen in relation to one target organ, namely the uterus, although it had been hoped that a more sustained benefit on the fibroids would have been evident. The oestrogen-dependent nature of this tissue is very clearly demonstrated with a significant positive correlation between volume reduction and mean urinary oestrogen. Oestrogen receptors have been identified in fibroid tissue and their content found to vary during the menstrual cycle (Soules & McCarty, 1982; M. Lumsden, personal communication, Edinburgh 1987). The reduction in uterine volume seen in all the subjects during therapy is consistent with the reduction of circulating oestradiol and loss of ovarian cyclicity. The method of measurement of the fibroids included the volume of the uterus itself and thus a reduction of 100% was not anticipated although complete fibroid regression was obtained in at least two of the subjects, including the one illustrated in figure 5.5.2a. However, cessation of therapy after 6 months was accompanied by rapid return of uterine volume to pretreatment values in parallel with the return of ovulatory menstruation. A more sustained benefit was reported in some or all of the subjects in the other published series (Maheux et al, 1985; Coddington et al, 1986; Healey et al, 1986). The reason for this difference in outcome is not clear but more information is needed in larger numbers of women. Our results are based on only 6 months therapy with incomplete ovarian suppression in some of the subjects and the effect of more prolonged agonist administration has yet to be determined. However, for reasons mentioned below, prolonged and profound ovarian suppression may carry disadvantages for premenopausal women unless they are being treated for a malignant condition where the benefits outweigh the disadvantages.

In addition to ovarian oestrogen suppression, a significant reduction of circulating testosterone was seen compared with mid-luteal phase pre-treatment control values. Other workers have not examined this aspect of ovarian function, except in women suffering from polycystic ovarian disease (Chang et al, 1983; Couzinet et al, 1986). The developing follicle and corpus luteum are both an important source of androgens (McNatty et al, 1976) and thus the ovarian component of circulating testosterone can be expected to fall during therapy. Peripheral conversion of androstenedione also contributes significantly to circulating testosterone (Horton & Tait, 1966) and as this is also derived from the ovary it is surprising that a similar degree of suppression of androstenedione was not observed during therapy with the agonist. This may in part reflect its continuing production from small and atretic follicles (McNatty et al, 1979) as well as the normal adrenal production (Baird et al, 1969). It is also possible that conversion of androstenedione to testosterone is gonadotrophin dependent so that this pathway is active post-menopausally when gonadotrophin levels are high but not when gonadotrophins are suppressed during agonist therapy. However the latter statement is purely speculative. It is presumably the parallel reduction in both ovarian oestrogens and testosterone which resulted in the lack of overall change in SHBG levels, as these two steroids exert a counterbalancing effect (Anderson, 1974).

These observations on androgen levels during agonist therapy may have important metabolic implications. The relatively hypo-oestrogenic state induced by therapy with LHRH agonists has been referred to as

'medical oophorectomy' (Meldrum et al, 1982) and has certain similarities to the post-menopausal state. Both these situations are associated with alterations in serum lipids (Oliver & Boyd, 1959; Patterson et al, 1979) and an increased risk of ischaemic heart disease (Gordon et al, 1978) although the latter association has been challenged (Lapidus et al, 1985). However in contrast to the post-oophorectomy situation (Vermulen, 1976), normal levels of androstenedione are available during Zoladex therapy for peripheral conversion to oestrone (Grodin et al, 1973) and in some cases continuing low levels of oestradiol production are maintained. Endocrine profiles are also different following the natural menopause where continuing ovarian production of testosterone (Longcope et al, 1980) occurs in the stroma and appears to be dependent on the elevated gonadotrophins (McNatty et al, 1979). This state of relative androgen-dominance (Judd, 1976) may also be important in the aetiology of the rising incidence of cardiovascular morbidity seen following the menopause. It is unlikely to be of relevance in women receiving therapy with LHRH agonists although results of studies on plasma lipid profiles are awaited. The effects of exogenously administered androgens and related steroids in relation to lipids and cardiovascular morbidity is also discussed in another section of this thesis (section 4.4).

Oestrogen suppression has other potentially important consequences in premenopausal women. One of the major considerations is the effect on bone density, which is known to be oestrogen-dependent (Nordin, 1971; Lindsay et al, 1976). Studies of bone density during LHRH agonist therapy are still in progress so it is too early to reach definite

conclusions. However currently the use of these agents seems likely to be restricted to short term or intermittent therapy, such as for the management of endometriosis. They may also be of value for preoperative shrinkage of fibroids (Lumsden et al, 1987) and in the management of women with fibroids who are nearing the age of the natural menopause.

The clinical application of LHRH agonists is also likely to be limited by the occurrence of side effects associated with reduced circulating oestrogens, namely hot flushes and atrophic vaginitis. However, these problems did not result in any of the subjects presented above withdrawing from the study. Partial oestrogen suppression with lower intranasal doses of agonist, such as those investigated for contraception (section 5.1.2) are not associated with these side effects but here irregular bleeding becomes a problem, together with the potential hazard of the effect of unopposed oestrogen on the endometrium. One therapeutic strategy, which we are currently investigating in relation to the management of fibroids, is to combine an LHRH agonist in the dose and regime described above, with an oestrogen receptor blocker in order to counteract the effect of the remaining circulating oestrogen on its target tissue. One such agent is the antioestrogen tamoxifen, already used widely in the management of oestrogen-dependent breast cancer. An alternative strategy would be the combination of an LHRH agonist with a pure progestogen, such as medroxyprogesterone acetate. The latter reduces the frequency of menopausal flushes when given orally (Albrecht et al, 1981) or by depot (Bullock et al, 1975). Progestogens may also exert a protective effect against bone loss (Lindsay et al, 1978).

In conclusion, Zoladex depot produces reproducible and reversible suppression of pituitary-ovarian activity in premenopausal women. Although oestrogen levels are maintained just above the postmenopausal range, symptoms of oestrogen deficiency are frequent and the long term effects of therapy have yet to be clarified. While Zoladex produces shrinkage of uterine fibroids and relief of associated symptoms during therapy, rapid regrowth after its cessation limits its usefulness as a single agent in clinical management at the present time. However, further investigation of the use of the depot in other oestrogen-dependent conditions is indicated and its potential role in the evaluation and management of premenstrual complaints is the subject of the next chapter.

CHAPTER 6

A DESCRIPTIVE STUDY OF THE EFFECT OF ZOLADEX DEPOT (GOSERELIN) ON CYCLICAL MENTAL AND PHYSICAL SYMPTOMS

6.1 - Introduction

The relationship between cyclical changes in ovarian steroids and menstrual cycle related symptoms remains unresolved (see chapter 3). Attempts to abolish cyclical symptoms by hormonal suppression of ovulation with progestogens have yielded largely negative results (chapter 4), complicated by variable cycle control and possibly by direct effects of the steroids themselves. An alternative strategy is the use of LHRH agonists which suppress ovarian function by pituitary desensitisation (see chapter 5) and have no steroid-like action of their own. Three groups have published the results of such investigations, one using daily subcutaneous injections (Muse et al, 1984), and the others with intranasal spray (Backstrom, 1986; Bancroft et al, 1987). The results of these studies are discussed in greater detail later in this chapter but both these methods of administration have disadvantages in terms of reproducibility of endocrine response and patient acceptability (see section 5.1.2). The more recently developed subcutaneous depot, described in chapter 5, has the advantage of convenience for patients and a more consistent endocrine response. The aim of the present study was to investigate the effect of pituitary-ovarian suppression with the LHRH agonist Zoladex depot (goserelin) on cyclical mood and physical symptoms in women with premenstrual complaints. The endocrine and clinical effects of therapy have already been described in detail in chapter 5.

6.2 - SUBJECTS AND METHODS

6.2.1 - Subjects

Of the 20 subjects recruited for therapy with Zoladex depot (section 5.2.1), 7 had presented primarily with premenstrual problems. They had been initially assessed by daily completion of a set of visual analogue scales to establish the relationship of their symptoms to the premenstrual phase of the cycle (see section 2.2.2). The other 13 had presented with various menstrual-cycle related symptoms and were subsequently found to have uterine fibroids. The women in this latter group were also asked about the presence of premenstrual problems. Six of the 13 claimed to experience such symptoms, later confirmed by daily recording in four of the six. Indeed, in two, these problems had contributed to their initial presentation. The data later presented in this chapter will be concerned with the effects of therapy in the 11 women experiencing cyclical symptom prior to therapy, either as their principal complaint or in association with uterine fibroids.

6.2.2 - Therapy

The dose and administration of Zoladex depot is described in section 5.2.2.

6.2.3 - Assessment of response

The subjects with cyclical symptoms were asked to complete a daily symptom chart, starting at least one complete menstrual cycle prior to administration of the initial depot, continuing for the duration of

therapy and after its completion until the second post-treatment menstrul bleed. The chart used has been described in sections 1.10.2 and 2.6.2 and is shown in figure 1.4. All symptoms were subjectively scored from 0 (none) to 3 (severe). The subjects were also interviewed monthly and asked about their response to therapy as well as any side effects (see section 5.3.6).

6.2.4 - Data analysis

The data from the daily symptom records were initially plotted out for each individual subject together with the results of twice weekly urinary endocrine monitoring (see sections 5.2.3 and 5.2.7 for methods). Symptom profiles for the group as a whole were obtained by calculating the total daily scores for individual symptoms, standardising results for treatment cycles around the day of administration of individual depots and for pre and post-treatment cycles around the first day of menstruation. Data from treatment cycle 1 was also standardised around day 1 of menstruation to allow for the different timing of administration of the initial depot (luteal phase in some subjects and early follicular phase in the remainder). Total daily scores were used in preference to median daily scores for greater sensitivity as median daily scores during the treatment months were generally zero (see section 6.3.3).

Symptom scores for each treatment cycle were calculated by adding the daily scores for individual symptoms for each 28 day interval between depot injections. Pre and post-treatment cycles were standardised to 28 days to allow for differences in cycle length so that each included the first 5 days of menstruation, the preceding 14 premenstrual days

and 9 'intermenstrual' days. Results were expressed as the median and interquartile range of the individual scores. Statistical differences between pretreatment and treatment cycles were calculated using the Friedman non-parametric two-way analysis of variance for related samples. P values for the Friedman test were obtained from tables of the Chi-squared distribution using the method described by Colquhoun (1971).

6.3 - RESULTS

6.3.1 - Patient characteristics and compliance

Of the eleven women whose pre-treatment assessment confirmed the presence of premenstrual problems, seven had presented with these as their primary complaint (group A) and four had been recruited for therapy on account of uterine fibroids (group B). All eleven subjects completed daily symptom charts for the duration of therapy although two subjects from group A withdrew before its scheduled completion (see section 6.3.3). Table 6.1 summarises the pre-treatment characteristics of the women in groups A and B. The premenstrual mood and physical symptom scores and degrees of relief following menstruation were derived from analysis of data from one complete pre-treatment cycle using the 4-point symptom scales and the methods described in section 2.2.3). The mood scores are the mean of depression and irritability and the physical scores the mean of swelling and breast discomfort. The table also indicates whether the mental symptoms were relieved or exacerbated during menstruation.

TABLE 6.1

CHARACTERISTICS OF SUBJECTS IN GROUPS A AND B

Subject	Age	Parity	Start	Premenstrual mood score	Postmenstrual mood relief	Menstrual relief	Premenstrual physical score	Postmenstrual physical relief
GROUP A								
1	44	1	Lut	0.78	88%	yes	1.97	89%
2	35	1	Lut	0.93	81%	yes	1.65	94%
3	44	1	Lut	1.25	100%	yes	0.43	100%
4	41	4	Lut	1.32	38%	yes	1.63	69%
5	40	2	Lut	0.74	45%	no	1.68	83%
6	33	2	Lut	1.33	86%	yes	1.21	100%
7	31	1	Foll	2.18	84%	yes	0.00	-
GROUP B								
8	46	2	Lut	0.57	100%	no	0.29	60%
9	44	1	Lut	0.29	100%	no	1.29	65%
10	42	3	Foll	0.83	92%	yes	0.22	100%
11	41	2	Foll	1.00	86%	yes	0.79	91%

None of these women had a past history of psychiatric problems or treatment and all were physically healthy.

6.3.2 - Overall effects of therapy on mental and physical symptoms

Complete data over 6 months from the daily charts was available from five women in group A and from all four in group B. The median symptom scores for the pre-treatment cycle, all six treatment cycles and the first full post-treatment cycle are shown for these nine subjects in figure 6.1. All symptoms were significantly improved during therapy, as calculated by Friedman's analysis of variance, although this method determines only overall significance and does not distinguish between individual cycles. Physical symptoms appear to have been more completely suppressed than mental symptoms. Not surprisingly, improvement was not seen during the first treatment cycle because of initial endocrine stimulation prior to onset of suppression (see section 5.3.2) although no overall worsening of symptoms was apparent. When the data was included from the two subjects in group A who withdrew before completion of therapy (figure 6.2), median symptom scores for depression failed to show a significant improvement over the initial three treatment cycles, although the other symptoms were significantly improved. Two other subjects from group B, who failed to complete the charts, claimed relief from cyclical symptoms during therapy.

Total daily symptom scores from those nine subjects with complete data over six treatment cycles (figure 6.3) showed loss of the cyclical pattern after the initial treatment cycle. Thereafter, the persisting low level of symptomatology was apparently unrelated to the timing of

Figure 6.1
Physical and mental symptom scores (median & interquartile range) for each cycle before, during and after 6 months therapy with Zoladex depot in 9 subjects who completed the study. P values obtained by Friedman's analysis of variance.

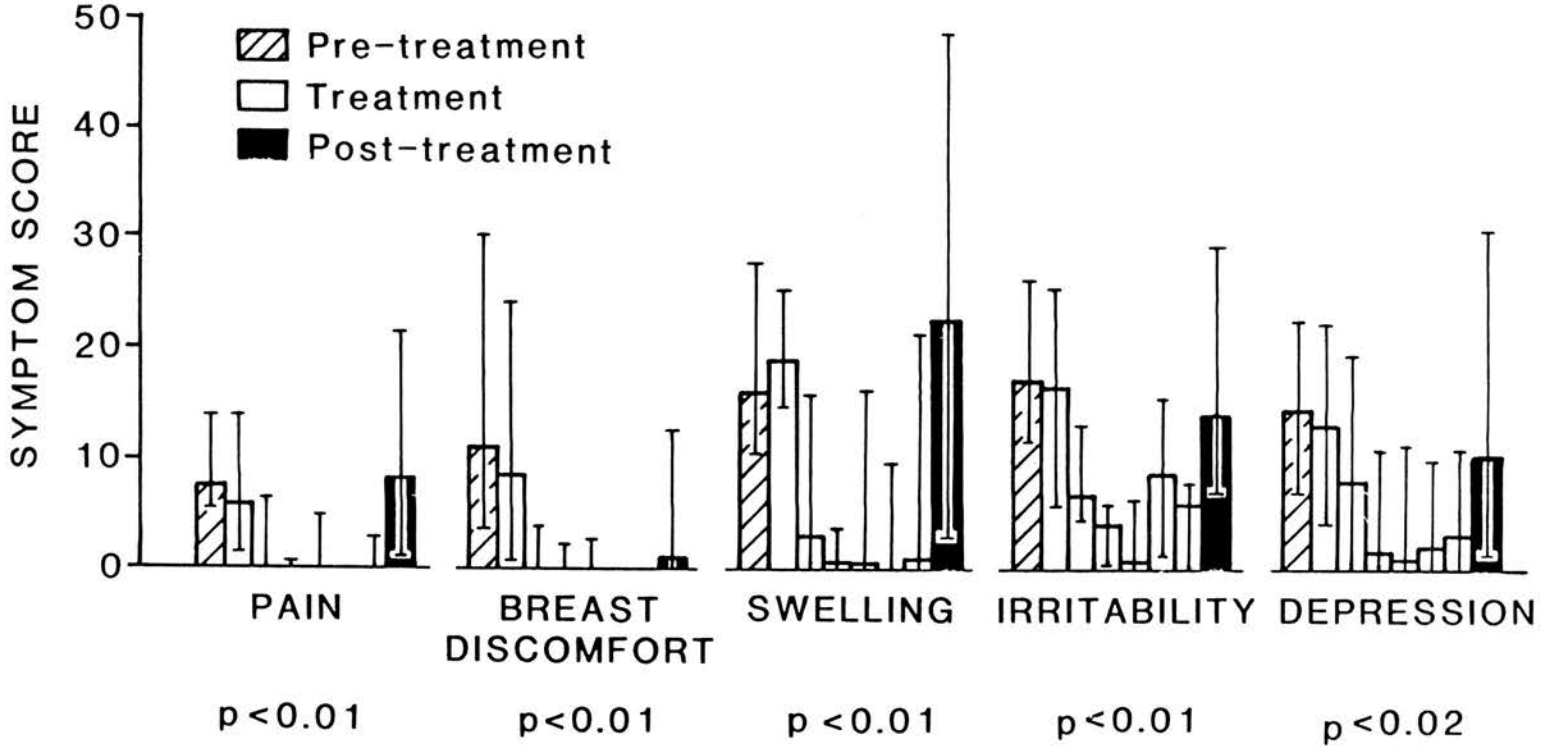


Figure 6.2
Symptom scores (median & interquartile range) pretreatment and during the initial 3 treatment cycles in all 11 subjects.

Figure 6.3
Effect of Zoladex depot on daily symptom profiles (total scores) before, during and after 6 months therapy in the 9 subjects who completed the study.

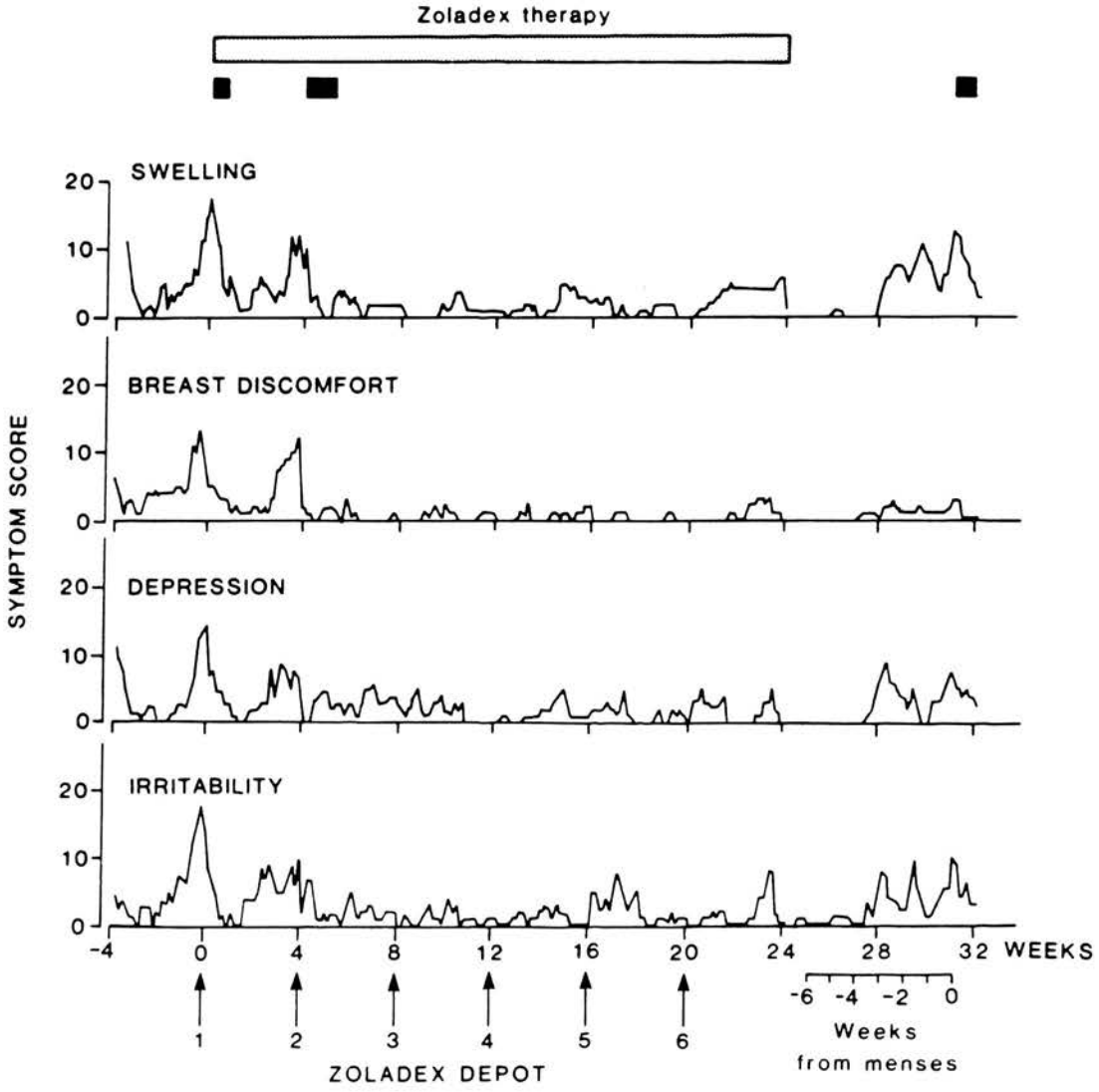
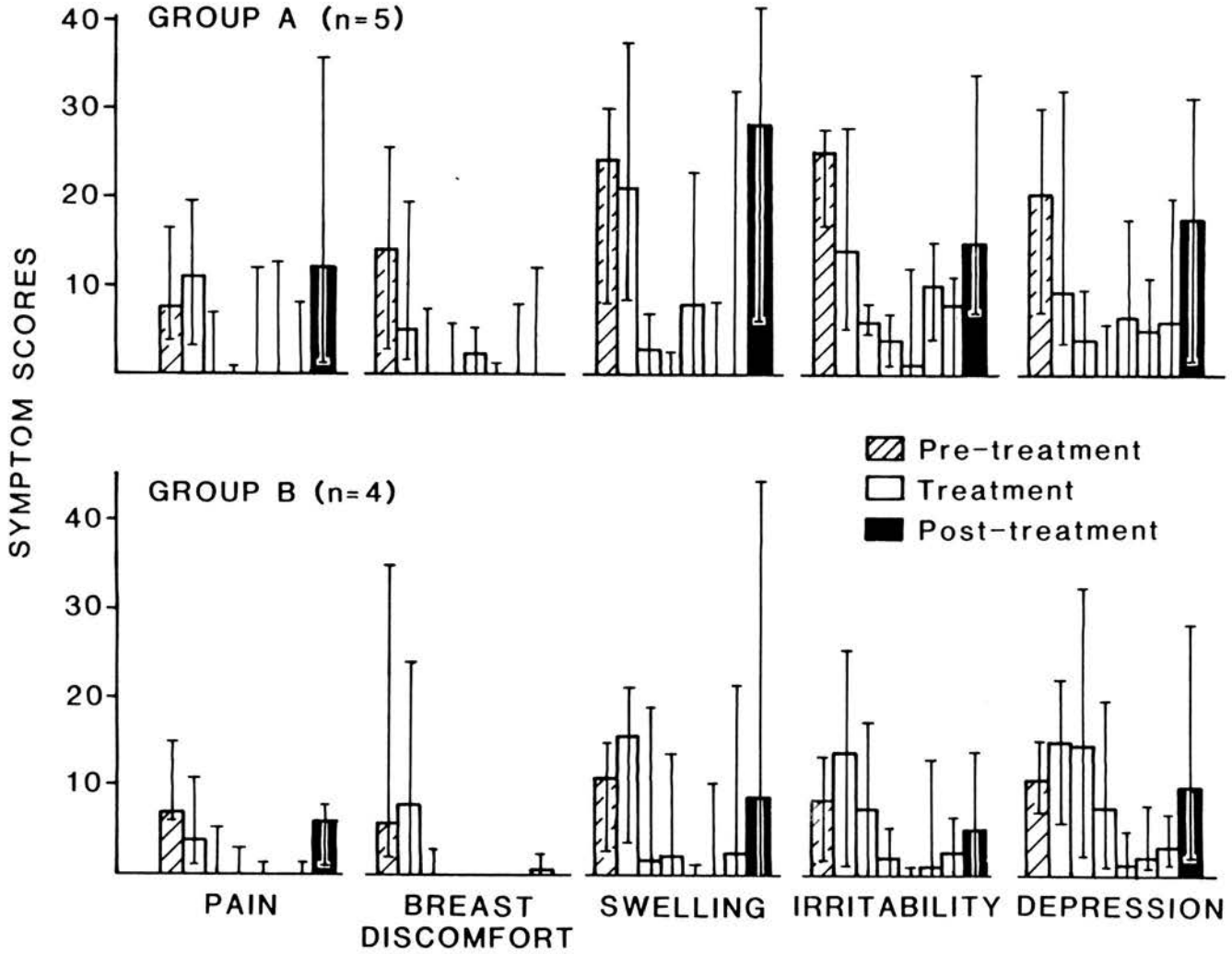


Figure 6.4 - Effect of Zoladex depot on symptom scores (median & interquartile range) according to whether premenstrual problems were the primary (Group A) or secondary (Group B) complaint.



individual depots. After cessation of therapy there was a prompt recurrence of symptoms (see figures 6.1 & 6.3) with the exception of breast discomfort where the effect of therapy appeared to be sustained for at least the initial post-treatment cycle. The return of symptoms appeared to coincide with or actually predate the time of the first post-treatment ovulation (see figure 5.4.1).

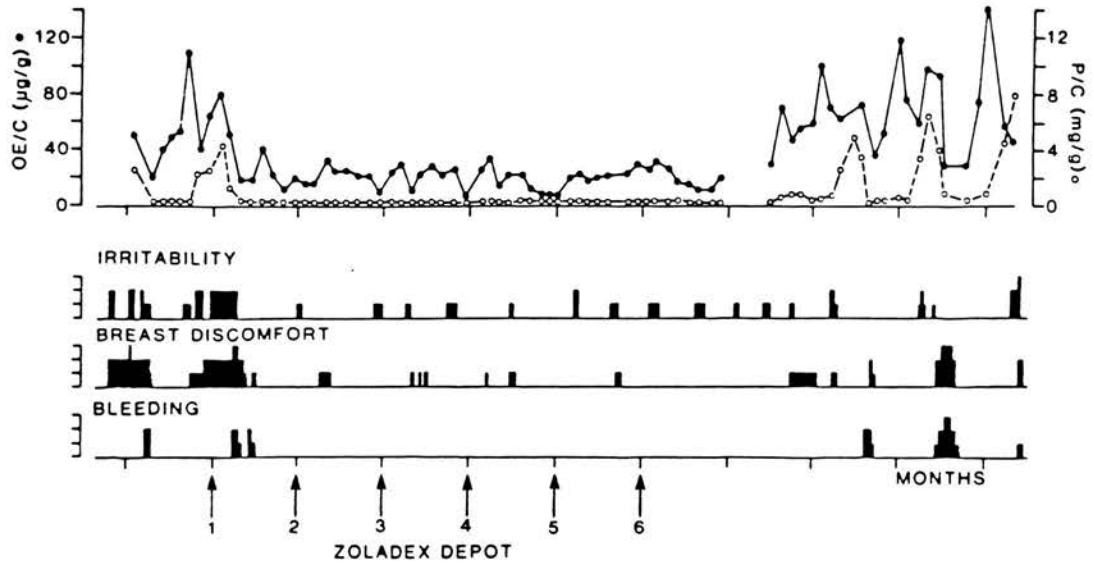
The response to therapy shown by the women in group A and those in group B are compared in figure 6.4, which is based on those completing six months treatment. In view of small numbers in the two groups a statistical comparison has not been attempted. However overall profiles appear similar, apart from an apparent worsening of all symptoms in the initial treatment cycle of those in group B and a comparative delay in improvement of the emotional symptoms compared with those in group A. The median pretreatment scores were, not surprisingly, lower in the group B subjects with the exception of pelvic pain.

6.3.3 - Relationship of individual symptom and endocrine profiles

The results of twice weekly assay of urinary ovarian steroids (see section 5.3.2c) in the individual subjects were compared with the daily symptom profiles. Subjects 1 & 7 from group A showed marked symptom relief during therapy (figure 6.5), with urinary oestrogen excretion maintained in or below the early follicular phase range. By contrast, subject 3 (figure 6.6a) showed oestrogen suppression into the castrate range associated with almost complete relief of the sensation of swelling but intermittent episodes of irritability at least as severe as those present prior to therapy and totally

Figure 6.5
Urinary steroid excretion, symptoms and menstrual bleeding patterns (expressed on 4-point scale) in (a) subject 1 and (b) subject 7 showing symptomatic improvement during therapy with Zoladex depot.

a)



b)

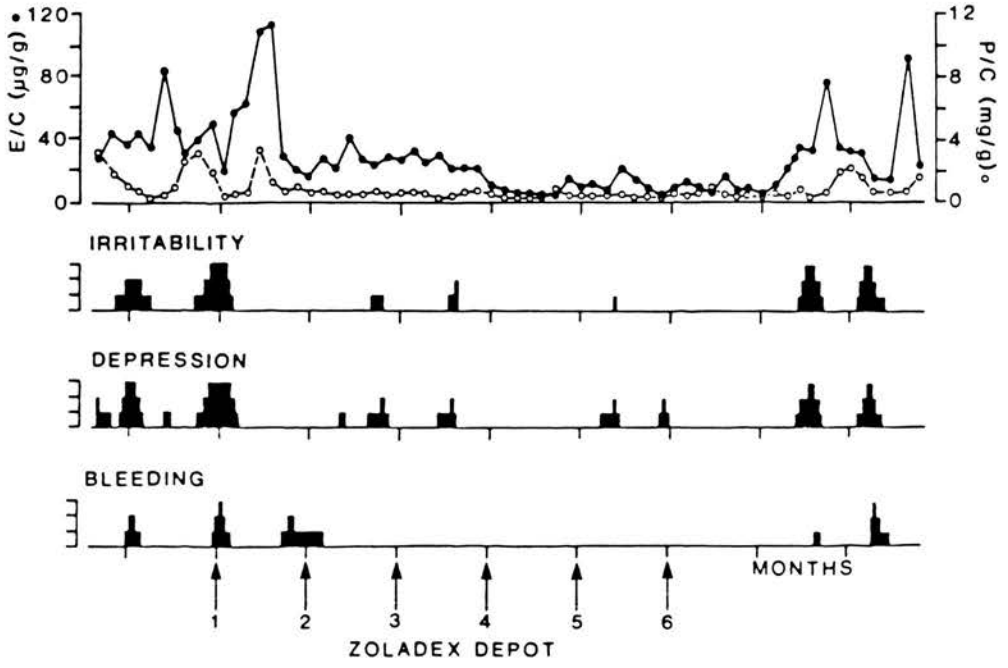
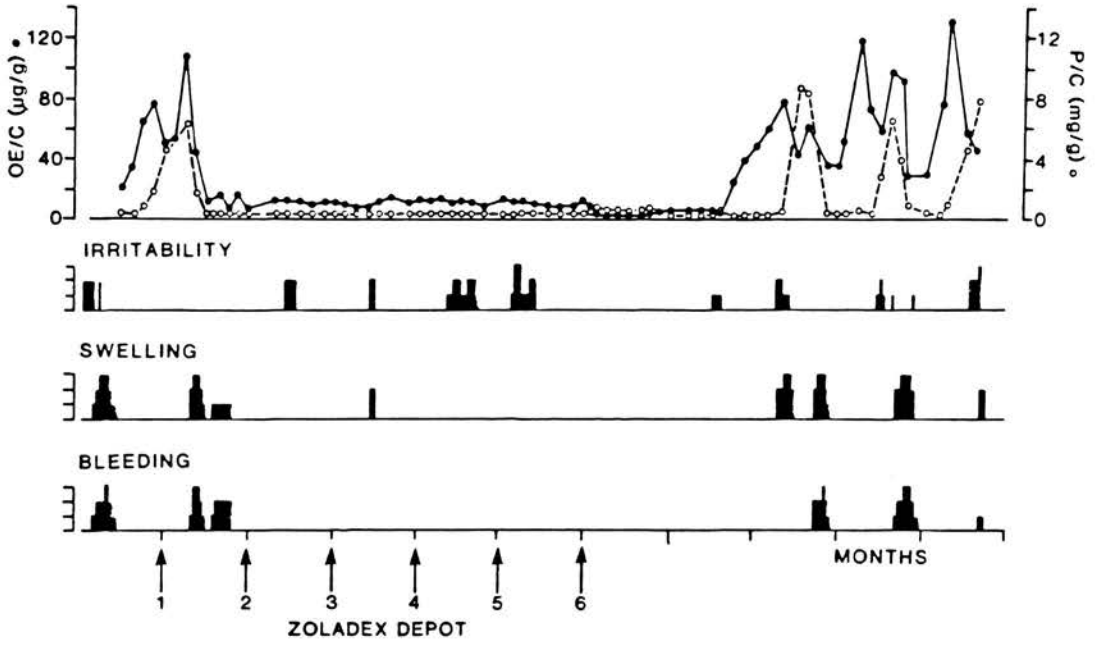
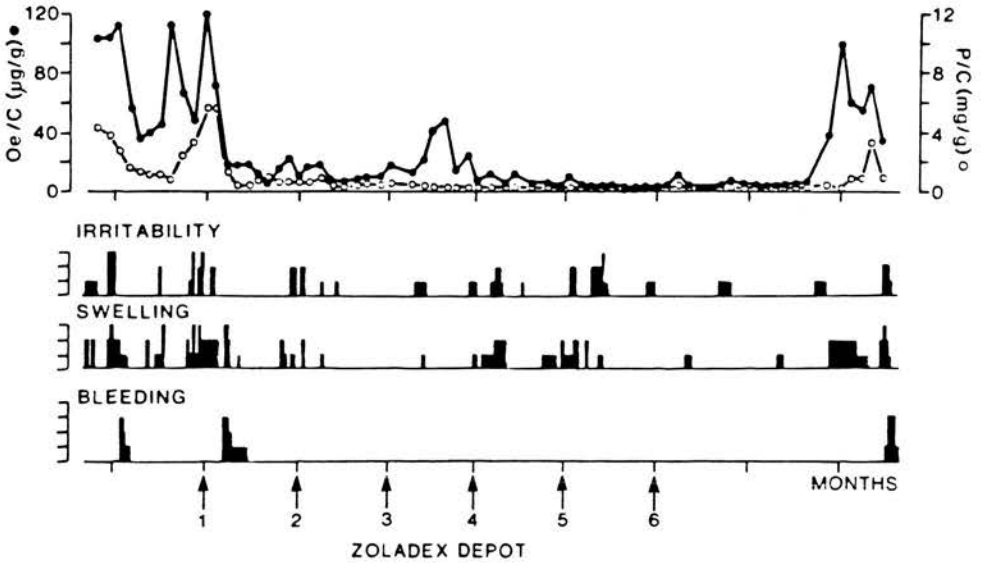


Figure 6.6
Urinary steroid excretion, symptoms and menstrual bleeding patterns (expressed on 4-point scale) in (a) subject 3 and (b) subject 2 showing partial symptomatic response.

a)



b)



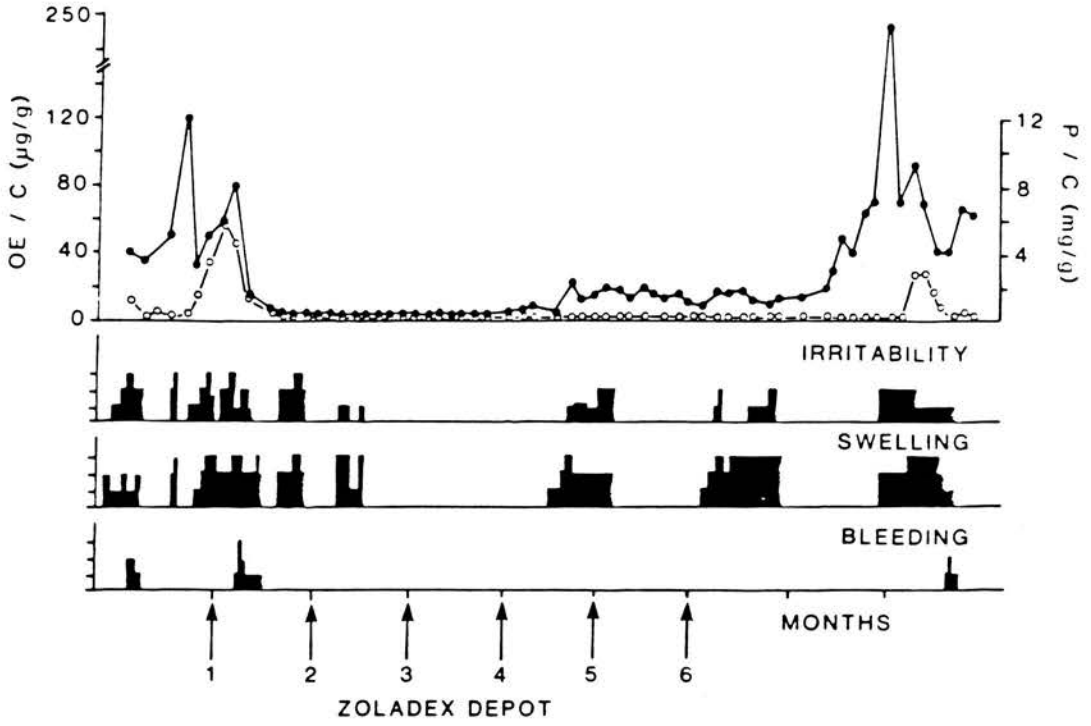
unrelated to endocrine activity. She later described these symptoms as 'the way I feel when my period is due'. Similarly, subject 2 (figure 6.6b) also recorded intermittent episodes of swelling and irritability, one of which may have been triggered by an episode of follicular activity but with no apparent endocrine basis for the others. Subject 2 always marked her chart with a large red cross to indicate when her period would have been due, to which she related the symptomatic episodes.

Subject 4 (figure 6.7a) whose pretreatment records indicated incomplete post menstrual mood relief (38% - see table 6.1) also recorded prolonged symptomatic episodes of swelling and, to a lesser extent, irritability which were unrelated to ovarian activity and apparently more severe than those normally present premenstrually. However the last of these episodes coincided with the post-ovulation phase of the first post-therapy menstrual cycle. The other subject with incomplete post-menstrual mental relief prior to therapy (subject 5 - 45%) also recorded recurrent symptomatic episodes while on therapy (not illustrated) and withdrew from the study after completion of the fourth cycle.

Three of the subjects, two from group B and one from group A, recorded episodes of depression early on during therapy and worse than any similar symptom normally present premenstrually. A similar problem was reported by a fourth subject, one of those who complained of premenstrual problems prior to therapy, but did not consistently complete the symptom charts. The group A subject (subject 6) later withdrew from therapy after completion of treatment cycle 3. The

Figure 6.7
(a) Recurrence of symptoms prior to cessation of therapy in subject 4.
(b) Prolonged anxiety/depression after onset of therapy in subject 9.

a)



b)

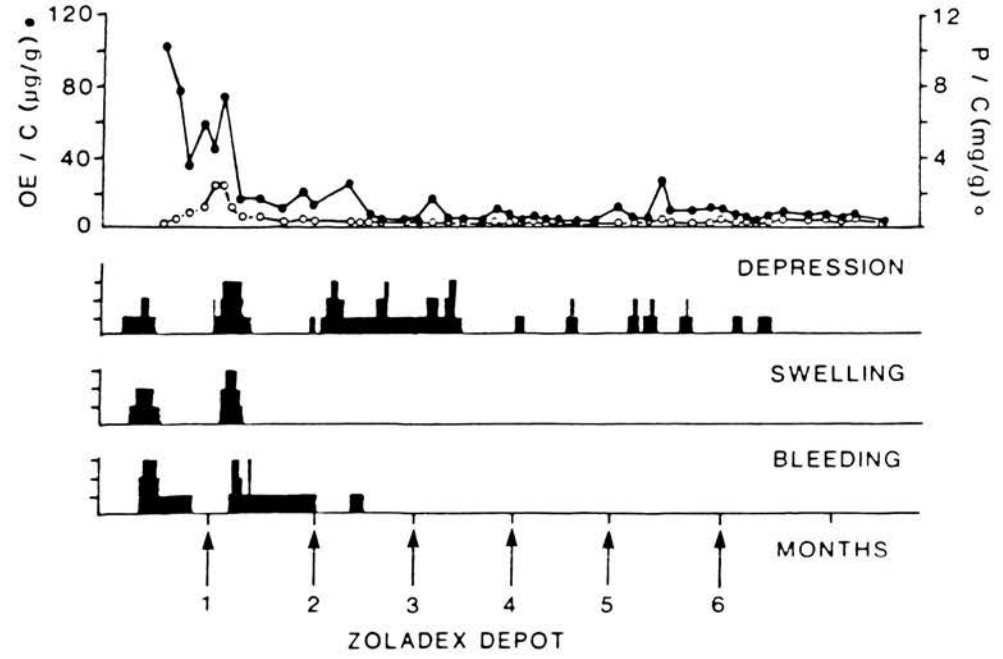
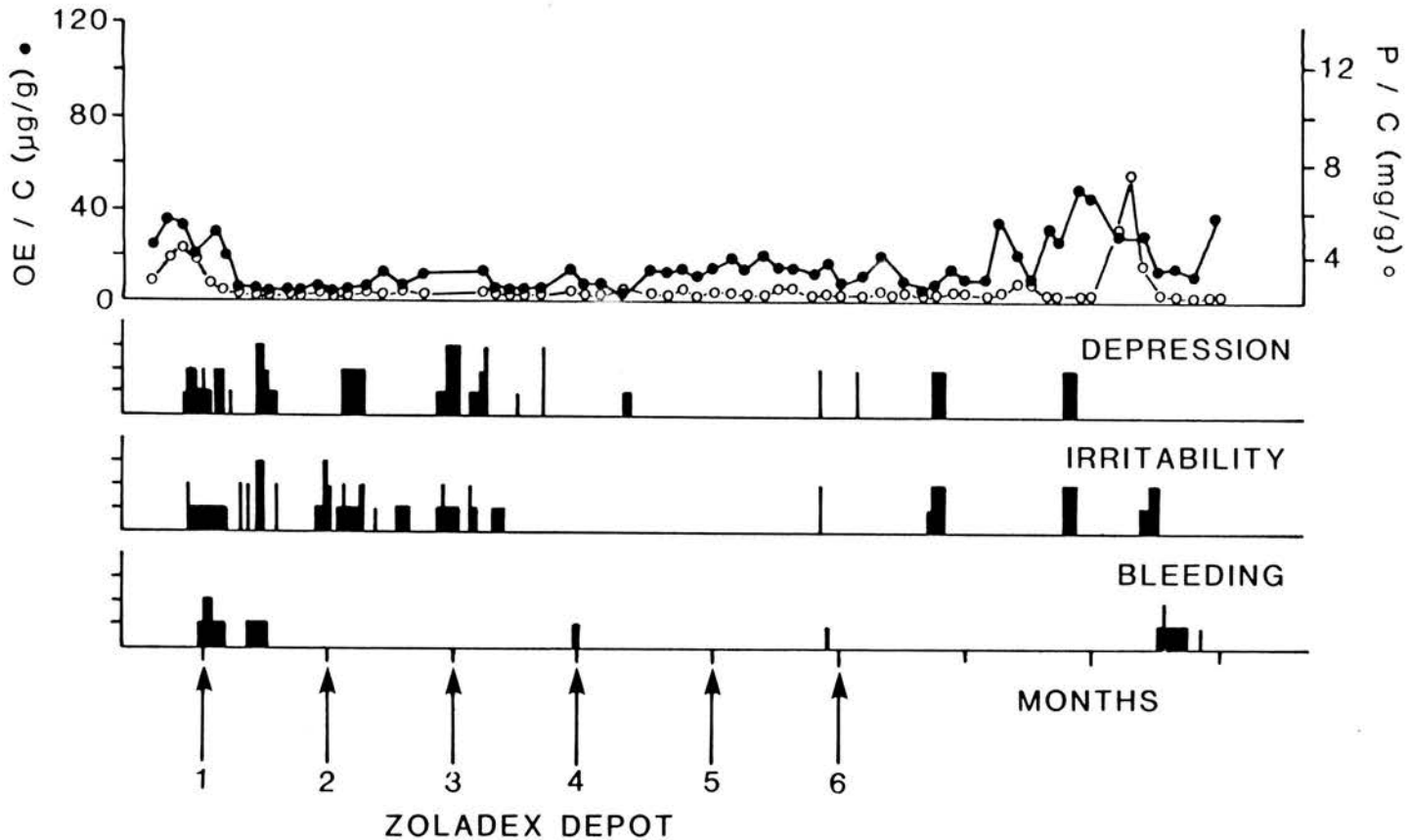


Figure 6.8
Urinary steroid excretion, symptoms and menstrual bleeding subject 10 showing exacerbation of symptoms early in therapy and 2 bleeding episodes unrelated to endocrine activity.



depression is illustrated in figure 6.7b (subject 9) and to a lesser extent in figure 6.8 (subject 10). Onset of depression occurred after administration of depot 2 and when oestrogen concentrations were already suppressed. However resolution occurred with continued duration of therapy in both these subjects.

In the majority of the examples illustrated, therapy was commenced in the luteal phase. The numbers are too small to permit a comparison of the effect of timing of depot 1 on cycle-related symptoms. None of the subjects recorded a marked worsening of symptoms in cycle 1, although overall symptoms were unchanged during the initial cycle, in keeping with the delay in onset of ovarian suppression (figures 5.4.1 - 2). In figure 6.5b, the marked initial oestrogen stimulation after early follicular phase administration of depot 1 (subject 7) was not associated with any adverse symptoms.

These individual profiles illustrate differences in the recurrence of symptoms after cessation of therapy. In subject 1 (figure 6.5a) where breast discomfort was the predominant pretreatment complaint, the symptomatic improvement was sustained over three post-treatment cycles. By contrast, in the subjects illustrated in figures 6.5b, 6.6b and 6.7a, recurrence of symptoms actually predated or paralleled the first mid-cycle oestrogen surge.

6.4 - DISCUSSION

The results presented in this chapter and in chapter 5 show rapid and effective suppression of pituitary-ovarian function during treatment with Zoladex depot. After completion of treatment cycle 1, follicular activity was minimal in the majority of cycles studied with consistent inhibition of ovulation. It is thus not surprising that an overall significant reduction of cycle-related symptomatology was seen. Physical symptoms were usually more completely abolished than were psychological ones, consistent with the findings during progestogen therapy (chapter 4) although the latter did not produce significant improvement of swelling, as compared with breast discomfort. Results from individual subjects however showed differences in the degree of symptom relief. Although the numbers are too small to permit definitive conclusions, the two subjects with the lowest pretreatment relief of their mental symptoms following menstruation (subjects 4 & 5 in table 6.1) both showed a poor response to therapy, supporting the importance of pretreatment assessment of symptom profiles as discussed in chapter 2. The results from one of these subjects (illustrated in figure 6.7a), who continued to record symptomatic episodes and where severe bloating was a predominant problem, suggest the alternative diagnosis of cyclical oedema (see section 1.8.5) rather than a premenstrual problem. The problem of preconditioning (see section 1.7) is illustrated by subject 2 who continued to record cyclical symptoms in the absence of menstrual or ovarian cyclicity.

The results presented are based on two different groups of subjects with cyclical symptoms, group A where these were the primary complaint and group B where they were associated with another presenting

problem, uterine fibroids. The reason for inclusion of both groups was in part because of limits on the recruitment of subjects (see section 5.1.3). It was also in order to compare the effects of therapy in the two groups, as their expectations are likely to be different. The results do not however show any marked differences between the two groups although the numbers are too small for a statistical comparison to be made. Apart from differences in magnitude of premenstrual symptom scores prior to treatment, the characteristics of the two groups were similar. It is however possible that some of the benefits of therapy in group B were secondary to relief of menstrual discomfort and heavy menstrual flow associated with the fibroids. In this context, it is thus interesting that pretreatment pain scores were not higher in the group with fibroids.

The results clearly show recurrence of symptoms around the time of the first post-treatment ovulation. It is difficult to explain this other than by a true endocrine effect as none of the subjects, or indeed the investigators knew how soon ovarian activity would return after cessation of therapy. It is also interesting that in some cases recurrence of symptoms appeared to coincide with the 'mid-cycle' oestrogen surge whereas the earlier prospective study showed the increase in adverse symptoms to occur later in the cycle (chapter 2). The sustained improvement in breast discomfort seen after completion of therapy is in contrast with the recurrence of the other symptoms, including swelling and requires further investigation. It also contrasts with the lack of sustained effect on uterine fibroid volume after stopping LHRH agonist therapy (chapter 5).

It is impossible to assess the extent to which the improvement seen during therapy would have also been present with a placebo and a placebo-controlled study is in progress. This is important because the results from an investigation of the use of oestradiol implants in the management of premenstrual problems (Magos et al, 1986) suggest that the placebo effect may be particularly high where a 'surgical' approach to therapy is used. However the design of a placebo controlled study involving an LHRH agonist depot poses problems because of the amenorrhoea associated with active therapy and such a study would not be truly double-blind. It is unlikely that the response seen over six months in the present study is entirely attributable to a placebo effect as the latter response has been shown to be most marked in the initial treatment cycle (Sampson, 1979) and to decline over the first three months (Magos et al, 1986; Watts et al, 1987). The results illustrated in figure 6.1 are consistent with slight loss of a placebo response for depression and irritability during treatment cycles 5 and 6 compared with the sustained improvement in physical symptoms.

There have been two published placebo-controlled studies of the use of LHRH agonists in women with premenstrual tension. The first of these (Muse et al, 1984) was a 6 month cross-over study of 8 subjects who self-administered the agonist by daily subcutaneous injection. With the exception of the initial treatment cycle, where the expected ovarian stimulation was seen with the agonist, cyclical symptoms were abolished during agonist therapy but not during placebo administration. A preliminary report of the second, a cross-over

study of 26 subjects given 400 mcg of buserelin daily by the intranasal route (Backstrom, 1986) confirmed the beneficial findings of the first study.

Less successful results were reported by Bancroft et al (1987) from an open study. Most of the 20 subjects received 600 mcg of buserelin intranasally in three divided daily doses starting in the early follicular phase. Half the women stopped treatment after a mean of 7 weeks because of a worsening of their pretreatment symptoms or because of side effects. Aggravation of both mental symptoms and swelling was reported by some subjects during the early stages of treatment, corresponding to the more prolonged ovarian stimulation seen with the intranasal route of administration (section 5.1.2). Symptomatic improvement increased with longer duration of therapy although follicular activity was less well suppressed than with the depot and a proportion of the women continued to menstruate irregularly without ovulation. These anovular bleeds were preceded by recurrence of physical symptoms although the mental symptoms lost their relationship to menstruation. In keeping with the results of the present study, these authors found return of symptoms to predate ovulation after cessation of therapy.

It was interesting that four of the subjects in the present study (section 6.2.3; figures 6.7b & 6.8) experienced a worsening of symptoms of anxiety and/or depression early on during treatment although this problem lessened with duration of therapy in the three who continued the study. All four had reported cyclical mood changes prior to therapy although only one, the one who subsequently withdrew,

had this as her presenting problem. In all four, the problem started after oestrogen levels were suppressed. In other words, it was not related to any initial ovarian stimulation and appears to have been triggered by oestrogen withdrawal. This might support the theory that oestrogen withdrawal is involved as an initiating factor in some cases of emotional disturbance occuring during the the menopause (Coppen & Wood, 1978) and in the early puerperium (Nott et al, 1976). In an extensive review, Greene (1984) concluded that depression during the menopause is a consequence of increased vulnerability to minor life events and is not relieved by oestrogen therapy. Sherwin & Gelfand (1985) studied women randomised to treatment with hormone replacement therapy or with placebo following oophorectomy. The surgical menopause is comparable to initiation of Zoladex therapy because hormone withdrawal is abrupt, unlike the gradual changes of the natural menopause. They found greater adverse psychological symptoms and reduced well-being among those given a placebo. Their results however indicated that androgen withdrawal contributed more to loss of well-being than did withdrawal of oestrogen alone.

The sudden withdrawal of placental steroids following childbirth (West & McNeilly, 1979) is another clear-cut endocrine event. Increased emotional lability is common in the early days of the puerperium (Pitt, 1973; Kendell et al, 1981), the so-called postnatal 'blues'. In a study, based on daily visual analogue scale recordings for the first 21 days after childbirth (Kendell et al, 1984), we found a significant association between the fifth day blues and neuroticism, measured antenatally by the Eysenck Personality Questionnaire. This complex interaction between environmental factors, personality and

endocrine change is similar to that which may operate both premenstrually and during the natural menopause. Oestrogen suppression by LHRH agonists offers an interesting model for the study of the effect of oestrogen withdrawal on mood as it is dissociated from the emotional and psychosocial components of childbirth or the menopause.

Adverse physical effects of oestrogen withdrawal in the form of hot flushes were experienced by the majority of the women treated with Zoladex depot (section 5.3.6) and their reported severity was associated with the degree of oestrogen suppression. It is possible that their severity and the associated sleep disturbance may have triggered or aggravated other mental symptoms such as irritability and depression (Campbell & Whitehead, 1977) although none of the subjects reported awareness of such a relationship. In practice however they will limit the acceptability of therapy. Vaginal dryness, although much less frequent was another consequence of ovarian suppression in some subjects. The influence of ovarian steroids on other aspects of human sexuality is still unclear. A direct relationship is in doubt (Utian, 1975; Campbell & Whitehead, 1977; Dow et al, 1983) and only one of this group of women reported reduced libido. She differed from the others in being in the early stages of a new relationship.

Patient compliance during the study was extremely good and only two out of 13 women with cyclical symptoms failed to fully complete the daily assessment charts. This compares very favourably with the progestogen study (section 4.3.1) where non-compliance was much higher as was the drop-out rate from therapy. This may reflect the nature of

the therapy, the frequency of follow-up or patient selection. In particular, the group being treated for uterine fibroids may have been particularly motivated to continue therapy in order to avoid hysterectomy. The use of the simpler daily charts may have reduced the sensitivity of symptom recording (see section 2.6.4) and had disadvantages in terms of statistical analysis because of the need to use non-parametric methods (section 1.10.2). However they had the advantage of simplicity in comparison with the visual analogue scales which may not have been completed so consistently over the nine month period of the study.

The future role of LHRH analogues in the management of women with severe cyclical problems has yet to be defined. As discussed in section 5.4, more information is required about their long-term effects before their therapeutic use can be widely advocated in young premenopausal women. However these results indicate ways in which LHRH agonists can be used in the investigation and research into this difficult clinical problem. The observation that menstrual cycle related symptoms persist in some individuals after ovarian suppression confirms the importance of other factors in their aetiology. It illustrates a potentially useful role of LHRH agonists in establishing the association between such symptoms and ovarian activity in women who present difficulties in assessment or management. In particular, LHRH agonists might be used to predict the likely success of ovarian suppression as an approach to therapy. LHRH depots may also be used in conjunction with various doses of exogenous oestrogen and progestogens to study the effect of the latter on mood and physical state. This would go a long way towards clarifying the role of

ovarian steroids in the aetiology of cycle-related symptoms, where the literature is still very confused (see chapter 3). Combined therapy is also a therapeutic possibility in women with cyclical symptoms or indeed those with other menstrual problems. Inhibition of endogenous pituitary-ovarian activity by LHRH agonist depots could be accompanied by low dose 'hormone replacement therapy' which would prevent the symptoms and consequences of prolonged oestrogen suppression while avoiding the possible metabolic consequences of the larger doses of exogenous ovarian steroids required for inhibition of ovulation (see section 4.4).

6.5 - Conclusions

This preliminary investigation of the effect of the LHRH agonist depot goserelin (Zoladex), has demonstrated its effectiveness in ovarian suppression. Abolishing the menstrual cycle substantially improves cyclical symptoms, in particular physical symptoms but the effect on mental symptoms is less predictable and the benefits are rapidly reversed after cessation of therapy. The presence of symptomatic episodes in some of the women studied, in the absence of alterations in ovarian activity, confirms doubts about the precise relationship between mood and the menstrual cycle. However the results also demonstrate that endocrine changes can trigger symptoms in individuals so predisposed. Although the use of these agonists as a long term therapy for premenstrual problems remains to be established, there are clearly a number of areas in which their use will facilitate clinical management and act as a useful research tool.

CHAPTER 7

THE ROLE OF ENDOGENOUS OPIOID PEPTIDES IN MENSTRUAL CYCLE SYMPTOMATOLOGY - INVESTIGATION OF THE EFFECT OF AN ORAL OPIATE ANTAGONIST

7.1 - Introduction

7.1.1.- Endogenous opioid peptides and neuroendocrine control

Opiate alkaloids such as morphine are known to have a wide range of actions in addition to analgesia (Jaffe & Martin, 1980), including an inhibitory effect on ovulation (Packman & Rothchild, 1976). Investigation of these actions and the evidence for the presence of specific opiate receptors has led to the identification of a group of endogenous opioid peptides (EOP) which are present within the central nervous system and in certain peripheral sites such as the gastrointestinal tract (see reviews by Grossman, 1983; Cicero, 1986). They include the enkephalins, which are thought to act as neurotransmittors, the dynorphins and the endorphins. The most potent of the latter group is beta-endorphin which appears to be located predominantly in the arcuate nucleus of the hypothalamus and thus is likely to be involved in the control of secretion of the hypothalamic releasing factors (see section 1.2.2).

Much of our current knowledge about EOPs has been obtained from animal studies (Cicero, 1986). Two main approaches have been used in human subjects, one involving the study of the effects of administration of opioids, the other by the use of specific opiate antagonists, in

particular naloxone. There is currently evidence for an inhibitory effect of opioids on release of ACTH and gonadotrophins with possible stimulatory effects on TSH, growth hormone and, in particular, prolactin (Stubbs, 1978; Reid et al, 1981), the latter by inhibition of dopaminergic pathways. Control appears to be at the hypothalamic level and to involve several different receptor types (Grossman, 1983), characterised by differences in sensitivity to antagonism by naloxone. Thus high doses of naloxone are required to overcome the inhibitory effect on ACTH while small doses will cause an elevation of basal LH (Grossman et al, 1986). Plasma prolactin concentration was not altered by naloxone administration (Martin et al, 1979).

7.1.2 - Opioid peptides and the menstrual cycle

In women, studies of the effect of administration of naloxone during different phases of the menstrual cycle have indicated that opioid inhibition of gonadotrophin release is greatest during the late follicular and luteal phases and minimal during the early follicular phase (Quigley & Yen, 1980) as well as following the menopause (Reid et al, 1983). Opiate antagonism is accompanied by an increase in the frequency (Moult et al, 1981) and amplitude (Blankstein et al, 1981; Ellingboe et al, 1982) of LH pulses. In postmenopausal women, administration of oestrogen and/or progestogen is followed by a return of the LH response to naloxone (Casper & Alopin-Rabilloutz, 1985; Shoupe et al, 1985). It is thus possible that feedback of ovarian steroids may, in part, act via opioid-mediated mechanisms although opioids do not appear to be involved in the genesis of the LH surge (Grossman et al, 1981). They may be involved in some disorders of the hypothalamo-pituitary ovarian axis (Quigley et al, 1980; Blankstein et

al, 1981). The opioid most likely to be involved in modulation of LHRH release is thought to be beta-endorphin but it is currently uncertain whether its effect is a direct one or whether it is exerted via catecholamine neurotransmittors (Vane, 1987). In primates, direct sampling of hypophyseal portal blood (Wehrenberg et al, 1982) has confirmed a cyclical alteration in the level of beta-endorphin, which is undetectable at menstruation and during the early follicular phase of the cycle but high during the remainder of the cycle. It is undetectable following oophorectomy but restored by hormone replacement (Wardlaw et al, 1982).

The observation that EOP inhibition of LHRH is highest during the luteal phase and falls prior to menstruation has led to speculation that these peptides may be involved in premenstrual symptomatology (Reid, 1983). Further evidence for a role in disorders of mood is provided by a report of adverse symptoms provoked in healthy adult males given large doses of naloxone, some of which were similar to symptoms associated with premenstrual tension (Cohen et al, 1981). One way of testing this theory would be by administration of an opiate antagonist to symptomatic women in order to study the effects of modification of the normal cyclical pattern of opioid inhibition and its release. Use of an antagonist such as naloxone which needs to be administered parenterally and has a very short half life has obvious disadvantages because effective plasma concentrations can only be maintained by intravenous infusion or by very frequent bolus injections. The recent availability of an opiate antagonist which may be administered orally made such a study feasible.

7.1.3 - Nalmefene - an orally active opiate antagonist

Nalmefene is a new narcotic antagonist structurally similar to naloxone and naltrexone but with greater potency and a longer duration of action. After oral administration peak plasma concentrations are seen after one and a half hours and its plasma half life is ten hours. Preliminary animal studies showed no evidence that tolerance developed over a seven day period and a lack of toxicity. Unpublished data (Nalmefene - Information for Physicians, 1984) from healthy male volunteers showed the drug to be well tolerated at oral doses of up to 100 mg with no evidence of any agonist actions. Obese hyperinsulinaemic women have been shown to have elevation of EOP levels (Givens et al, 1980). In a pilot study, five such women were treated with an oral dose of 20 mg nalmefene twice daily for five days with reduction in both fasting insulin concentrations and the insulin response to an oral glucose load, when compared with placebo therapy. Circulating concentrations of gonadotrophins, prolactin, cortisol, growth hormone, androgens and urinary catecholamine outputs were apparently unchanged (Nalmefene - Information for Physicians, 1984). However mild side effects of fatigue, dizziness and nausea were reported by all five subjects on the active therapy which was interpreted as being confirmatory of elevated levels of EOP in this group of women.

7.1.4 - Aims and objectives of the current study

The hypothesis to be tested was that premenstrual symptoms involve excessive endogenous opioid activity during the early to mid luteal phase of the cycle followed by withdrawal in the late luteal phase (Reid, 1983). If so, then blockade of opiate receptors by a specific

antagonist throughout the luteal phase of the cycle may modify these symptoms. An initial pilot study was planned in which therapy would be commenced in the early luteal phase and continue until the onset of menstruation using an initial dosage of 10 mg nalmefene twice daily (the dose recommended for clinical trials), with the option of altering the dose or the duration of therapy depending on the clinical effects. As an additional assessment of opiate inhibition, the effect of therapy on LH pulse frequency during the mid luteal phase would be measured in all the subjects. A maximum of six subjects would be studied initially. To act as a control, placebo tablets would be administered for 10 days prior to the introduction of the active therapy. Ethical committee approval for this pilot study was obtained.

7.2 - SUBJECTS AND METHODS

7.2.1 - Subjects

The subjects were recruited from those presenting with premenstrual problems (see section 2.2.1, who had already completed two months preliminary assessment. Only those who showed symptom relief of 50% or more postmenstrually were considered suitable for the study. All were in good physical health, none had a history of current or past psychiatric treatment and none were receiving any chronic medication prior to or during the study, with the exception of occasional simple analgesia in one case for a back problem. All were using non-hormonal methods of contraception. The nature and purpose of the study was explained to all the subjects and written consent obtained.

7.2.2 - Therapy

Therapy was administered over two consecutive menstrual cycles. According to the initial protocol, placebo tablets were started on day 7 of the cycle and continued twice daily for 10 days when (day 17) nalmefene 10 mg twice daily was commenced for 12 days. This was repeated during the second treatment cycle. As described in the results section, severe effects attributed to opiate withdrawal were experienced by the three subjects initially recruited to the study. The regime was therefore modified so that active treatment was commenced on day 8 of the cycle when endogenous opioid activity should be less marked (see section 7.1.2), testing the effect both of a reduced daily dosage (5 mg twice daily) or a more gradual introduction of active therapy over three days, building up to a dose of 10 mg bd. Placebo tablets were taken between days 1 and 7 of the cycle inclusively.

7.2.3 - Assessment of response

Daily self-assessment of mood and physical symptoms was by means of the visual analogue scales described in earlier sections of this thesis (1.10.1 and 2.2.2). All the subjects also completed these charts for at least two pretreatment assessment cycles prior to their inclusion in the study. The data was analysed descriptively by plotting out individual symptom profiles for each subject and also by comparison of the mean mental and physical symptom scores for the different cycle phases in individual subjects before and during therapy. A mean of the scores for tension, irritability and depression was calculated for the mental symptoms and of breast

tenderness and swelling for the physical symptoms. Lethargy was excluded because of its prominence as a side effect of therapy (see below). The postmenstrual phase was taken from days 6-12 inclusive, 'midcycle' from days 13-20, premenstrual from days 21-28 and menstrual from days 1-5 inclusive.

7.2.4 - Endocrine measurements

The subjects were asked to collect twice weekly early morning samples of urine for measurement of oestrone glucuronide and pregnanediol as described in section 5.2.7, both metabolites being expressed as the steroid:creatinine ratio. In addition, the effect of therapy on pulsatile LH secretion was assessed by sampling peripheral venous blood via an in-dwelling cannula every 15 minutes over four to six hours during the mid-luteal phase of the pretreatment and the initial treatment cycle. LH was measured by double antibody radioimmunoassay as described in section 5.2.7. A pulse was defined as occurring when the hormone concentration of two consecutive samples was greater than that of the mean of the two previous samples, providing that the value of at least one of the peak samples exceeded the mean of the two basal samples by more than twice the coefficient of variation of the assay (Baird et al, 1977).

7.3 - RESULTS

7.3.1 - Compliance

Three subjects were initially recruited to the study, commencing placebo tablets on day 10 and active therapy on day 17 of the cycle.

TABLE 7.1

CHARACTERISTICS OF SUBJECTS RECEIVING NALMEFENE AND DURATION OF PLACEBO AND ACTIVE THERAPY

Subject	Age	Premenstrual mood score	Postmenstrual mood relief	Dose of nalmefene	Duration	Onset of active	Outcome
1	38	5.86	65%	10mg bd	days 7-28	day 17	completed 2 cycles
2	32	6.67	72%	10mg bd	days 7-28	day 17	discontinued cycle 2
3	35	3.59	91%	10mg bd	days 7-28	day 17	discontinued cycle 1
4	28	3.19	87%	5mg bd	days 1-28	day 8	completed 2 cycles
5	37	2.86	93%	10mg bd	days 1-28	day 8-10 (gradual)	discontinued cycle 1

All experienced adverse effects on the day of onset of active treatment (see below and table 7.2) and only one of the three completed two treatment cycles, one withdrawing during the initial treatment cycle and one during cycle 2. The protocol was thus altered as above with initiation of placebo therapy on day 1 of the cycle and active therapy on day 8. One subject taking the reduced dose of nalmefene (5 mg bd) completed the study. The other withdrew because of adverse effects experienced after the onset of active therapy. Details of the subjects who entered the study, together with the severity of their premenstrual mental symptoms and the degree of postmenstrual mood relief, based on two control cycles, are given in table 7.1, which also shows the dose and duration of placebo and active therapy.

7.3.2 - Adverse effects of therapy

All the subjects documented side effects of treatment in the space provided at the bottom of the visual analogue scale charts. All five experienced adverse symptoms at or soon after the onset of active therapy, leading to withdrawal from the study in three of the five as above. Full details of these effects and their timing are given in table 7.2. All three who commenced active therapy on day 17 of the cycle reported the sudden onset of adverse effects very soon after the first tablet had been taken. In the other two, onset of adverse effects was apparently less sudden, particularly in subject 5 where active therapy was introduced gradually over 3 days (days 8-10. Only one woman (subject 4) recorded any adverse effects while on placebo tablets, in this case headaches. Dizziness, lightheadedness and weakness were the symptoms most frequently reported, with nausea,

TABLE 7.2

SIDE EFFECTS OF NALMEFENE AND PLACEBO

Subject & cycle	Cycle day of onset	Day of therapy (active)	Symptoms	Comments
1.1	17	10 (1)	Dizziness, weakness, blurred vision	lasted 5 days
		12 (3)	nausea, lethargy, thirst	
1.2	17	10 (1)	Lightheadedness, nausea, weakness	lasted 6 days
		12 (3)	Nasal stuffiness, thirst	
2.1	17	10 (1)	Dizziness, faintness, flu-like symptoms, nausea, headaches	severe 4 days mild 10 days
2.2	17	10 (1)	As above	discontinued day 12
3.1	17	10 (1)	Malaise, weakness, lightheadedness depression	discontinued day 11
4.1	5	5	Headaches	
		8 (1)	Thirst	lasted 7
		11 (4)	Insomnia, irritability	days
4.2	8	5	Headaches	
		8 (1)	Tiredness	lasted 5
		10 (3)	Irritability	days
5.1	9	9 (2)	Insomnia	
		11 (4)	Dizziness, depression flu-like symptoms	
		13 (6)	Panic attacks, irritability	discontinued day 13

thirst and mental symptoms also documented. These effects were least marked in subject 4 who took the reduced dosage of nalmefene.

7.3.3 - Effect on cyclical mental and physical symptoms

The effect of therapy on individual symptoms assessed by daily visual analogue scales is shown in figures 7.1 and 7.2. In subjects 1 (figure 7.1a) and 2 (figure 7.2a), it is apparent that mental symptoms of irritability and tension reached a peak in the early luteal phase of treated cycles, corresponding to the onset of active therapy, with improvement in the late luteal phase. Similarly, onset of active therapy in the follicular phase in subject 5 (figure 7.2b) was accompanied by a peak of tension which resolved once therapy was discontinued but a premenstrual build up of symptoms occurred later in the cycle. However subject 4 (figure 7.1b) recorded an apparent improvement in her normal cyclical pattern of irritability in treatment cycle 1 which was not sustained during cycle 2.

In figure 7.3, the effect of therapy on both mental and physical symptoms by cycle phase in individual subjects is illustrated. Loss of the normal cyclical pattern of mental symptoms was seen in subjects 1 and 2, who started active therapy on day 17, with maximal intensity between days 13-20. In subject 4, where a lower dose of nalmefene was started in the follicular phase, the cyclical pattern of both mental and physical symptoms appears to have been maintained, with reduced symptom intensity. The peak of mental symptoms at the onset of therapy in subject 5 (days 8-12) was not accompanied by any physical symptoms.

Figure 7.1
Effect of nalmefene therapy on irritability (daily VAS score) and urinary steroid metabolites in (a) subject 1 who commenced active therapy with nalmefene 10mg bd on day 17 of the cycle and (b) subject 4 who commenced nalmefene 5mg bd on day 8.

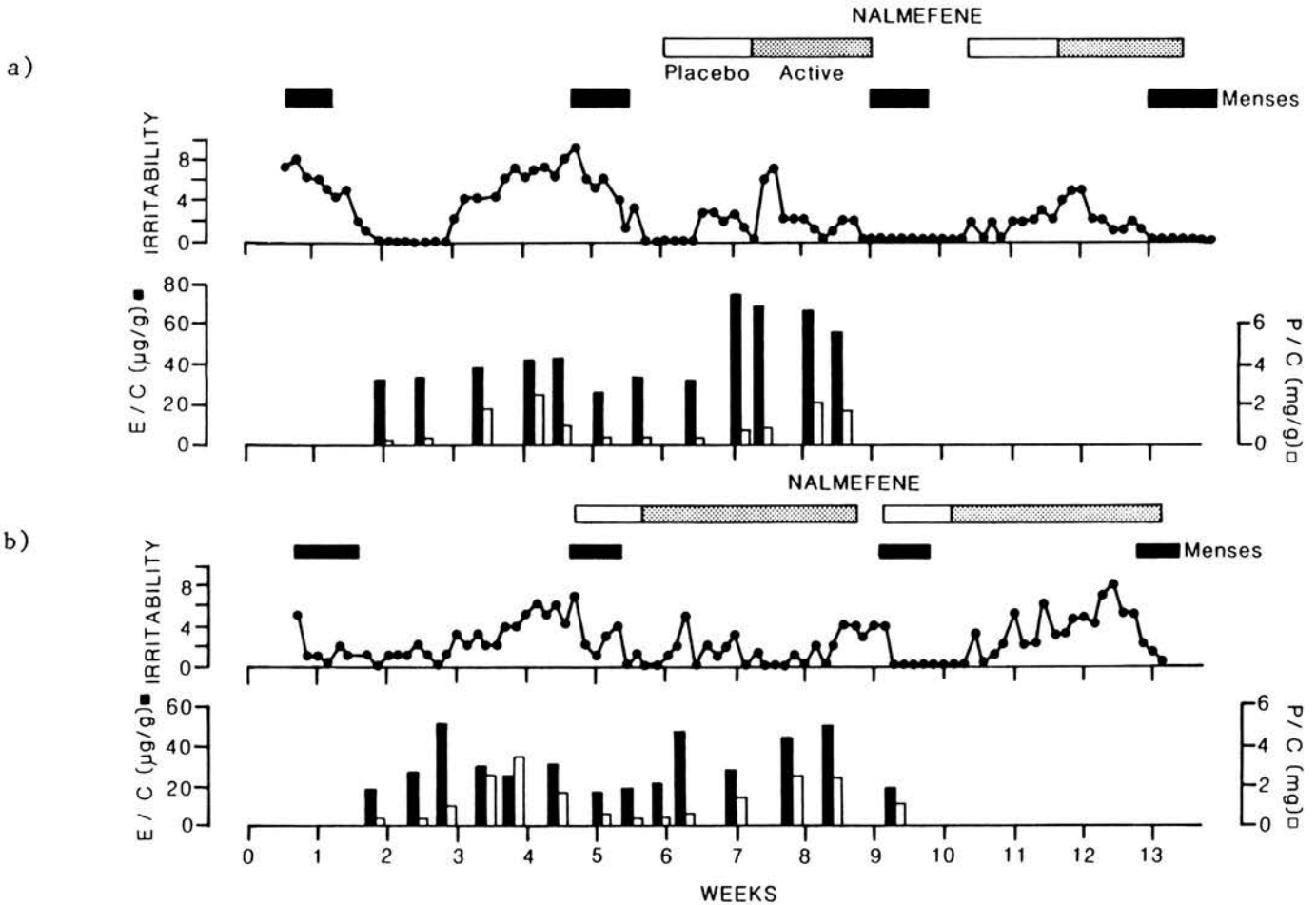


Figure 7.2
Effect of nalmefene therapy on tension (daily VAS score) and urinary steroid excretion in (a) subject 2 who commenced active therapy with nalmefene 10mg bd on day 17 and (b) subject 5 where active therapy was gradually introduced from days 8-10.

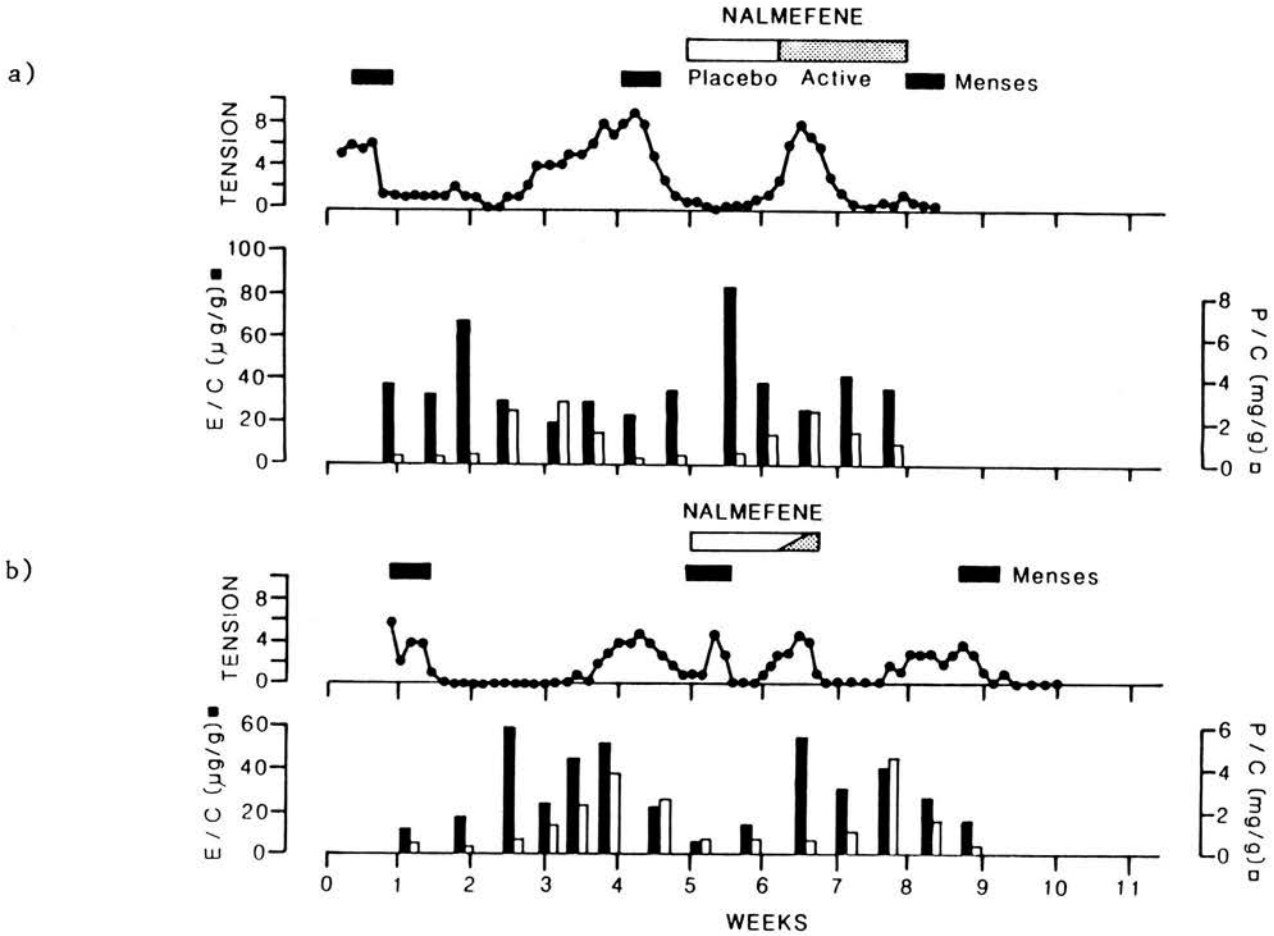
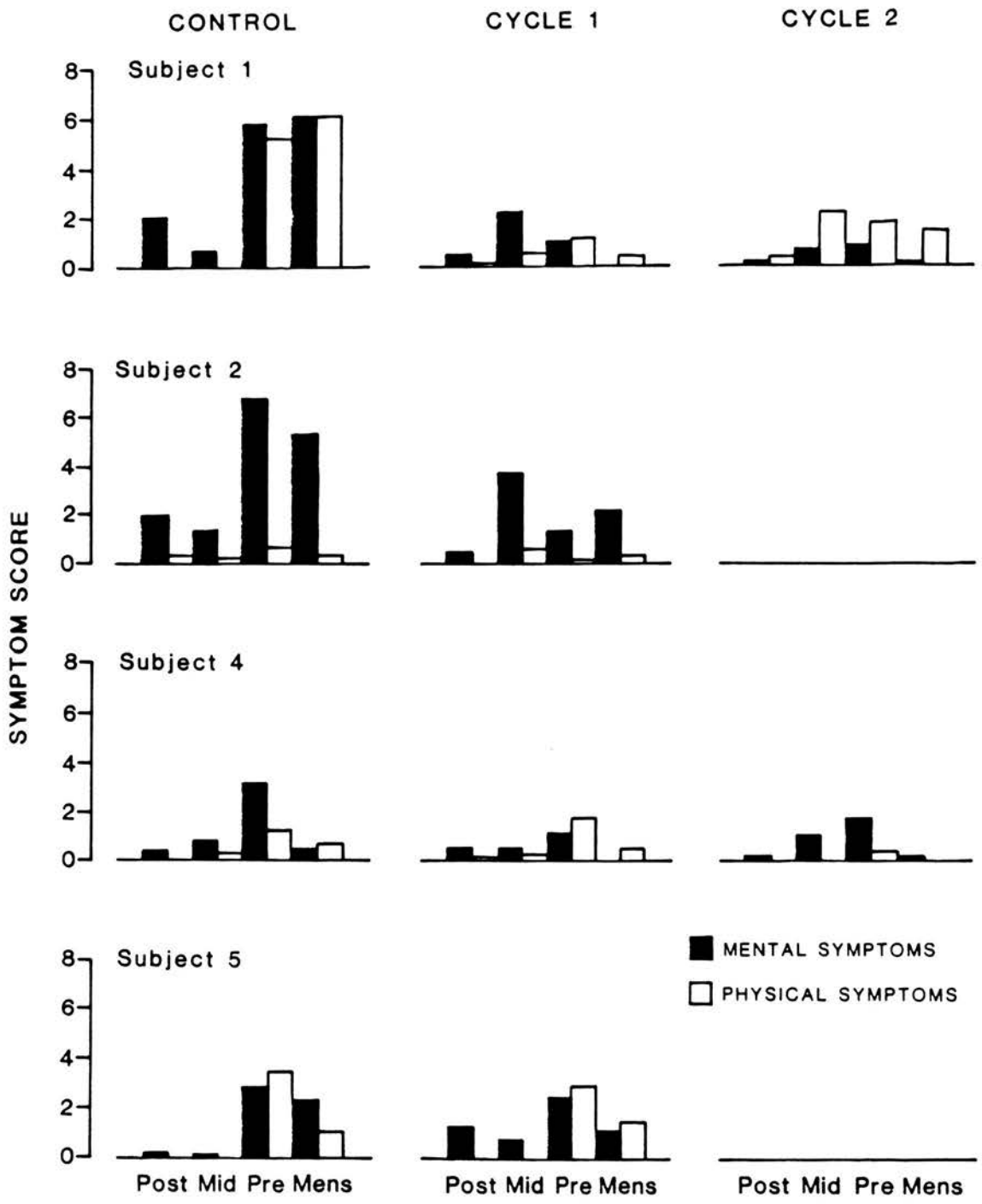


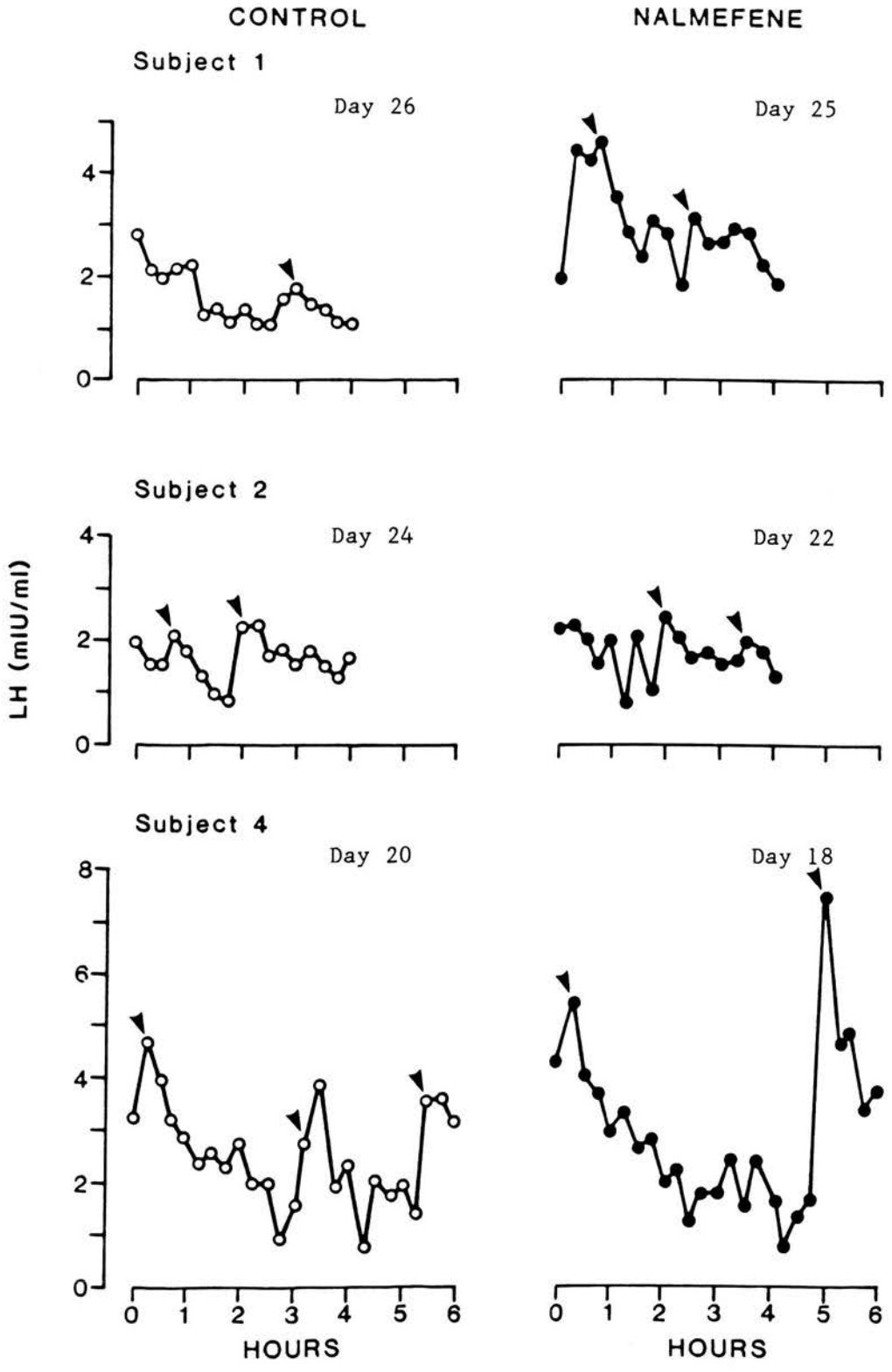
Figure 7.3
Mean mental and physical symptom scores in each cycle phase before and during nalmefene therapy in subjects 1 & 2 who commenced active therapy on day 17 and subjects 4 & 5 who commenced active therapy on day 8 of the cycle.



7.3.4 - Effect on urinary ovarian steroid excretion and LH pulsatility

As seen in figures 7.1 and 7.2, nalmefene therapy produced no consistent alteration of urinary ovarian steroid excretion although only the initial treatment cycles were monitored. All treated cycles were of normal length and no breakthrough bleeding occurred. There was no apparent effect of therapy on LH pulse frequency or amplitude (figure 7.4) in the three subjects who continued therapy for long enough to enable the sampling to be completed.

Figure 7.4
Luteal phase plasma LH concentrations (15 min samples) in a control cycle and during treatment with nalmefene 10mg bd (subjects 1 & 2) and nalmefene 5mg bd (subject 4). Arrows indicate individual LH pulses.



7.4 - DISCUSSION

The numbers of subjects treated with nalmefene in this small pilot study were too few to permit any meaningful conclusions about the role of opiate antagonists in the management of premenstrual tension. However some consistent findings are apparent and are worthy of discussion. All the subjects given nalmefene 10 mg bd experienced unpleasant symptoms very soon after the onset of active therapy, with some of the symptoms resembling those experienced premenstrually and accompanied by others classically associated with opiate withdrawal (Jaffe, 1980). Such effects were unexpected with the doses of nalmefene selected and may support the theory that endogenous opioids are involved in the aetiology of premenstrual mental changes. No associated physical changes of swelling or breast discomfort were evoked, supporting a different mechanism for the latter. In view of the limited experience of the use of nalmefene it is not possible to exclude a dose-related opioid withdrawal effect similar to that reported in normal male volunteers given very large (2-4 mg/kg) intravenous doses of naloxone (Cohen et al, 1981). For reversal of the effects of exogenous opiates, an intravenous dose of around 0.05 mg/kg of naloxone is normally used and at these doses effects on mood have not been observed (Grevert & Goldstein, 1978). Compared with naloxone, nalmefene appears to have approximately 5-fold greater potency. The oral equivalent of nalmefene for opiate reversal would appear to be around 0.25 mg/kg. However male volunteers given much larger doses in preliminary studies (section 7.1.3) tolerated five-fold higher doses that those used in the present study before effects attributable to opioid withdrawal became apparent. In one small study of the use of nalmefene in dementia, one out of five women

experienced side effects of nausea, headaches and dysphoria at a dosage of 10 mg twice daily (Weiss, 1987) but none apparently suffered the severe symptoms reported by the subjects in the present study.

Opioid-withdrawal effects were rapid in onset and severe in the three women who commenced therapy in the luteal phase when the inhibitory effects of endogenous opioids on hypothalamic release of LHRH are presumed to be greatest (see section 7.1.2). When therapy was continued until the end of the cycle, subsequent 'premenstrual' symptoms appeared to be improved possibly suggesting that the opiate antagonist had shifted an opioid withdrawal phase to an earlier stage in the cycle. However further placebo-controlled studies would be required to confirm this. Only two subjects in the current study had therapy initiated during the follicular phase and effects became severe by day 11 in subject 5, corresponding to the time when therapy had reached full dosage. Milder and less specific symptoms were noted at the same stage in subject 4 with a smaller daily dosage and here the subsequent premenstrual build up of symptoms appears to have been retained. It would be of interest to study the effect of initiating therapy even earlier in the follicular phase when EOP inhibition has been shown to be minimal (section 7.1.2). More information about the effects of oral nalmefene in different phases of the menstrual cycle is needed in normal women before reaching any firm conclusions from the above results. However they do appear to support a role for endogenous opioids in the aetiology of cyclical mood changes.

Two groups have studied concentrations of beta-endorphin in peripheral plasma in premenstrual tension sufferers, in comparison with normal

control subjects. Chuong et al (1985) sampled their subjects twice during the menstrual cycle and found the symptomatic women to have significantly lower concentrations on day 25 of the cycle, with no difference between the groups on day 7. Faccinetti et al (1987) also reported that circulating concentrations of beta-endorphin were significantly lower 0-6 days prior to the onset of menstruation in patients with premenstrual symptoms compared with asymptomatic volunteers, with no differences during the remainder of the cycle. Cyclical variations were not seen in the normal control group, unlike results of direct hypophyseal blood sampling in primates (Wehrenberg et al, 1982) and a study of daily peripheral venous blood samples in normal women (Vrbicky et al, 1982). Shoupe et al (1985) found peripheral levels of beta-endorphin to be a poor indicator of central opioid activity and thus only limited conclusions may be drawn from the above studies. Perhaps of more significance is the finding of Faccinetti et al (1987) that the LH response to a 4 mg IV bolus of naloxone was significantly lower during the late luteal phase in the patients than in the controls, while the response during the mid luteal phase was similar in both groups. They concluded that adverse premenstrual symptoms are a consequence of opioid withdrawal during the late luteal phase of the cycle. This would be compatible with the pattern of symptoms identified in the subjects described in chapter 2. However they do not confirm the hypothesis that abnormally high opioid activity is present earlier in the cycle. Neither this report or that of Reid et al (1986) in which a naloxone infusion was given to women with premenstrual symptoms associated with 'hypoglycaemia', mentioned any adverse side effects provoked by naloxone but doses used were relatively low.

Nalmefene in the doses and regimens used above produced no obvious alteration of cycle length or ovarian function although more detailed endocrine monitoring would be required to confirm this observation. In addition, there was no effect on the pulsatile release of LH, even when this was tested in the early luteal phase. As described above (section 7.1.2,) single intravenous doses or infusions of naloxone cause a prompt increase in the frequency and amplitude of LH pulses during the luteal phase of the cycle in healthy volunteer subjects. The lack of such an effect with chronic oral therapy may reflect the development of tolerance to the opiate antagonist, as demonstrated by Owens & Cicero (1981) in rats given repeated injections of naloxone. This could be clarified by studies of LH pulse frequency and amplitude before and after single oral doses of nalmefene.

If opioids are involved in the aetiology of premenstrual symptomatology, it is not clear why tissue concentrations should differ from those of asymptomatic women. They may be affected by ovarian steroid feedback (see section 7.1.2) but it is more likely that any small differences in circulating steroids which may be present in symptomatic women (section 3.2) are a consequence rather than a cause of abnormalities in the central control of the cycle. An attractive hypothesis would be that the entire syndrome is stress-related and that symptomatic women experience differences in their response to either normal or abnormal levels of environmental stress during the premenstrual phase of the cycle. Endogenous opioids are known to inhibit the response to certain well defined stressful stimuli, for example the catecholamine response to insulin induced

hypoglycaemia (Bouloux et al, 1985a) and the cold pressor test (Bouloux et al, 1985b). Similarly, opioid antagonists have been used in states of severe shock to assist resuscitation by removing opioid mediated inhibition of the stress response (Faden, 1984) and have been shown to enhance adrenal medullary catecholamine release (Critchley et al, 1988). It is much more difficult to objectively study responses to mental stress because of difficulties in defining or quantifying such stresses. Symptoms of anxiety are, in part, attributed to increased activity of the sympathetic nervous system, both peripherally and centrally. Thus, in states of chronic emotional stress opioids may modulate the activity of the sympathetic nervous system. The degree of inhibition may vary with menstrual cycle phase, cyclical opiate withdrawal resulting in rebound hyperactivity of adrenergic neurones (Llorens et al, 1978). It has been suggested that many of the symptoms of opiate withdrawal are due to hyperactivity in the locus coeruleus, a noradrenergic centre in the midbrain. It is involved in feelings of alarm, fear and anxiety (see Jaffe, 1980) and is considered to be inhibited by alpha-adrenergic neurones and endogenous opioids (Gold et al, 1978). It is also postulated that this centre, which has hypothalamic connections via noradrenergic neurones, is involved in the genesis of the LH surge (see Reichlin, 1985), which may explain the inhibitory effect of opiates and emotional stress on ovulation.

There is evidence that noradrenergic activity varies with menstrual cycle phase in normal women. A study based on daily sampling of volunteers showed venous plasma and urinary noradrenaline concentrations to be significantly higher during the luteal phase of

the cycle, compared with the follicular phase, concentrations increasing prior to ovulation and reaching a peak in the mid to late luteal phase (Goldstein et al, 1983). Premenstrual symptoms may be attributable to the balance between the activity of the sympathetic nervous system and the degree of endogenous opioid inhibition (see above). To date, no studies of catecholamine concentrations in premenstrual tension sufferers have been reported although studies based on peripheral venous catecholamine estimations must be interpreted with caution because of rapid reuptake of plasma catecholamines by the tissues (Critchley & West, 1977).

The above theory most readily explains the adverse symptoms in those women whose premenstrual and menstrual problems represent an exacerbation of symptoms present throughout the cycle and where environmental and personal stress factors can frequently be identified (see chapter 2). A similar mechanism may exist in women with premenstrual exacerbation of an underlying depression. There is believed to be an abnormality of catecholamine activity in depressive states (Rose, 1985) although the exact mechanisms involved have not been clarified. In addition, some patients with endogenous depression show elevation of circulating ACTH, cortisol and CSF cortisol with impaired cortisol response to dexamethasone suppression, reflecting lack of inhibition of the hypothalamo-pituitary-adrenal axis (Carroll et al, 1976; Rubin et al, 1987). Opioids are known to have an inhibitory effect on the HPA axis (Grossman et al, 1982; Taylor et al, 1983) in addition to their modulating effect on adrenergic systems. While the role of endogenous opioids in the aetiology of chronic depressive states has not been clarified, it is possible that changing

activity in opioid-mediated pathways is involved in the aetiology of menstrual cycle related depressive symptoms.

The above theory must remain purely speculative and does not offer such a plausible explanation for those in whom stress factors are not apparent. Such women may be excessively sensitive to the normal fluctuations in endogenous opioid peptides which occur during the menstrual cycle. This might explain the sensitivity of the subjects in the present study to relatively small doses of nalmefene. It is evident that the factors which influence central control of the menstrual cycle are highly complex but the link between the menstrual cycle and mood is more readily explained by consideration of these mechanisms than by simple study of peripheral ovarian steroid concentrations or excretion. However, the methodological difficulties involved in clarifying these central mechanisms are considerable.

In summary, all five women in this pilot study developed marked adverse effects on commencement of therapy with an oral opiate antagonist at doses well below those tolerated without ill effect by healthy volunteers. These effects are attributable to opiate withdrawal and suggest that these women either had abnormally high endogenous opioid peptide activity or increased sensitivity to the normal fluctuations in activity. In the women who continued therapy, the usual premenstrual peak of adverse mood symptoms was reduced. These findings give indirect support for an involvement of endogenous opioid peptides in the aetiology of menstrual cycle related disorders of mood. No alteration in LH pulse frequency and amplitude during chronic oral administration of the opiate antagonist was detected, in

contrast with the results of acute intravenous administration, presumably reflecting the development of tolerance to the effects of the antagonist.

Because of organisational changes in the pharmaceutical company supporting the above pilot study, it was not continued beyond the initial stages described here. Further investigations of opiate antagonists in women with premenstrual problems and in healthy control subjects appear to be justified along the lines discussed above although additional caution in terms of dose and duration of therapy will be required in view of the adverse effects encountered.

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