THE EFFECT OF NORETHISTERONE ENANTATE ON POSTNATAL DEPRESSION.

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A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy.

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DECLARATION

I, Theresa Anne Lawrie, declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted previously for any degree or examination at this or any other University.

_____day of_____, 1998

In memory of my son

Samson

16.07.1995 – 19.07.1995

PUBLICATIONS AND PRESENTATIONS

PUBLICATIONS

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ABSTRACT

Background Postnatal depression affects approximately 10% of women and is responsible for considerable postnatal morbidity. Progestogens have psychoactive and endocrine properties and progesterone deficiency has been considered as an aetiological factor in postnatal depression. Although progesterone is used in the prevention and treatment of postnatal depression, progestogens may cause depressive symptoms. The psychological impact of using progestogen contraceptive agents in the postnatal period is unknown.

Objectives To determine the effect of postnatal administration of the long-acting progestogen contraceptive, norethisterone enantate, on postnatal depression and on serum sex hormone concentrations, and their association with depression.

Design Double blind randomised placebo-controlled trial.

Setting A tertiary care hospital in Johannesburg, South Africa.

Population Postnatal women using a non-hormonal method of contraception (n = 180).

Methods Random allocation within 48-hours of delivery to norethisterone enantate by injection, or placebo.

Main outcome measures 1) Depression scores in the first three months postpartum as rated by the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Edinburgh Postnatal Depression Scale (EPDS). 2) Serum 17β-oestradiol, progesterone, testosterone and the 17β-oestradiol:progesterone ratio at six weeks pospartum.

Results There was a chance excess of Caesarean section deliveries in the progestogen group. Mean depression scores were significantly higher in the progestogen group than in the placebo group at six weeks postpartum (mean MADRS score 8.3 [0.9] vs 4.9 [1.1], p=0,0111; mean EPDS score 10.6 [0.7] vs 7.5 [0.8], p=0.0022). Mean serum 17β-oestradiol and the 17β-oestradiol:progesterone ratio were significantly lower in the progestogen group compared to the placebo group, with the lowest levels occurring in breast-feeding women in the progestogen group. There were no correlations between any of the hormone parameters and depression at six weeks except in the formula-feeding subgroup of the placebo group, where formula feeding and 17β-oestradiol concentrations were positively associated with depression.

Conclusions Norethisterone enantate given within 48 hours of delivery is associated with an increased risk of developing postnatal depression and causes suppression of endogenous 17β-oestradiol secretion below levels induced by lactation. Progestogen contraceptives should be used with caution in the postnatal period, particularly in women with a history of depression.

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LIST OF ABBREVIATIONS

CI	Confidence Interval
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders (version III, revised)
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (version IV)
EPDS	Edinburgh Postnatal Depression Scale
HRT	Hormone Replacement Therapy
5HT	5-Hydroxytryptamine (serotonin)
MADRS	Montgomery-Åsberg Depression Rating Scale
NET	Norethisterone
NET-EN	Norethisterone enantate
NPV	Negative Predictive Value
PMS	Premenstrual Syndrome
PPV	Positive Predictive Value
RR	Relative Risk
SD	Standard deviation
SEM	Standard error of the mean

CHAPTER ONE INTRODUCTION

1.1 BACKGROUND

It is well recognised that childbearing contributes to the increased rate of depression in women (Kendell et al, 1981, Cox et al, 1993). Postnatal depression, affecting approximately 10%of women in the first six months postpartum, is probably the most common complication of the puerperium. Cox et al (1993) estimate that the risk of non-psychotic depression increases three-fold after childbirth. The incidence of postnatal depression is consistent across cultures (Kumar, 1994).

Postnatal depression has all the characteristics of depression occurring at other times, with irritability, anxiety, impaired concentration and depressed mood being prominent (Dean and Kendell, 1981, Murray and Carothers, 1989, Cooper and Murray, 1995). Symptoms of postnatal depression are most commonly manifest within three months of delivery and are usually self-limiting, resolving spontaneously within three to six months (Cooper and Murray, 1995). However, for many women, depressive symptoms in the postnatal period are the beginning of a history of recurrent episodes of a depressive disorder.

1.2 CLASSIFICATION OF POSTNATAL MENTAL DISORDERS

Romito (1989) considers the term "postnatal depression" an obstacle to a better understanding of what she calls "unhappiness after childbirth" whilst others (Cooper and Murray, 1995) consider postnatal depression to be distinct from depression at other times. This illustrates the controversy surrounding the diagnostic concept of puerperal mental disorders, particularly postnatal depression. As the mechanism/s of depression in the postnatal period have not been proven conclusively to be different from that occurring at other times, many psychiatrists have not supported a separate category of classification. Until 1992, puerperal mental disorders were not classified as a separate category in the World Health Organisation's (WHO) *International Classification of Diseases* (ICD-10) (Cox, 1994). Since 1992, mental disorders occurring in the postnatal period (commencing within six weeks of delivery) may now be categorised as puerperal, provided that they cannot be otherwise classified. In the ICD-10, postnatal depression is classified as "*Mild* mental and behavioural disorders associated with the puerperium". Puerperal psychosis is classified as "*Severe*".

It is important to consider postnatal depression different from other depression for the following reasons. Firstly, it has a predictable time of onset and an association with childbirth. Secondly, the impact of postnatal depression on a woman's social and personal adjustment is arguably greater than depression occurring at a less critical time

in a woman's life. Thirdly, the term postnatal depression is considered a useful diagnostic term by most women, and for this reason alone, in a user-orientated service, it should be included as a category (Cox, 1994). Finally, postnatal depression may have a detrimental long-term effect on mother-infant bonding (Robson and Kumar, 1980) and the family as a whole. Infant development has been shown in various studies to be adversely affected (Murray and Stein, 1989, Caplan et al, 1989, Murray et al. 1991, Philipps and O'Hara, 1991, Sharp et al, 1995, Hay and Kumar, 1995, Hagan et al, 1996). Marital difficulties and partner depression (Areias et al, 1996a) may occur.

1.3 RISK FACTORS FOR POSTNATAL DEPRESSION

The aetiology of postnatal depression is most likely multi-factorial, with an interaction between psychosocial and hormonal elements. Vulnerability to postnatal depression may be enhanced by certain risk factors, although findings are inconsistent. The strongest predictors of vulnerability to postnatal depression are stressful life events, a history of affective disorder including previous postnatal depression, a lack of social support and maternity blues (Table 1.1).

Table 1.1 Vulnerability Factors for Postnatal Depression

Factor	*Evidence for association*	*No evidence for association*
Unplanned pregnancy	Warner et al (1996)	Dalton (1971), Paykel et al (1980), Watson et al (1984)
Anxiety during pregnancy	Dalton (1971), Watson et al (1984)	Pitt (1968), Kumar and Robson (1984)
Depression during pregnancy	O'Hara et al (1984), Dennerstein et al (1989), O'Hara et al (1991), Gotlib et al (1991)	
Marital conflict	Paykel et al (1980), Kumar et Robson (1984), Watson et al (1984), O'Hara et al (1986), Webster et al (1994), Hagan et al (1996)	
Poor relationship with own mother	Nilsson and Almgren (1970), Kumar and Robson (1984)	Paykel et al (1980)
Social class		Pitt (1968), Paykel et al (1980), Kumar and Robson (1984), Watson et al (1984), Cox et al (1989), Areias et al (1996)
Age >30	Paykel et al (1980)*, Kumar and Robson (1984), Dennerstein et al (1989), Webster et al (1994)*	Pitt (1968)
Unmarried mother	Kendell et al (1981), Cox et al (1982), O'Hara et al (1986)	Kendell et al (1976), Paykel et al (1980), Watson et al (1984)
Hospital Vs home delivery		Pop et al (1995)
Obstetric complications	Kendell et al (1981), O'Hara et al (1984), Kumar and Robson (1984)[a], Boyce and Todd (1992)[b], Astbury et al (1994)	Pitt (1968), Kendell et al (1976), Paykel et al (1980), Cox et al (1982), Stein et al (1989), Pop et al (1995)
Parity (Primigravida)	Pitt (1968), Nott et al (1976), Kendell et al (1981), Astbury et al (1994), Webster et al (1994)	Paykel et al (1980), Cox et al (1982), Watson et al (1984), Cox et al (1989)
Labour support	Trotter et al (1992)*, Wolman et al (1993)*	

**Factors negatively associated with depression.*

[a] Preterm birth
[b] Emergency Caesarean section

Vulnerability factors cont.

Factor	*Evidence for association*	*No evidence for association*
History of psychiatric disorder	Paykel et al (1980), O'Hara et al (1984), Watson et al (1984), O'Hara et al (1986), Dennerstein et al (1989), O'Hara et al (1991), Areias et al (1996)	Pitt (1968), Dalton (1971), Cox et al (1982), Kumar and Robson (1984)
Family history of psychiatric disorder	O'Hara et al (1984), Harris et al (1992)	Kumar and Robson (1984)
Formula feeding	Astbury et al (1994)	
Breast-feeding	Dalton (1971), Alder and Cox (1983), Dennerstein et al (1989), Warner et al (1996)	Paykel et al (1980), Cox et al (1982), Kumar and Robson (1984)
Oral Contraception (Combined and progestogen only)	Alder and Cox (1983)	
Premenstrual depression	Pitt (1968), Nott et al (1976), Dennerstein et al (1989), Chuong and Burgos (1995)	O'Hara et al (1984)
Maternity blues	Pitt (1968), Kendell et al (1981), Oakley (1980), Cox et al (1982), Romito (1989), Fossey et al (1997)	Kumar and Robson (1984)
Infant temperament	O'Hara et al (1984), Cutrona and Troutman (1986)	
Stressful life events	Paykel et al (1980), Watson et al (1984), O'Hara et al (1986), Brown et al (1987), Stein et al (1989), O'Hara et al (1991), Areias et al (1996)	Pitt (1968), Kumar and Robson (1984)
Lack of social support	Paykel et al (1980), Kumar and Robson (1984), Cutrona and Troutman (1986), Dennerstein et al (1989)	

**Factors negatively associated with depression.*

1.4 BRIEF RESUMÉ OF THIS THESIS

Ten percent of women suffer from postnatal depression after childbirth. Due to the dramatic fall in progesterone and oestrogen serum levels after delivery, an hormonal aetiology has been suggested, but not proven. Progesterone therapy has been recommended for prophylaxis and treatment of postnatal depression (Dalton, 1996) but this, too, has not been substantiated with adequately controlled trials. Progestogen contraceptive agents are used by millions of women in the postnatal period. The psychological sequelae of this practice are unknown. The hypothesis of the thesis is stated in Chapter Three. The aim of this thesis was firstly to review the literature on the effect of progestogens on mood (Chapter Two). Since no information was available on the suitability of the Edinburgh postnatal depression scale (a commonly used clinical and research tool in other countries) for screening for depression in South Africa, a validation study of this screening tool was undertaken (Chapter Four). The methodology and results of the main trial are described in Chapters Five and Six respectively. Chapter Seven holds the discussion, summary and conclusions.

CHAPTER TWO PROGESTOGENS AND MOOD

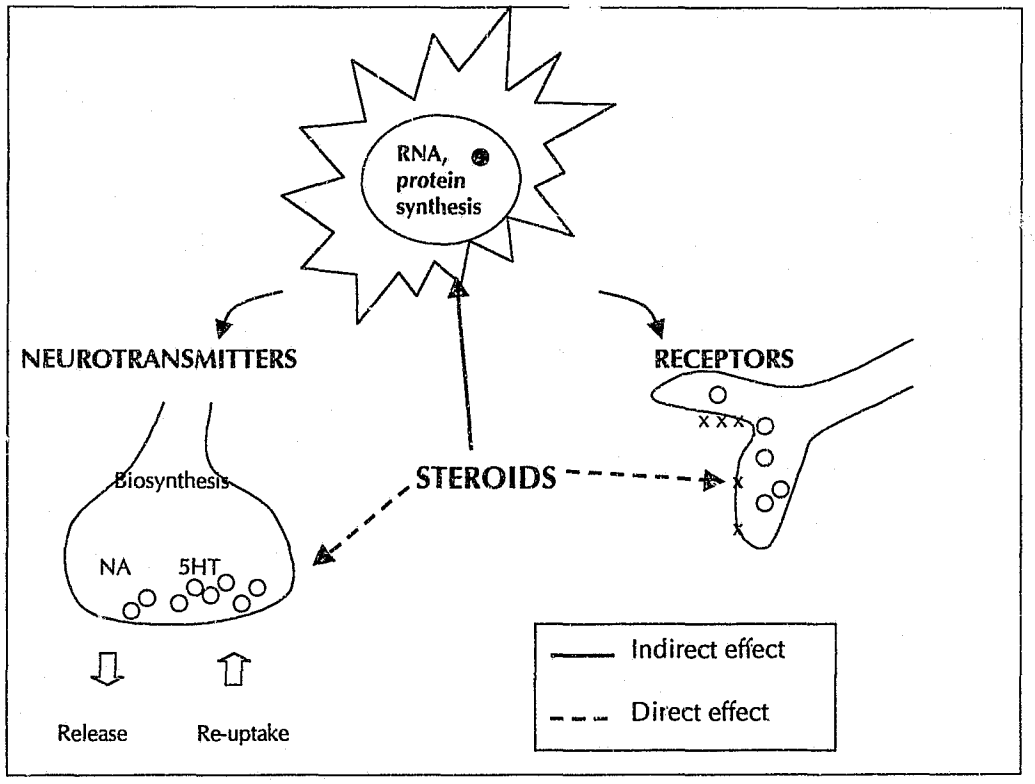
2.1 INTRODUCTION

Both oestrogen and progesterone have psychoactive as well as endocrine properties (Bäckström et al, 1985). In the circulation they gain rapid and relatively unrestricted access to all parts of the central nervous system (CNS). Once in the CNS, they may be metabolised or interact with receptor sites to produce an effect (McEwan et al, 1979) (Figure 2.1). Whilst much is known about oestrogen in the CNS and its ability to modulate the synthesis of proteins, neurotransmitters and receptors (Schmidt and Rubinow, 1991, Fink et al, 1997), less is known about the role of progesterone and progestogens in the CNS. However, there are several theoretical reasons why progestogens should affect mood and behaviour, together with some clinical evidence of an association.

2.2 PHYSIOLOGY OF PROGESTOGENS

Progestogens are defined as compounds that act on the uterus to induce endometrial changes characteristic of pregnancy, and which maintain pregnancy in animals (Sonnendecker, 1994). In addition to this common ability to cause secretory

Figure 2.1 Possible effects of steroid hormones in pre- and post-synaptic events.



Direct or non-genomic effects may involve the action of the hormone on the pre- or post-synaptic membrane to alter permeability to neurotransmitters or their precursors, and/or functioning of neurotransmitter receptors. Indirect or genomic effects of the steroid leads to altered synthesis of proteins, which are transported to nerve synapses (McEwan et al, 1979).

transformation of an oestrogen-primed endometrium, they have a wide spectrum of physiological activity. These include various agonistic, antagonistic and synergistic effects by interaction with progesterone, oestrogen, androgen, glucocorticoid and mineralocorticoid receptors (Kuhl, 1990). Progesterone-oestrogen synergism occurs only when the ratio of oestrogen to progesterone and the time-sequence of their interaction is optimal, otherwise progesterone behaves antagonistically towards oestrogen (Neumann, 1978).

2.3 THEORETICAL REASONS FOR AN EFFECT OF PROGESTOGENS ON MOOD

Impairment of noradrenergic and serotonergic function is considered to be a central feature of depressive illness. It is thought that the symptoms of depression are caused by a decrease in the effective concentration of noradrenalin and/or serotonin at central receptor sites (Butler and Leonard, 1986). Antidepressant drugs are considered to act by modulation of these neurotransmitter systems.

An experiment with ovariectomised rats pre-treated with progesterone showed higher brain serotonin concentrations than controls (Ladisich, 1977). In addition, Biegon et al

(1983) found that chronic treatment with progesterone induced an increase in serotonin-2 (5HT-2) receptors in the rat cerebral cortex and decreased the numbers of serotonin-1 (5HT-1) receptors. Whilst the functional significance of these changes is unknown, they suggest that progestogens may have effects on neurotransmitter function and, hence, on psychological symptomatology.

Progestogens have been shown to modulate anxiety evidenced by electro-encephalogram (EEG) profiles. Itil et al (1974) performed EEGs on human subjects given high and low dosages of cyproterone acetate, an anti-androgenic progestogen, or placebo. Although EEG profiling has poor specificity, high dosages of cyproterone acetate showed similar patterns to those of anxiolytic drugs, whilst in low dosages resembling those of "sedative" antidepressants. Mesterolone, an androgen, in high dosages showed EEG profiles similar to "stimulatory" tricyclic antidepressants, and in a pilot study, elevated mood in nine out of ten depressed males (Itil et al, 1974).

In another study, levonorgestrel (a 19-nortestosterone derivative), a progestogen with androgenic properties, has also been shown to give an EEG profile resembling an anxiolytic (Herrmann and Beach, 1978). Therefore androgenic progestogens may have an antidepressant and anxiolytic effect (Neumann, 1978). In support of this, Rodriguez-Sierra et al (1986) demonstrated an anxiolytic effect in oestrogen-primed female rats given progesterone.

Pregnane derivatives are known to have sedative properties and, in high doses, have been used for anaesthesia (Merryman, 1954, 1967, cited from Herrmann and Beach, 1978). Progesterone is a potent barbiturate-like modulator of the γ-amino-butyric acid (GABA) receptor in the brain in animal experiments (Majewska et al, 1986). This may be the mechanism for the anaesthetic and hypnotic actions of naturally occurring and synthetic progestogens.

2.4 EVIDENCE FOR AN EFFECT OF PROGESTOGENS ON MOOD

2.4.1 POSTNATAL DEPRESSION

The postnatal period is associated with a precipitous decline in circulating sex steroids. Total progesterone is reported to drop 100-fold in the first few days following childbirth, and oestradiol, 10-fold within 24 hours of delivery (Willcox et al, 1985a, Butler and Leonard, 1986). Levels usually remain very low until a maturing ovarian follicle resumes steroid production several weeks or months later. Oestradiol increases first, then progesterone. About 1-3% of circulating ovarian hormones is unbound to plasma proteins and so free to enter the brain (Willcox et al, 1985b). It is plausible that low levels of progesterone and oestradiol, the precipitate nature of the decline, or the ratio of the two steroids may influence mood in the postnatal period. Numerous

investigators have tried to link postnatal depression with reproductive endocrinology, with limited success.

Most studies have measured serum levels of total progesterone. Nott et al (1976) measured serum oestradiol and progesterone in the first ten weeks postpartum in 27 women, and examined the ratio of the two hormones, and found no consistent association with depressive symptomatology. In subsequent studies, no significant differences were found between serum progesterone levels in depressed women and controls at six to eight weeks postpartum and all levels were within the normal range (Butler and Leonard, 1986, Harris et al, 1989a). O'Hara et al (1991) found no correlation between serum progesterone levels taken in the first eight days after delivery and depression at nine weeks postpartum.

Harris et al (1989a) measured progesterone concentrations in saliva collected three times in one day at six to eight weeks postpartum. Salivary measurements have been recommended as useful to detect the free fraction of progesterone, especially since it is non-invasive and so many specimens can be obtained (Feksi et al, 1984). They found that salivary progesterone levels correlated positively with depression in women who were bottle-feeding their babies and negatively in women breast-feeding. This implies that too little or too much progesterone may enhance a woman's vulnerability to depression. The authors suggest that depressed breast-feeding women may benefit from progesterone supplementation. However, the sample size was small and in a later study

by the same group (Harris et al, 1996), no association was found between salivary progesterone collected twice daily after delivery for 35 days and postnatal depression at six weeks postpartum. The authors acknowledge that there is insufficient evidence to support progesterone supplementation as a treatment strategy. There has been no replication of these findings.

2.4.2 MATERNITY BLUES

Women who experience maternity blues (transient depression or lability of mood in the first ten days after delivery) are at a greater risk of developing postnatal depression. An association between the massive drop in progesterone after delivery and the blues would give support to the progesterone deficiency theory of postnatal depression. However, studies of serum progesterone have yielded conflicting results for maternity blues (Nott et al, 1976, Ballinger et al, 1982, Kuevi et al, 1983, Gard et al, 1986).

Feksi et al (1984) performed frequent sampling of saliva during the first five days postpartum and found that mean concentrations of progesterone were significantly higher in blues sufferers on the day that symptoms occurred than in matched controls. In contrast, Harris et al (1994) found that high postpartum scores for the maternity blues were associated with high antenatal salivary progesterone concentrations on the day before delivery, rapidly falling progesterone concentrations after delivery, and *low*

progesterone concentrations on the day of the peak blues score. Harris et al (1994) concludes that maternal mood in the days immediately after delivery is associated with withdrawal of progesterone and suggests progesterone therapy to prevent the occurrence of the blues.

2.4.3 OTHER ASSOCIATIONS WITH REPRODUCTIVE FUNCTION

Depression is more common in women than men. Many authors have postulated a common link between depression associated with the menstrual cycle, childbirth, contraception and the menopause (Parry, 1989, Gitlin and Pasnau, 1989). Whilst a close link between psychological symptoms and reproductive endocrinology is plausible, it would be simplistic to assume that mental illness in women can be understood within a single (hormonal) frame of reference.

PREMENSTRUAL SYNDROME

Depression is usually one of the symptoms experienced in severe premenstrual syndrome (PMS), which is more common in women with a history of postnatal depression (Chuong and Burgos, 1995). While the exact cause of PMS is unknown, it

appears to occur in the presence of cyclical ovarian activity (Magos and Studd, 1984, Magos et al, 1986, van Leusden, 1995). Evidence of the need for cyclicity can be found in an open crossover study of long-acting injectable norethisterone enantate (a synthetic progestogen) or a combined oral contraceptive in 20 women with severe PMS (Gunston, 1995). Gunston compared premenstrual symptom scores and found symptoms were significantly improved by norethisterone enantate ($p < 0.005$). The mechanism for this marked improvement is most likely the disruption of the menstrual cycle, although intrinsic properties of norethisterone enantate (e.g. its androgenicity) cannot be excluded from making a contribution.

As with postnatal depression, a popular theory of the aetiology of PMS is progesterone deficiency (Dalton, 1989a). Haspels reported in 1981 that the oral synthetic progestogen, dydrogesterone, which is structurally similar to natural progesterone, significantly improved depression associated with PMS (cited from Sonnendecker, 1991). However, in at least two double-blind randomised placebo controlled trials of progesterone for PMS, no significant difference was found between treatment and placebo groups (Sampson, 1979, Freeman et al, 1995). Despite a lack of evidence, progesterone therapy is apparently prescribed by many PMS clinics in the United States (Moline, 1993).

THE CLIMACTERIC

Contrary to earlier reports, the menopause is not associated with an increase in major depressive illness (Nicol-Smith, 1996). However, symptoms of the menopause are associated with a hypo-oestrogenic state and hormone replacement therapy (HRT) seems to be of benefit in reducing depressive symptoms at this time (Blake, 1997). Numerous trials have shown that oestrogen, in various forms and dosages, improves mood and psychological function in symptomatic (Montgomery et al, 1987, Studd and Smith, 1994) and asymptomatic women (Ditkoff et al, 1991). Recently, a meta-analysis by Zweifel and O'Brien (1997) revealed that oestrogen significantly reduced depressed mood in postmenopausal women, progesterone alone and in combination with oestrogen was associated with smaller reductions in depressed mood, and androgen alone or in combination with oestrogen was associated with greater reductions in depressed mood.

Norethisterone has been shown to be useful for some climacteric symptoms. In a randomised placebo-controlled double-blind cross-over trial in 23 postmenopausal women, the number of hot flushes decreased from 50 per week to <10 per week ($p<0.001$) in women receiving 5mg of norethisterone daily (Paterson, 1982). Anxiety was also significantly reduced in this trial ($p<0.01$). However, no significant difference (in either direction) was evident for depressive symptoms. The effect on anxiety may be

attributable to direct progestogenic or androgenic properties of norethisterone, or be due to the reduction in vasomotor symptoms.

In contrast to these findings, in a double-blind randomised placebo-controlled trial, Magos et al (1986) found that giving 5mg of norethisterone for seven days to postmenopausal hysterectomised women receiving oestradiol HRT induced psychological changes similar to the premenstrual syndrome. The effect was dose-dependent and not evident when a dose of 2.5mg norethisterone was used. These so-called "progestogenic" symptoms were observed to be more severe when oestradiol levels were dropping which suggests that the ratio between oestradiol and progestogen may be important. Other investigators have reported that norethisterone is less likely to cause symptoms of negative affect than other synthetic progestogens used in the climacteric (Smith et al, 1994).

HORMONAL CONTRACEPTION

Depression is reported to be a side effect of the combined oral contraceptive pill, which has been postulated to decrease levels of brain serotonin (Adams et al, 1974). Psychological symptoms in response to oral contraceptive use are highly variable, with authors reporting both positive and negative effects. In addition, the separate effects of

oestrogenic and progestogenic components or their ratio on mood and behaviour, are not clear. Worsley (1980) compared women taking one of three combined oral contraceptives with the same oestrogenic but different progestogenic components, to intra-uterine device users. Of the 35 women studied, the eight intra-uterine device users had significantly fewer symptoms of depression, anger and tension when assessed blindly using various psychological scales. These symptoms varied with the contraceptive and were worse with those containing norethisterone (1mg).

Alder and Cox (1983), in a postal survey of 103 postnatal women, found that women taking oral contraception (n=49) (combined or progestogen only) were more likely to be depressed than those not taking oral contraception (n=38). These findings were similar to those of Nilsson and Almgren (1968) in an open cohort study. Neither study used a randomised design. To our knowledge, the only randomised placebo-controlled trial of hormonal contraceptives is a small trial (n=20) by Grounds et al (1970). In this trial, ten women received a combined oral contraceptive pill and ten women received placebo. Side effects including depression were more prevalent in the contraceptive pill group in the first month of the trial but had decreased substantially by the second month. Recent opinion is in favour of a progestogenic role in contraceptive-associated depression (Magos et al, 1986, Wagner and Berenson, 1994, Wagner, 1996) but there is little controlled evidence to support this view.

2.5 PROGESTOGENS IN THE PREVENTION AND TREATMENT OF POSTNATAL DEPRESSION

Research into hormonal prophylaxis and treatment of postnatal depression is limited. High dose oestrogen therapy has previously been recommended for the treatment of severe persistent depression in women (Klaiber et al, 1979) and has recently been used to treat women with severe postnatal depression. In a double–blind randomised placebo-controlled trial of high dose transdermal oestrogen, women receiving oestrogen improved rapidly and to a significantly greater extent than controls (Henderson et al, 1991, Gregoire et al, 1996). There has to date not been a study of oestrogen in the prevention of postnatal depression and Gregoire et al's findings have not yet been replicated.

Dalton popularised the use of progesterone for prophylaxis against postnatal depression (Dalton 1985, 1989,1996). In an open non-randomised study, where women who had experienced previous postnatal depression self-selected to take prophylactic progesterone treatment, Dalton showed a reduction in the recurrence rate of postnatal depression from 68% to 10%(Dalton, 1985). She repeated these findings in a later study with similar methodological shortcomings (Dalton, 1989). There have been no randomised placebo-controlled trials investigating progesterone for the prevention or treatment of postnatal depression. Despite this, progesterone is used for these purposes (Dalton, 1989, Gregoire et al, 1996).

2.6 SUMMARY

Progestogens have been shown to have anxiolytic, hypnotic and anaesthetic properties. Therefore changes in circulating progesterone, like those after childbirth, may influence neurotransmitter concentrations and thereby predispose some women to depression. It is plausible that progestogen therapy could be used to prevent or treat postnatal depression. However, there is a shortage of factual evidence to support a causal role for progesterone deficiency in postnatal depression and even less evidence to support progestogen therapy. It is likely that progestogen contraceptive agents used in the postnatal period will have a mood-altering effect, positive or negative. To our knowledge, there has been no previous randomised placebo-controlled trial addressing the role of progestogens in the prevention (or treatment) of postnatal depression. Given the widespread use of progestogens for postnatal contraception and of progesterone for the prevention of postnatal depression, it is clear that research in this area is desperately needed.

CHAPTER THREE HYPOTHESIS

Progestogen contraceptive agents are frequently prescribed to women in the postnatal period and in some countries, particularly developing countries, immediately after childbirth (Sapire, 1991, Guillebaud, 1994). Progestogens theoretically have the potential to modulate mood. If the progesterone deficiency theory is correct, by interaction of the synthetic progestogen with progesterone receptors, women using progestogen contraceptives may be protected from developing postnatal depression. Alternatively, if only naturally occurring progesterone that has antidepressant properties (which is not supported by the existing evidence), the synthetic progestogen may compete with natural progesterone for progesterone receptors and increase the risk of depression. On the other hand, synthetic progestogens may have an effect on mood that is totally independent of naturally occurring progesterone.

To our knowledge, progesterone and progestogens have not been studied, by means of a randomised placebo-controlled trial, in terms of their effect on postnatal psychological morbidity. The objective of this trial was to assess the effect of a synthetic progestogen contraceptive agent, norethisterone enantate, when administered intramuscularly within 48 hours of delivery, on postnatal depression.

As there is a theoretical framework to support norethisterone enantate either reducing or increasing postnatal depression, our hypothesis was bi-directional:

1. Norethisterone enantate reduces the incidence of postnatal depression.
2. Norethisterone enantate increases the incidence of postnatal depression.

CHAPTER FOUR: VALIDATING THE EDINBURGH POSTNATAL DEPRESSION SCALE

4.1 INTRODUCTION

The 10-item Edinburgh Postnatal Depression Scale (EPDS) was developed for clinical and research purposes and initially validated on British women (Cox et al, 1987). It is a self-report scale designed specifically for the postnatal period in that it makes little reference to the somatic symptoms of depression, which may be caused by the normal physiological changes associated with child-bearing. Most studies show the EPDS to be a valid and reliable screening scale. In South Africa, where the majority of the population has been denied accessible health care in the past, it is not surprising that screening for postnatal depression amongst women has not been a priority. The EPDS, a commonly used screening tool in other countries, has not been validated for use in South African women.

The initial validation of the EPDS against the Research Diagnostic Criteria by Cox et al (1987) suggested a threshold score of 12/13 out of 30 to identify women with major depression (sensitivity 86%, specificity 78% and positive predictive value 73%). This is supported by others (Murray and Carothers, 1990, Boyce et al, 1993 and Webster et al,

1994). However some researchers have used a threshold score of 9/10 (Jadresic et al, 1995; Areis et al, 1996b) or 11/12 (Wickberg and Hwang, 1996) to identify cases of major depression. A lower threshold of 9/10 was recommended by Cox (1994) to be used at a primary care level which, according to Murray and Carothers (1990), would identify 92.6% of cases of major depression and 73.2% of cases of minor depression.

4.2 OBJECTIVES

There are eleven official languages in South Africa. However, many women in urban areas have a reasonable command of English or Afrikaans, the official languages of the apartheid era. As a result, a substantial number of clinician-patient interviews are conducted in English (the de facto lingua franca), or are facilitated with the help of a translator. The objective of this study was to determine whether the EPDS could be administered verbally, with the help of a translator where necessary, to screen a cohort of South African women for postnatal depression and, if so, which threshold would be most appropriate. In addition to interest in it's clinical value, this study was undertaken as a pilot study for the randomised placebo-controlled clinical trial of the effect of norethisterone enantate on postnatal depression, which required the use of a self-report scale to screen women for postnatal depression.

4.3 METHODS

4.3.1 PARTICIPANTS AND SETTING

The research project was conducted at Coronation Hospital in Johannesburg, the setting of the subsequent randomised controlled trial. Coronation Hospital serves primarily a low-income, socially disadvantaged urban community. Approximately 7000 deliveries are performed annually. Postnatal check-ups are no longer routinely booked at Coronation Hospital and only women who have experienced an obstetric complication, required a Caesarean section or requested sterilisation for family planning are seen six weeks after delivery. The postnatal clinic is open only one morning per week and is poorly attended.

4.3.2 INSTRUMENTS

The EPDS (Appendix 1) consists of 10 multiple choice questions, each having four possible answers. The answers are scored 0, 1, 2 or 3, according to the severity of the symptom in the previous seven days.

During initial interviews, it became evident that some patients had difficulty with the language used in the scale and so some minor changes, which do not alter the English

meaning of the scale, were made. For example the phrases "rather less than I used to" and "definitely less than I used to" were changed to "a little less than I used to", and "much less than I used to" which was easier for the women to understand. The phrases "very often", "quite often" and "not very often" were changed to "very much", "quite a lot" and "not very much", respectively. In addition, in item 4, the word "worried" was better understood than "anxious" and the latter was best left out. In item 6, "cope" was replaced with "manage". Many women did not differentiate between difficulty sleeping due to "unhappiness" and that due to baby waking, in item 7. To clarify this, "not due to the baby" was added. "Sometimes" replaced "occasionally" in item 9. Literacy rates amongst South African women differ considerably. To avoid excluding a large number of potential subjects from the study and to make the study results more widely applicable, the EPDS was read to study participants. (See the Appendix 2 for the modified EPDS.)

A structured psychiatric interview using DSM-IV criteria for depression (American Psychiatric Association, 1994) was used to identify depressed women. This was considered the "gold standard" against which the EPDS was evaluated. In addition, the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) was administered (Appendix 3). The MADRS is an observer rating scale composed of 10 items, each graded 0 to 6. It places less emphasis on somatic symptoms and is sensitive to changes in mood. This should, theoretically, make it a useful scale in the postnatal period (Harris et al, 1989b).

4.3.3 PROCEDURE

The study was conducted over a period of 3 months. A total of 108 consecutive women attending the postnatal clinic were asked to participate. All the women were approximately six weeks postpartum. Two French-speaking women and one Gugerati-speaking woman were excluded. Only two women refused to take part in the study. Verbal consent was obtained from all participants. The EPDS was read to the women by a research midwife in a private consulting room, and translated, if necessary, by one of two multi-lingual nursing sisters experienced in translation. A doctor (TAL) blind to the EPDS scores conducted structured psychiatric interviews using DSM-IV criteria and the MADRS. If the participant had difficulty understanding preliminary questions with regard to her family, employment, health and recent pregnancy, a translator was used.

4.3.4 STATISTICAL METHODS

The Epi-info version 6.0 computer software was used for data analysis, which includes sensitivity, specificity, positive predictive values and negative predictive values of the EPDS against the DSM-IV at various thresholds.

Ethics approval for the study was obtained from The University of the Witwatersrand Committee for Research on Human Subjects, Johannesburg.

4.4 RESULTS

A total of 103 women were interviewed. One woman was excluded from analysis due to a missing questionnaire. The mean age of the women was 28.1 years and mean parity was 2.2. Of the women, 69.6% were married or co-habitant, 19.6% had a primary school education or less, 55.8% had started but not completed secondary school, 19.6% had matriculated and 4.9% had attended college. Over half were unemployed. The monthly household income in 24% of the women was less than R500, in 71% was less than R2000 and in 95% was less than R5000. Eight women (7.8%) had experienced postnatal depression with a previous pregnancy, for which none had sought or received treatment. Seven women recalled having depression previously, one of whom had been treated. Most (88.2%) of the women were delivered of their babies by Caesarean section.

Table 4.1 shows the frequency of the different South African languages of those interviewed and the percentage in each group requiring a translator. Afrikaans was the most common language spoken, followed by Zulu and Tswana. Thirty-two women were not sufficiently proficient in English and needed a translator.

Table 4.1 Frequency of languages in the sample and the frequency of translation in each language group.

Language	Language frequency	Language percent(%)	Translation frequency	Translation percent(%)
Afrikaans	30	29.4	10	33.3
Zulu	21	20.6	10	47.6
Tswana	19	18.6	4	21.1
English	14	13.7	0	0.0
Sothu	8	7.8	4	50.0
Xhosa	4	3.9	2	50.0
Other	6	5.9	2	33.3
Total	102	100	32	31.4

Table 4.2 shows a range of EPDS thresholds for major depression only and major and minor depression combined. They are shown with the corresponding values for the sensitivity (the proportion of women with depression correctly identified), specificity (the proportion of well women correctly identified), positive predictive value (the probability that a score above the threshold value will identify a depressed woman) and negative predictive value (the probability that a low score will identify a well woman). Eight women fulfilled DSM-IV criteria for a major depressive disorder and seventeen women for a minor depressive disorder. The recommended EPDS threshold of 12/13 identified 7 cases of major depression, giving a sensitivity of 87.5% and specificity of 72.3%. At this threshold, twelve of the seventeen cases (70.6%) of minor depression were identified, giving a combined sensitivity of 76%, specificity of 81.8% and PPV of 57.6%. Lowering the threshold to 11/12 improved the combined sensitivity (80%) and

the sensitivity for major depression alone (100%) but the number of cases of minor depression identified remained the same.

A total of 38 women scored above the 11/12 threshold, 20 of which were true-positive cases and 18 of which were false-positive cases. The threshold of 9/10, recommended for primary level use by Cox (1994), seems a bit low for use in our setting as, in this study, for one more true positive, 15 more false positives would be identified.

The sensitivity, specificity, PPV and NPV of the MADRS against DSM-IV criteria for major and minor depression at a threshold of 9/10, was 80%, 100.0%, 100.0% and 93.9% respectively (although the MADRS and DSM-IV were conducted by the same observer and so the assessments were not blind). When an EPDS threshold of 11/12 was compared to a MADRS threshold of 9/10, the sensitivity, specificity, PPV and NPV were similar to those when compared to the DSM-IV criteria (85.0%, 74.4%, 44.7% and 95.3%, respectively).

4.5 DISCUSSION

The incidence of depression in our sample is quite high (24.5%). This possibly reflects the socially disadvantaged characteristics of the women in the sample. Another contributory factor could be that most of the women had undergone Caesarean section

and so were a select group. Those who chose to keep their appointments at the postnatal clinic may have had more problems than those choosing not to do so, although most studies show that depressed women do not exhibit treatment-seeking behaviour (Cox, 1984, Jadresic et al, 1992, Studd and Smith, 1994).

The results of this study are similar to those found by other researchers and validate the EPDS as a screening questionnaire for postnatal depression in our community. The 12/13 threshold recommended by Cox et al (1987) identified 7 of 8 women with major depression in our sample but the lower threshold of 11/12 identified all women with major depression and improved the detection of minor depression. The 9/10 threshold increased false-positives from 18 to 33 cases. We therefore recommend the use of the 11/12 threshold for screening disadvantaged urban South African women.

Positive predictive values in this study were lower than in other studies (Cox et al, 1987, Murray and Carothers, 1990). The mean score in the women who were not depressed was 9.0. This is rather high and may reflect difficulties the women encountered with certain items on the EPDS, in particular, items 4 and 5. The subtlety of the statements "I have felt worried and anxious for no very good reason" and "I have felt scared or panicky for no very good reason" was often overlooked by the women; many of whom had very good reason to be anxious or scared. This resulted in high scores for items 4 and 5. A similar problem was encountered by Thome (1991) in Iceland (cited from O'Hara, 1994).

Item 3 deals with self-blame. Almost half the women identified as not depressed scored a 2 or 3 for this item. This suggests that guilt, self-blame and low self-esteem is commonplace amongst women in our urban community. This is in contrast to Cox's study on a cohort of semi-rural Ugandan women (Cox, 1979) in which this characteristic was uncommon.

Limitations of this study should be emphasised. The sample size is small. The cultural composition of the sample and its urban character do not make these results readily applicable to all South African women, particularly rural women. The use of a translator, although carefully instructed on the EPDS and the psychiatric interview, inevitably imposes certain limitations on the reliability of the data. Furthermore, a "climate of openness" has been distinctly lacking in South Africa for decades and even the health services have been viewed with suspicion. This may have influenced some women not to answer honestly.

However, there are two unique aspects to this study. To our knowledge, this is the first time that the EPDS has been used in South Africa. It is also, to our knowledge, the first time that the self-report scale has been read to women, in order to attempt to overcome the problem of illiteracy.

The primary motivation for doing this study was to validate the use of the EPDS for research purposes on this particular Johannesburg community. It is evident from this

study and an earlier study (Wolman et al, 1993) that postnatal depression is at least as common in our communities as those in developed countries. Sadly, routine screening for postnatal depression in our postnatal clinics is far from a reality, and community psychiatric services are poorly organised and overloaded. Systematic study of postnatal depression is urgently needed to quantify the extent of the problem among South African women.

Table 4.2 Range of EPDS thresholds and corresponding sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for major depression only and major and minor depression combined.

EPDS	Major Depression				Major/Minor Depression			
Threshold	Sens(%)	Spec(%)	PPV(%)	NPV(%)	Sens(%)	Spec(%)	PPV(%)	NPV(%)
7/8	100.0	35.1	11.6	100.0	92.0	40.3	33.3	93.9
8/9	100.0	43.6	13.1	100.0	84.0	48.1	34.4	90.2
9/10	100.0	51.1	14.8	100.0	84.0	57.1	38.9	91.7
10/11	100.0	58.5	17.0	100.0	80.0	64.9	42.6	90.9
11/12	100.0	68.1	21.1	100.0	80.0	76.6	52.6	92.2
12/13	87.5	72.3	21.2	98.6	76.0	81.8	57.6	91.3
13/14	62.5	78.7	20.0	96.1	60.0	87.0	60.0	87.0

CHAPTER FIVE METHODS

5.1 PARTICIPANTS AND SETTING

The randomised trial of postnatal norethisterone enantate was conducted at Coronation Hospital, an academic Woman and Child hospital, serving a low-income urban population in Johannesburg. One hundred and eighty women were recruited between December 1995 and March 1997. All postnatal women were eligible to enter the study provided they met the following criteria:

5.1.1 INCLUSION CRITERIA

1. Participants were at least 18 years old.
2. Participants were requesting non-hormonal contraceptive methods for at least the first three months after delivery. That is, if women were requesting tubal ligation, an intra-uterine contraceptive device or barrier methods for postnatal contraception, or if they had undergone tubal ligation at the time of Caesarean section, they were asked to participate. This made it possible to randomise the women to the study treatment, an

hormonal contraceptive agent, or placebo, as the women were using alternative methods of contraception.

3. Participants were within 48 hours of delivery.

5.1.2 EXCLUSION CRITERIA

1. Women were to be excluded if they were currently taking antidepressant medication or if they were receiving psychotherapy. However, none of the women approached fell into this category.
2. There were no other exclusion criteria per se but common sense was applied when recruiting women. For example, ill patients were not approached to participate in the trial. Women who lived beyond an approximate forty-kilometer radius of the hospital and women without a contact telephone number were enrolled cautiously.

5.2 CONSENT

Written informed consent (Appendix 4) was obtained in English or Afrikaans from all participants, except for two women who had a poor understanding of these languages. A Zulu-speaking translator was used in these two cases for written consent and subsequent interviews.

Less than one-quarter of the women approached agreed to participate. Reasons given by women choosing not to participate included previous heavy bleeding or migraines using injectable contraceptives, a dislike of injections, a lack of interest and other unspecified concerns.

5.3 INTERVENTION

5.3.1 INTRODUCTION

Long-acting synthetic progestogen contraceptive agents are currently used by more than 10 million women globally (Guillebaud, 1994). They are widely used in lactating women as they have the major advantage (like oral progestogen contraceptives) of not adversely affecting milk production or composition (Prema, 1982, Shaaban, 1991, Wang and Fraser, 1994). Norethisterone enantate is no exception (Koetsawang et al, 1982, Fotherby et al, 1983).

5.3.2 NORETHISTERONE ENANTATE

Norethisterone enantate (17alpha-ethinyl-17ß-heptanoyloxyester-4-ene-3-one) is a synthetic progestogen of the 13-methyl gonane group, also called estranes, which are

derived from 19-nortestosterone (Kuhl, 1990) (Figure 5.1). For contraception, it is administered to women at eight-weekly intervals, at a dose of 200mg of norethisterone enantate (1 ml) in a vehicle of benzyl benzoate and castor oil (Nur-Isterate®, Schering), by deep intra-muscular injection (Sapire, 1990, Guillebaud, 1994).

PHARMACOKINETICS

After injection of the oily solution, norethisterone enantate is released slowly from the depot and is converted by hydrolysis of the ester to the biologically active steroid, norethisterone. Two hundred milligrams of norethisterone enantate by injection is equivalent to 145mg norethisterone (Koetsewang et al, 1982). Initially, a daily dose of 3-4mg norethisterone and, later (60-90 days after the injection), one of 0.3mg can be estimated. Substance concentrations in plasma reach maximum levels 3-10 days after the injection (approximately 12ng/ml) and thereafter show a gradual decline. Four weeks after administration the serum concentration of norethisterone is approximately 3ng/ml and, at eight weeks, it is approximately 1ng/ml (Weiner and Johansson, 1975, Howard et al, 1975). Norethisterone is metabolised in the liver and the metabolites are eliminated approximately equally in the urine and faeces (Kuhl, 1990).

PHARMACODYNAMICS

Norethisterone enantate displays a progestational effect about five times more potent than progesterone (Neumann 1978). The progestational effect of norethisterone enantate is also reflected in a sustained elevation of basal body temperature. The change in the hormonal spectrum from androgenic to progestogenic activity (19-nortestosterone to norethisterone) is achieved by the removal of the angular methyl group at C19 and the introduction of the ethinyl group at C17α (Figure 5.1).

Norethisterone, like most other nortestosterone derivatives, exhibits some androgenic action, while oestrogenic effects have been noted in animal experiments (Larrea et al, 1984). The latter is thought to be due to an affinity of norethisterone metabolites for oestrogen receptors (Kuhl, 1990, Oropeza et al, 1994). Norethisterone also exhibits anti-gonadotropic properties (Neumann, 1978). These anti-gonadotropic properties are more consistent with an oestrogenic (Larrea et al, 1984) or androgenic (Perez-Palacios et al, 1981), rather than a progestogenic, mode of action. Some investigators have found small amounts of ethinyloestradiol in the circulation and urine after oral administration of norethisterone but they are considered to be clinically insignificant (Stanczyk and Roy, 1990). Further support for an oestrogenic mode of action comes from Jones and Edgren (1973) who showed that the vaginal epithelium in rats underwent cornification (an oestrogen-mediated phenomenon) following oral administration of norethisterone.

EFFECT ON ENDOGENOUS HORMONE PARAMETERS

In two studies on the effect of the norethisterone enantate 200mg depot injection on serum hormone levels, measurements were done weekly (Saleh et al, 1983) and daily (Weiner and Johansson, 1976) over a three month period or until ovulation occurred, respectively. Findings were consistent and showed the mean serum 17β-oestradiol and progesterone measurements to be in the follicular phase range (17β-oestradiol between 100 and 200pg/ml and progesterone between 1 and 2 ng/ml). Luteinising hormone (LH) and Follicle Stimulating Hormone (FSH) were never above mid-luteal phase levels. To our knowledge, no studies have been conducted on the effect of postnatal administration of norethisterone enantate on serum hormone concentrations. Figure 5.2 is a hypothetical example of this effect.

SIDE EFFECTS

Minor side effects in women using hormonal contraceptive agents are common (Fraser and Weinberg, 1981). Although minor, they can still cause major concern, particularly with an agent like norethistrone enantate that cannot be quickly removed from the system once injected (Table 5.1). Although some authors (Sapire, 1990, Guillebaud, 1994) do not recommend using injectable progestogen contraceptive agents in women

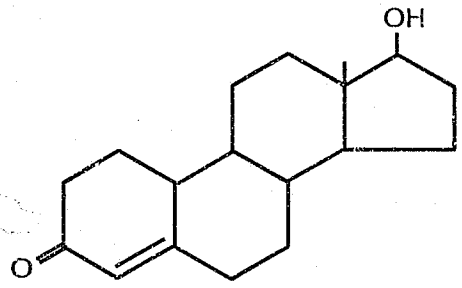
no have a history of severe endogenous depression, there is little evidence to date to support this recommendation (Westhoff et al, 1995).

Table 5.1 Common side effects of Nur-Isterate®*

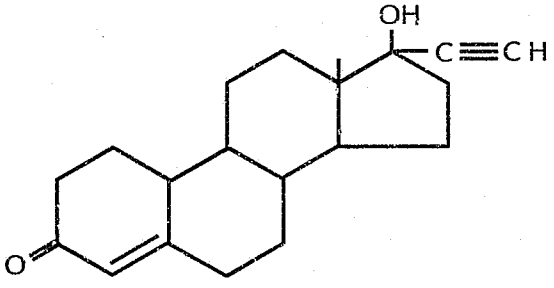
Side effect	*Comment*
Irregular menses	The most common side effect affecting 47% of women (Sapire, 1990). Bleeding is usually infrequent and light. There is some evidence that prolonged bleeding may occur if long-acting injectable progestogen contraceptives are given immediately after childbirth (Murphy, 1979, Sapire, 1991).
Amenorrhoea	After one year of treatment, 10-25% of women experience amenorrhoea of three months duration (WHO Task Force, 1978).
Headache	Seven percent of women experience headaches (Sapire, 1990).
Weight gain	Four percent of women complain of weight gain (Fraser and Weinberg, 1981).
Possible delayed return to fertility	The mean time for return of ovulation after using Nur-Isterate® is 2-6 months (Weiner and Johansson, 1976, Garza-Flores et al,1985). Fotherby et al (1984) showed that 52.5% of women fell pregnant in the six months following discontinuation (nine months after the last injection). This is only slightly lower than normal pregnancy rates.
Acne	Due to androgenic properties (Neumann, 1978).

*These side effects are common to other depot progestogen contraceptive agents in greater or lesser degrees.

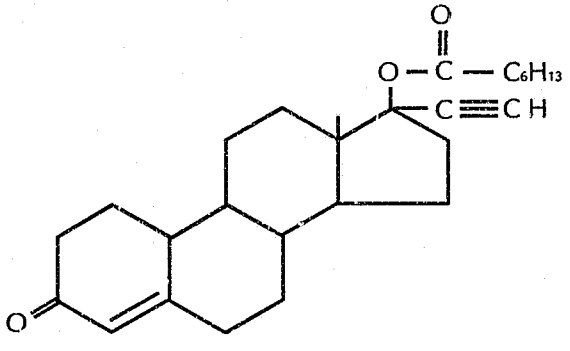
Figure 5.1 Structure of 19-Nortestosterone, Norethisterone and Norethisterone enantate



19 - Nortestosterone

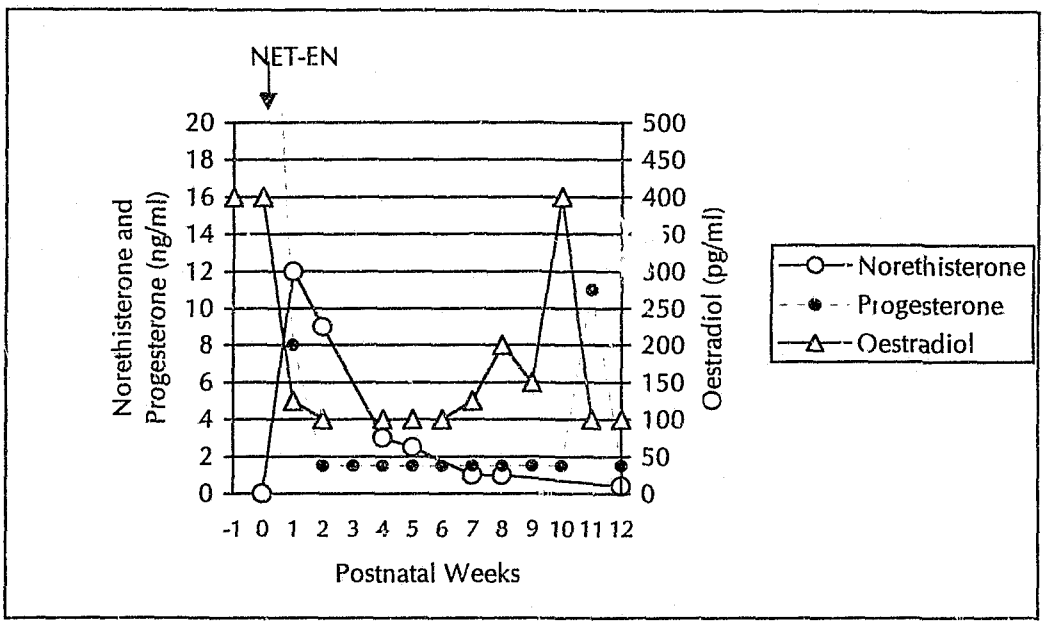


Norethisterone (NET)



Norethisterone enantate (NET-EN)

Figure 5.2 An example* of the hormone profile in non-lactating women receiving NET-EN after delivery.



*There are large inter- and intra-individual variations in serum concentrations of natural and synthetic sex steroids (Kuhl, 1990). Howie et al (1982) showed that the mean time to the first menses is ± 8 weeks (10.8 weeks to first ovulation) in formula-feeding women and ±32.5 weeks (36.4 weeks to first ovulation) in breast-feeding women, with wide variations in the latter group. In women exclusively breast-feeding, serum oestradiol and progesterone levels may remain low until weaning occurs.

5.3.3 CONCLUSIONS

Norethisterone enantate is a potent progestogen derived from19-nortestosterone. It also has androgenic and oestrogenic properties. Norethisterone enantate is theoretically capable of inducing or preventing postnatal mood disturbance by virtue of these diverse hormonal properties. To our knowledge there is no data on psychological symptomatology and hormone profiles in women using long-acting norethisterone enantate for immediate postpartum contraception.

In this trial, women were randomised to receive 1ml norethisterone enantate (200mg) or 1ml normal saline placebo by deep intramuscular injection, once only.

5.4 INSTRUMENTS

5.4.1 THE EDINBURGH POSTNATAL DEPRESSION SCALE (EPDS)

The Edinburgh Postnatal Depression Scale (EPDS) (Cox et al, 1987) (Appendix 1) was used as a subjective report of the women's well being in a modified format (Appendix 2). The EPDS was validated in women from the same population as the trial population (see Chapter 4). Reading of the questionnaire to participants was shown to give valid results against DSM-IV criteria, and a threshold of 11/12

identified 100% of women with major depression and 70.6% of women with minor depression.

5.4.2 THE MONTGOMERY-ÅSBERG DEPRESSION RATING SCALE (MADRS)

The Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) (Appendix 3) was selected as the single objective measure due to its sensitivity to change and the relatively small emphasis placed on somatic symptoms, which theoretically make it a useful scale for the postnatal period (Harris et al, 1989b). In addition, it has been found to perform better than other conventional depression rating scales, namely the Beck Depression Inventory and the Wakefield Inventory (Kearns et al, 1982). The MADRS is a ten-item scale with each item scoring a minimum of 0 and a maximum of six. Thresholds of 18/19 and 9/10 were used to categorise women at risk of major and major/minor depression respectively. A similar process has been used by other researchers, at slightly different thresholds (Snaith et al, 1986, Harris et al, 1989b).

5.4.3 THE SEVERITY OF PSYCHOSOCIAL STRESSORS SCALE

Psychosocial stressors were classified for each participant according to the DSM-III-R Severity of Psychosocial Stressors Scale (American Psychiatric Association, 1989).

For analysis, codes were grouped to form two categories of stressors: none to moderate (low) and severe to catastrophic (high) (Figure 5.3).

Figure 5.3 Severity of Psychosocial Stressors Scale for adults (DSM-III Classification)

Code	Term	Examples of stressors	
		Acute events	**Enduring circumstances**
1	None	No acute events that may be relevant to the disorder	No enduring circumstances that may be relevant to the disorder
2	Mild	Broke up with boyfriend; started or graduated from school; child left home	Family arguments; job dissatisfaction; residence in high-crime neighbourhood
3	Moderate	Marriage; marital separation; loss of job; retirement; miscarriage	Marital discord; serious financial problems; trouble with boss; being a single parent
4	Severe	Divorce; birth of first child	Unemployment; poverty
5	Extreme	Death of spouse; serious physical illness diagnosed; victim of rape	Serious chronic illness in self or child; ongoing physical or sexual abuse
6	Catastrophic	Death of a child; suicide of spouse; devastating natural disaster	Captivity as hostage; concentration camp experience
0	Inadequate information		

5.4.4 THE PERSONAL EXPERIENCES QUESTIONNAIRE

The Personal Experiences Questionnaire (Appendix 8) was designed by an Australian group for inquiry into sexual health in postmenopausal women (Dennerstein et al, 1997). It is a structured self-report questionnaire that consists of a range of questions regarding sexual function. Most of the answers are rated on a scale of one to five. Due to the small sample size, the answers were grouped into three categories where a rating of one/two meant "not much", three was "a moderate amount" and four/five was "very much". Although this questionnaire was not designed for the postnatal period, the questions are suitable for investigation into female sexuality at any time.

5.5 STUDY DESIGN

This study was a randomised placebo-controlled double-blind trial.

5.5.1 RANDOMISATION

Participants in the study were randomly allocated to receive a single dose of norethisterone enantate 200mg (1ml) or a 1ml normal saline placebo by intra-muscular injection. Randomisation was done in blocks of four as described by

Altman (1991) using a random number table so that the numbers in each group were approximately equal throughout the trial.

5.5.2 PROCEDURE

All data were collected prospectively and recorded on data collection forms (Appendix 5). The primary researcher (TAL) interviewed consenting women at enrolment, one week, six weeks and three months after delivery. The EPDS and MADRS were administered at each visit. The presence of headaches, backache, exhaustion, pain or other symptoms, as well as the mode of infant feeding, was noted. In addition, participants were asked to keep a daily diary regarding their bleeding after delivery. At the last interview, the women were asked when, if at all, their interest in sex had returned, and this was recorded as weeks' post-partum. Women who were clinically depressed at three months postpartum were referred to a psychiatrist for the appropriate treatment.

The presence of psychosocial stressors was recorded throughout the three-month period. Final assessment of stressors was made at the last visit and categorised according to DSM-III-R criteria (American Psychiatric Association, 1989). Participants from randomisation numbers 91 to 173, excluding those who failed to return for follow-up at three months postpartum and those who were unable to read, were asked to complete the self-report Personal Experiences Questionnaire at three months postpartum (67 women).

Blood and saliva specimens were taken at the six-week visit, centrifuged and stored at –70°C until completion of the data collection stage of the trial. Ten minutes prior to taking the saliva specimen, the women were asked to rinse their mouths with 30mls of water. Specimens were analysed for various hormone parameters.

5.5.3 CONTROL OF BLINDING

The participant and the interviewer were both blind to the allocation of treatment and placebo (double-blind). Preparation of the trial medication and the randomisation code was the responsibility of an author (GJH) not involved in the clinical assessment of the women. The syringes for injection were masked with tape, such that the contents could not be ascertained, and were administered intra-muscularly by another author (MDJ) or by a nursing sister not directly involved with the trial. Injections were warmed slightly in the palm of the hand before administration, and administered slowly (over two minutes), so as to prevent any guessing of their contents based on the different viscosities of the saline and test medication.

Various reports have shown that injectable progestogens cause increased bleeding when given postpartum (Murphy, 1979, Sapire, 1991). Participants were instructed to consult a doctor not involved in the study if bleeding was considered a problem. This precaution ensured that the interviewer remained blind to any potential difference in bleeding patterns between the two groups.

5.6 OUTCOME MEASURES

5.6.1 PRIMARY OUTCOME MEASURES

In general, a broad definition of postnatal depression was used that ignores the cause or the timing of onset of the depression. The primary outcome measures were depression scores as rated by the MADRS and the EPDS at six weeks and three months postpartum. These rating scales are not designed for the diagnosis of depression. However, for the purpose of this study, categorical variables were created by allocating thresholds to define major depression (MADRS > 18) and major/minor depression combined (MADRS > 9, EPDS > 11) (see Instruments). Serum progesterone, 17β-oestradiol and testosterone levels were compared between depressed and not depressed women, controlling for mode of delivery.

5.6.2 SECONDARY OUTCOME MEASURES

Secondary outcome measures included mode of infant feeding, return of libido (as week when first interested in sexual activity) and vaginal bleeding. A subgroup of 67 women completed the Personal Experiences Questionnaire, a more detailed inquiry into sexual activity.

5.7 STATISTICAL METHODS

5.7.1 SAMPLE SIZE

One hundred and eighty women were recruited. The sample size was calculated using Altman's nomogram (Altman, 1991) for continuous variables ($\alpha = 0.05$, $1-ß = 80\%$). For this calculation, the MADRS score was considered the primary outcome measure. A clinically relevant difference between the treatment and placebo groups in the mean MADRS score was considered to be three. The standard deviation (SD) was calculated using MADRS scores of the first 50 women in the study at 6 weeks postpartum (SD = 7.81).

5.7.2 DATA ANALYSIS

There were no post-randomisation exclusions. The randomisation code was broken only after the data were captured and checked. Women were analysed in the groups to which they were allocated (intention-to-treat), including eight women who had subsequently elected to use a progestogenic contraceptive agent. The MADRS and EPDS scores were analysed independently of each other as continuous and categorical variables. Continuous data were analysed by Student's t test or, when the subgroup for analysis was < 30, the U-test of Mann-Whitney. Categorical data was

analysed using the $\chi 2$ test with Fisher's exact test (two-tailed) where appropriate. The significance of primary outcomes and secondary outcomes was assessed at $p=0.05$. Relative risks (RR) and 95% confidence intervals (CI) were calculated for outcomes using Statistical Analysis Systems (SAS) version 6.09.

Due to a chance discrepancy in the mode of delivery between the progestogen and placebo groups, results of the depression scales have been shown separately for mode of delivery. All analyses performed for depression scales, secondary outcomes and somatic complaints have been corrected for this discrepancy, for continuous variables, by performing an analysis of co-variance where mode of delivery is the co-variant, and for categorical variables, by performing the Cochran-Mantel-Haenszel test. Serum hormone calculations are, however, not controlled for mode of delivery, as when only these women were considered (134 women had blood samples taken), the groups were comparable with respect to this variable.

5.8 LABORATORY METHODS

Assays were performed by the South African Institute of Medical Research (SAIMR) on the serum specimens using chemiluminescent immunoassays for progesterone, 17β-oestradiol and testosterone (Chiron Diagnostics). Prior difficulties when assaying saliva specimens, including damage to SAIMR equipment, led to an understandable

reluctance to process the saliva specimens from this trial. As a result, these specimens remain frozen at -70°C.

5.9 ETHICAL CONSIDERATIONS

Contraception in breast-feeding women generally becomes necessary from about six weeks postnatal, whereas in non-lactating women it becomes necessary almost immediately after delivery (Wang and Fraser, 1994). Whilst manufacturers of progestogen contraceptive agents caution against their use in the immediate postnatal period because of the possibility of breakthrough bleeding, the experience at our institution and others (Sapire, 1991, Guillebaud, 1994) is that post-delivery provides a good opportunity to commence family planning and the option of progestogen contraception is used extensively. All women participating in the trial were using non-hormonal contraception in addition to the trial medication so that the contraceptive efficacy of the trial medication was not an issue. A written (Appendix 4) and verbal explanation was given of the fact that the injection might not be of any benefit to the woman and that side effects might be experienced. Ethics approval for the trial was obtained from the University of the Witwatersrand Committee for Research on Human Subjects.

CHAPTER SIX RESULTS

6.1 RECRUITMENT AND FOLLOW-UP

Ninety women were enrolled to each group. There were no significant differences in the timing of the follow-up visits. The first visit was held at a mean of 9.9 days postpartum (n = 168), the second visit at a mean of 7.0 weeks postpartum (n = 163) and the third follow-up visit at a mean of 12.5 weeks postpartum (n = 168). Women who missed their follow-up appointments were contacted by telephone, where possible. If a woman was unable to come to the hospital for her visit, for example, if she could not get off work, the interview was held telephonically. When it was not possible to contact a woman by telephone, the interviewer (TAL) visited her at home (Table 6.1).

Three month follow-up was 93.3% overall, with 96.7% and 90% follow-up in the progestogen group and placebo group, respectively. An imbalance in the follow-up between the two groups (86 in the progestogen group and 77 in the placebo group) was present at six weeks (p = 0.03, Fisher's Exact test). When controlled for mode of delivery, follow-up at six weeks was poorer in the group that delivered vaginally (89.0% in vaginal group Vs 94.1% in Caesarean group). Women who missed the six

week visit were more likely to be employed (78.6% Vs 47.1%, p=0.028) and less likely to have undergone tubal ligation after delivery (28.6% Vs 70%, p=0.0028). There were no other differences in baseline characteristics between the women who attended the six-week visit and those who missed the visit.

Table 6.1. Follow-up of women in the progestogen (n=90) and placebo (n=90) groups.

Group	Interview held			Interview missed	P (Chi-square)	P (interview held Vs missed)[1]
	Hospital	Telephone	Home			
Baseline						
Progestogen	90	0	0	0		
Placebo	90	0	0	0		
One week					0.592	0.390
Progestogen	63	16	7	4		
Placebo	63	12	7	8		
Six weeks					0.110	0.030[2]
Progestogen	65	14	7	4		
Placebo	56	15	6	13		
Three months					0.092	0.065
Progestogen	67	10	10	3		
Placebo	56	15	10	9		
Total (%)	551(76.5)	82 (11.4)	47 (6.5)	40 (5.6)		

[1] Corrected for mode of delivery using the Cochran-Mantel-Haenzel Test
[2] P<0.05 is considered a statistically significant difference

Significant differences were present between those who missed and those who attended the six-week visit with regard to categorical variables for major/minor depression (MADRS>9, EPDS>11) at baseline, although not for major depression

(MADRS > 18) alone and not for continuous variables (Appendix 7). A higher proportion of those who missed the six-week visit was depressed at the baseline visit. The mean EPDS score at three months was significantly higher in the group that missed the six-week visit but who subsequently returned at three months (six women), than the group that attended the six-week visit. This suggests that the imbalance in follow-up at six weeks could influence the results presented in the direction of decreasing their significance.

6.2 BLINDING

Blinding was compromised in only one woman who complained of excessive bleeding at the three-month interview, leading the interviewer (TAL) to suspect that she may belong to the progestogen group. Although this was confirmed when the randomisation code was broken, it is unlikely to introduce bias into the assessment of depression, as the hypothesis was bi-directional. The woman scored high on both depression scales at six weeks and three months.

6.3 CHARACTERISTICS OF THE SAMPLE

Overall, characteristics of the groups were comparable except for a chance discrepancy in mode of delivery (Table 6.2). Twenty-four women in the progestogen group and 10 women in the placebo group underwent Caesarean section for delivery of their baby ($p=0.013$, Fisher's Exact test). Consequently, results of primary outcomes have been shown separately for mode of delivery (see Chapter 5.7, statistical methods).

The study protocol was violated in five of the ninety women given norethisterone enantate by injection and three of the ninety women given normal saline placebo, who received an additional progestogen contraceptive during the three month study period. Of the five women in the progestogen group, two received depot medroxyprogesterone acetate (Depo-Provera®, Pharmacia & Upjohn) for contraception at delivery (after enrolment and randomisation) by junior nursing staff in the postnatal ward and three received Depo-Provera® at six weeks at a family planning clinic. Of the three women in the placebo group, one woman received Depo-Provera® at delivery, one woman received depot norethisterone enantate (Nur-Isterate®, Schering) at six weeks and one woman received oral levonorgestrel (Microval®, Akromed) at seven weeks. All the women who received Depo-Provera®

after delivery, that is, two women in the progestogen group and one woman in the placebo group, had high depression scores at the six-week interview on the EPDS.

6.4 PRIMARY OUTCOME MEASURES

6.4.1 DEPRESSION

In comparison to the placebo group, those women receiving the progestogen injection were at a significantly greater risk of depression at six weeks postpartum according to mean depression scores on objective (MADRS) ($p = 0.0111$, analysis of co-variance) and subjective (EPDS) ($p = 0.0022$, analysis of co-variance) measures (Table 6.3). The relative risk (RR) of scoring greater than nine on the MADRS and greater than 11 on the EPDS for women in the progestogen group at the six week interview was 2.58 (95% CI 1.28-5.18) and 3.02 (95% CI 1.52-6.00) respectively. There was no significant difference in the number of women scoring greater than 18 on the MADRS at any time (major depression). This may be due to the small sample sizes concerned. No significant difference in depressive symptomatology was evident at three months on either of the scales.

Table 6.2 Baseline characteristics of the progestogen and placebo groups expressed as mean [SD] or total (%).

	Progestogen		*Placebo*		*p*
	n		*n*		
Age	90	32.6 [5.9]	90	32.3 [5.0]	0.684
Parity	90	4.1 [1.5]	90	3.8 [1.2]	0.247
Married/co-habitation	90	69 (76.7)	90	73 (90.1)	0.589
Employed	86	41 (47.7)	86	44 (51.2)	0.760
Leave for employed women (wks)	41	12.8 [7.8]	44	11.3 [9.2]	0.412
Household income < R2000/mth	89	54 (60.7)	89	61 (68.5)	0.347
Contraception	88		87		0.268
- sterilisation		62 (70.5)		54 (62.1)	
- non-hormonal		21 (23.9)		30 (34.5)	
-other progestogens (protocol violations)		5 (5.7)		3 (3.4)	
Caesarean section	90	24 (26.7)	90	10 (11.1)	0.013*
Hours in labour	86	7.3 [6.7]	88	7.4 [6.4]	0.906
"Coped" with delivery	89	16 (18.0)	88	12 (13.6)	0.537
Hospital stay > 5 days (mother)	90	23 (25.6)	90	17 (18.9)	0.370
Hospital stay > 5 days (baby)	90	18 (20.0)	90	20 (22.2)	0.855
Companion present at delivery	90	27 (30.0)	89	18 (20.2)	0.168
Complications	90	27 (30.0)	90	24 (26.7)	0.741
Birth weight of baby	88	2947.7 [571.7]	90	3081.3 [611.0]	0.134
Felt depressed during pregnancy	90	9 (10)	89	7 (7.8)	0.794
Previous postnatal depression	86	8 (9.3)	89	4 (4.5)	0.460
History of other depressive disorder	89	11 (12.4)	89	10 (11.2)	0.460
Family psychiatric history	90	5 (5.6)	90	6 (6.7)	1.000
Previous "maternity blues"	86	10 (11.1)	89	5 (5.6)	0.280
Previous irregular periods	88	14 (15.6)	88	22 (24.4)	0.171
History of premenstrual syndrome	90	7 (7.8)	90	10 (11.1)	0.611
EPDS score at enrolment	89	13.3 [5.8]	90	12.6 [5.4]	0.381
MADRS score at enrolment	89	6.2 [6.6]	89	6.4 [7.3]	0.872
Psychosocial stressors – high	82	19 (23.2)	82	17 (20.7)	0.851

$p < 0.05$ is considered a significant difference between the two groups. p-values were calculated using Student's t-test for continuous variables, and the χ^2–test or Fisher's Exact test for categorical variables.

Table 6.3. Primary outcome measures in the progestogen and placebo group expressed as mean score [SD] and total number of women with depressive symptomatology (%) defined by MADRS > 18 (major depression), MADRS > 9 (major and minor depression) and EPDS > 11 (major and minor depression). Results shown are controlled for mode of delivery.

	Vaginal Delivery		*Caesarean Section*		*Total*		*p*
	Progestogen	*Placebo*	*Progestogen*	*Placebo*	*Progestogen*	*Placebo*	
Six-weeks (n)	62	68	23	9	85	77	
a) Mean MADRS	9.1 [8.1]	5.9 [6.8]	7.5 [9.0]	3.7 [6.7]	8.3 [0.9]*	4.9 [1.1]*	0.0111
b) MADRS > 18	9 (14.5)	4 (5.9)	2 (8.7)	1 (11.1)	11 (13.0)	5 (6.5)	0.158
c) MADRS > 9	28 (45.2)	17 (25.0)	7 (30.4)	1 (11.1)	35 (41.2)	18 (23.4)	0.008[b]
d) Mean EPDS	11.6 [6.0]	8.4 [5.6]	9.6 [6.5]	6.8 [5.1]	10.6 [0.7]*	7.5 [0.8]*	0.0022
e) EPDS > 11	34 (54.8)	19 (27.9)	5 (21.7)[a]	1 (11.1)	39 (45.9)	20 (26.0)	0.002[c]
Three months (n)	63	71	24	10	87	81	
a) Mean MADRS	7.3 [8.3]	5.8 [6.9]	5.3 [7.2]	8.8 [7.9]	6.6 [0.9]*	6.1 [1.0]*	0.573
b) MADRS > 18	7 (11.1)	5 (7.0)	1 (4.2)	2 (20.0)	8 (9.2)	7 (8.6)	0.895
c) MADRS > 9	20 (31.7)	20 (28.2)	4 (16.7)	3 (30.0)	24 (27.6)	23 (36.4)	0.930
d) Mean EPDS	9.9 [6.7]	8.4 [5.6]	8.2 [6.5]	10.7 [6.2]	9.3 [0.7]*	8.5 [0.8]*	0.659
e) EPDS > 11	24 (38.1)	20 (28.2)	4 (16.7)	4 (40.0)	28 (32.2)	24 (29.6)	0.573

P < 0.05 is considered a significant difference between the two groups. *Results expressed as Least squares means [SEM]. p-values were calculated using the Cochran-Mantel-Haenszel test except for continuous variables (*f*) where analysis of co-variance was used.

[a] *P = 0.0075, Vaginal Vs Caesarean delivery*
[b] *RR 2.58, 95% CI 1.28-5.18*
[c] *RR 3.02, 95%CI 1.52-6.00*

6.4.2 HORMONE PARAMETERS

Of the 134 participants who had blood taken at the 6-week interview, 73 had received the progestogen contraceptive agent after delivery and 61 had received the placebo. All serum hormone concentrations were within normal physiological ranges. Table 6.4 shows the mean serum hormone values, standard deviations [SD] and p-values for each group overall and controlled for mode of infant feeding.

17β-OESTRADIOL

Mean serum 17β-oestradiol levels were significantly lower in the progestogen group compared to the placebo group (101.83 [98.42] pmol/L Vs 182.91 [138.63] pmol/L, p=0.0002, Student's t-test). As would be expected, serum 17β-oestradiol was significantly higher in formula-feeding women than breast-feeding women (232.41 [176.59] pmol/L Vs 112.87 [95.15] pmol/L, p=0.0016, U test of Mann-Whitney).

PROGESTERONE

Mean serum progesterone levels were not significantly different between the progestogen and placebo groups as a whole (0.64 [0.65] nmol/L Vs 1.76 [5.24] nmol/L, p=0.1028, Student's t-test). However, amongst formula-feeding women, mean serum progesterone was significantly lower in the progestogen group

compared to the placebo group (0.83 [0.65] nmol/L Vs 7.07 [12.11] nmol/L, $p=0.0394$, U test of Mann-Whitney).

TESTOSTERONE

There were no significant differences in mean serum testosterone levels between the progestogen and placebo groups overall, or when controlled for mode of infant feeding.

17β-OESTRADIOL:PROGESTERONE RATIO

The ratio of 17β-oestradiol to progesterone was significantly lower in the progestogen group compared with the placebo group (2440.9 Vs 3660.5, $p=0.0245$, Student's t-test), the main difference occurring amongst breast-feeding participants (2078.2 Vs 3639.7, $p=0.0030$, Student's t-test).

Table 6.4. Mean serum hormone values in the progestogen and placebo groups at six weeks postpartum, controlled for mode of infant feeding.

Group	Progestogen (A)		Placebo (B)		p (A Vs B)	Total (A + B)	
	n	Mean [SD]	n	Mean [SD]		n	Mean [SD]
17β-Oestradiol (pmol/L)							
Breast-feeding	54	76.34 [53.01]	49	152.58 [114.31]	0.0001	103	112.87 [95.15]
Formula-feeding	18	179.06 [154.49]	9	339.12 [177.25]	0.0569	27	232.41 [176.59]
p (Breast Vs Formula)		0.0095		0.0021			0.0016
Whole group	73	101.83 [98.42]	61	182.91 [138.63]	0.0002	134	138.74 [124.73]
Progesterone (nmol/L)							
Breast-feeding	54	0.56 [0.64]	49	0.60 [0.56]	0.7421	103	0.58 [0.60]
Formula-feeding	18	0.83 [0.65]	9	7.07 [12.11]	0.0394	27	2.91 [7.37]
p (Breast Vs Formula)		0.0236		0.0014			0.0004
Whole group	73	0.64 [0.65]	61	1.76 [5.24]	0.1028	134	1.15 [3.59]
Testosterone (nmol/L)							
Breast-feeding	54	0.94 [1.44]	49	1.62 [2.85]	0.1223	103	1.26 [2.24]
Formula-feeding	18	1.47 [2.15]	9	0.84 [0.54]	0.4072	27	1.26 [1.79]
p (Breast Vs Formula)		0.0077		0.1679			0.4855
Whole group	73	1.07 [1.63]	61	1.47 [2.57]	0.2760	134	1.25 [2.11]
E_2:Prog Ratio							
Breast-feeding	54	2078.2 [1701.9]	49	3639.7 [3162.6]	0.0030	103	2821.0 [2612.7]
Formula-feeding	18	3634.0 [4312.5]	9	3614.7 [4836.8]	0.4404	27	3627.5 [4399.8]
p (Breast Vs Formula)		0.2494		0.2013			0.7719
Whole group	73	2440.9 [2650.9]	61	3660.5 [3403.7]	0.0245	134	2996.0 [3066.0]

A p-value of <0.05 was considered statistically significant. p-values were calculated using Student's t-test unless $n<30$, in which case the U-test of Mann-Whitney was used.

6.5 SECONDARY OUTCOME MEASURES

The number of days of vaginal bleeding during the three month study period was significantly greater in the progestogen group when compared to the placebo group (25.5 versus 14.0, p=0.0001, Fisher's Exact test), as was the number of women who considered the bleeding troublesome (27 versus 8, p=0.001, Fisher's Exact test) (Table 6.5). There was no correlation between number of bleeding days and depression score on either scale. No significant differences between the placebo and progestogen groups were found in respect of mode of infant feeding and libido (week when first interested in sexual activity). The most common reason given in both groups for stopping breast-feeding was "not enough milk".

Table 6.5. Secondary outcome measures in the progestogen and placebo group expressed as mean [SEM] and total (%).

	Progestogen		*Placebo*		*p*
	n		*n*		
Libido					0.604*
- < 8 weeks postpartum	77	16 (20.8)	72	19 (26.4)	
- 8-12 weeks postpartum	77	10 (13.0)	72	11 (15.3)	
- none	77	51 (66.2)	72	42 (58.3)	
Breast-feeding (exclusive or partial)					
- on day 1	90	85 (94.4)	90	84 (93.3)	1.000∞
- at 6 weeks postpartum	86	63(73.3)	80	64 (80.0)	0.361∞
- at 12 weeks postpartum	87	59 (67.8)	81	61 (74.4)	0.398∞
- "not enough milk"	87	24 (26.7)	81	14 (17.2)	0.374∞
Vaginal bleeding (days)					
- after delivery	85	25.1 [2.0]	79	13.8 [2.8]	0.0011*f*
- at 6 weeks	85	26.3 [1.5]	79	17.0 [2.0]	0.0003*f*
- at 12 weeks	85	34.9 [2.1]	79	21.0 [2.9]	0.0001*f*
Considered bleeding troubling	85	27 (31.8)	80	8 (10.0)	0.001∞

*$p < 0.05$ is considered a significant difference between the two groups
*χ^2–test, ∞ Fisher's Exact test, *f* Student's t-test

6.6 SOMATIC COMPLAINTS

Somatic complaints including headaches, backache and pain occurred with similar frequency in both groups. However, significantly more women in the progestogen group reported being exhausted at one week ($p = 0.035$, Cochran-Mantel-Haenszel test) and three months ($p = 0.038$, Cochran-Mantel-Haenszel test) than in the placebo group (Table 6.6).

Table 6.6. Comparison of somatic complaints at one week, six weeks and three months postpartum.

	Headaches		*Backache*		*Exhaustion*		*Pain*[1]		*Other*[2]	
	n	*p*	*n*	*p*	*n*	*p*	*n*	*p*	*n*	*p*
One-week										
Progestogen	19	0.063	20	0.486	19	0.035*	26	0.496	11	1.000
Placebo	30		24		8		21		11	
Six weeks										
Progestogen	27	0.866	21	1.000	13	1.000	5	0.266	8	0.784
Placebo	23		20		11		9		6	
Three months										
Progestogen	27	0.225	20	0.569	16	0.038*	4	0.524	10	0.165
Placebo	18		15		6		6		4	

*$p < 0.05$ is considered a statistically significant difference. P-values were corrected for mode of delivery by using the Cochran-Mantel-Haenszel test.

[1] Including abdominal pain and pain from abdominal or vaginal sutures.
[2] Including dizziness, constipation, nausea, etc

6.7 THE PERSONAL EXPERIENCES QUESTIONNAIRE

Thirty-seven women in the progestogen group and 30 in the placebo group received this questionnaire at three months postpartum. There were no significant differences with respect to baseline characteristics between the two groups. However, in keeping with the main findings of the trial, significantly more women in the progestogen group were depressed at six weeks postpartum, compared with the placebo group. In addition, women in the progestogen group had significantly more bleeding days than the placebo group.

Due to the sensitive nature of the questions, response rate per question varied. The maximum response rate, to a question relating to sexual frequency in the past two weeks, was 65.7% (44/67). The least answered questions related to the relationship of women with their partners. There were no significant differences between the progestogen and placebo groups with respect of sexual interest or functioning, including specific questions on painful intercourse and lubrication. Likewise, there was no association between sexual functioning and mode of infant feeding. As would be expected, depression was significantly associated with sexual function, with depressed women (MADRS > 9 or EPDS > 11) more frequently reporting no sexual interest by three months postpartum ($p = 0.033$, χ^2 test), dissatisfaction with their partners as friends ($p = 0.001$, χ^2 test), less arousal during sex ($p = 0.031$, χ^2 test), pain on intercourse ($p = 0.005$, χ^2 test) and a fear of sexually related infections ($p = 0.021$, χ^2 test). Women who underwent Caesarean section for delivery of their baby were

less likely to enjoy sex at three months postpartum ($p=0.018$, χ^2 test). Sterilisation had no effect on libido in this sample.

6.8 OTHER FINDINGS

6.8.1 HORMONES VERSUS DEPRESSION

There was no significant difference in the mean serum progesterone, 17β-oestradiol, testosterone or 17β-oestradiol:progesterone ratio between the depressed and not depressed women at six weeks postpartum on either depression scale (see Table 6.7) (whether they were breast-feeding or formula-feeding) overall or for either randomisation group. Findings within the group of depressed women reflected the overall differences between the progestogen and placebo groups. When the placebo group was analysed separately, women who were depressed according to the MADRS at the six-week interview had a significantly higher serum 17β-oestradiol level (233.04 pmol/L Vs 168.48 pmol/L, $p=0.0467$, U test of Mann-Whitney) than well women. Hormone parameters at six weeks were not associated with depression scores at any of the other visits, and Pearson's correlation coefficients were consistently not significant.

Table 7. Mean serum hormone values for depressed (MADRS > 9) and not depressed women at six weeks postpartum, overall and for the progestogen and placebo groups separately.

Group	Progestogen (A)		Placebo (B)		P (A Vs B)	Total (A+B)	
	n	Mean [SD]	n	Mean [SD]		n	Mean [SD]
17β-Oestradiol (pmol/L)							
Depressed	29	107.67 [94.69]	15	233.04 [144.22]	0.0003	44	150.40 (132.66)
Not depressed	44	97.98 [94.69]	45	168.48 [135.21]	0.0055	89	133.60 (121.51)
P (depressed Vs not dep)		0.5420		0.0467			0.4688
Progesterone (nmol/L)							
Depressed	29	0.56 [0.51]	15	1.84 [4.27]	0.2329	44	1.10 (2.54)
Not depressed	44	0.69 [0.73]	45	1.70 [5.62]	0.2383	89	1.20 (4.04)
P (depressed Vs not dep)		0.6079		0.5308			0.7580
Testosterone (nmol/L)							
Depressed	29	1.12 [1.74]	15	2.06 [4.16]	0.2050	44	1.44 (2.79)
Not depressed	44	1.04 [1.57]	45	1.02 [0.43]	0.9318	89	1.03 (1.14)
P (depressed Vs not dep)		0.9412		0.9249			0.3561
E_2:Prog Ratio							
Depressed	29	2700.4 [2837.5]	15	4607.9 [3527.5]	0.0766	44	3350.7 (318.28)
Not depressed	44	2269.9 [2539.4]	45	3420.1 [3348.5]	0.0718	89	2851.5 (3015.3)
P (depressed Vs not dep)		0.4007		0.2492			0.3794

A p-value of <0.05 was considered statisticaliy significant. P-values were calculated using Student's t-test unless $n<30$, in which case the U-test of Mann-Whitney was used.

6.8.2 MODE OF INFANT FEEDING VERSUS DEPRESSION

Overall, the mode of infant feeding was not associated with depression on either depression scale. However, in the placebo group, breast-feeding women were significantly less prone to depression at six weeks postpartum as rated by the EPDS ($p=0.007$, Fisher's Exact test, RR=0.215, 95%CI 0.070 – 0.660) and the MADRS ($p=0.018$, RR=0.093, 95%CI 0.013 –0.667) compared to those formula-feeding their babies. These results were slightly enhanced in the women exclusively breast-feeding. By contrast, in the progestogen group, there was no association between the mode of infant feeding and depression at six weeks postpartum.

6.8.3 OTHER ASSOCIATIONS

PSYCHOSOCIAL STRESSORS

Women with severe psychosocial stressors ($p<0.001$) were at a greater risk of depression in both groups at baseline, one week, six weeks and three months.

PREVIOUS DEPRESSION

A history of depression (including postnatal depression) was, likewise, associated with higher mean depression scores at one week, six weeks and three months postpartum. Table 6.8 shows the relationship between previous depression and postnatal depression as a categorical variable in the study sample. Women who delivered vaginally were more likely to experience a recurrent episode of depression than women undergoing Caesarean section for delivery.

DEPRESSION SCORES AT ONE WEEK POSTPARTUM

Of all the women with an EPDS > 11 at the one-week interview, 55.3% (42/76) were depressed at the six-week interview. In addition, 75% (42/56) of women who were depressed at six weeks (EPDS > 11) had high depression scores at the one-week interview. This association is significant ($p = 0.0039$ using McNemar's test of symmetry).

Table 6.8. The relationship between psychiatric history and postnatal depression.

	Psychiatric history						
	Positive		Negative		p	RR	95%CI
Six weeks	n	depressed	n	depressed			
a) EPDS>11	32	15 (47%)	130	44 (34%)	0.141	1.84	0.82-4.14
b) MADRS>9	32	16 (50%)	130	37 (28%)	0.017*	2.58	1.18-5.63
c) MADRS>18	32	6 (19%)	130	10 (8%)	0.066	2.65	0.94-7.52
Three months							
a) EPDS>11	31	17 (55%)	137	35 (26%)	0.002*	3.57	1.62-7.87
b) MADRS>9	31	17 (55%)	137	14 (10%)	0.000*	4.40	2.00-9.71
c) MADRS>18	31	5 (16%)	137	10 (7%)	0.129	2.35	0.78-7.10

*P<0.05 is considered a statistically significant difference. p-values were calculated using the Cochran-Mantel-Haenszel test.

CHAPTER SEVEN DISCUSSION

O'Brien and Pitt (1994) note that obstetricians virtually never prescribe antidepressants and, as postnatal depression usually starts three weeks or more after delivery, they are usually not involved in the management thereof. They deduce that antidepressant treatment is far more likely than hormonal therapy. However, what they fail to consider is that a large proportion of postnatal women is already receiving "hormonal therapy" by means of hormonal contraception. The majority of hormonal contraception used postpartum contain progestogens only. Progestogens have psychoactive properties and the potential to modulate mood. This randomised placebo controlled trial of a contraceptive agent was made possible because contraceptive efficacy was not an outcome measure and participants were using other (non-hormonal) methods of contraception.

7.1 MAIN FINDINGS

7.1.1 FOLLOW-UP

The chance discrepancy in mode of delivery (a greater number of Caesarean sections had been performed in the progestogen group) and the discrepancy in the six-week

follow-up between the two groups could not be anticipated. The women that underwent Caesarean section for delivery were more compliant at the six-week visit than those who had a vaginal delivery, suggesting that there was an association between follow-up and mode of delivery. By correcting the results for mode of delivery as we have done, we may also have partly corrected for the difference in follow-up. In addition, as more women in the treatment group underwent Caesarean section than the placebo group, the depressive effect of the norethisterone enantate may be underestimated. Caesarean section was associated with less depression in this trial (Boyce and Todd (1992) found women who underwent emergency Caesarean section to have higher depression scores). Thirdly, the discrepancy in loss to follow-up at six weeks (4 versus 13) is too small to account for the difference in rates of depression (35 versus 18 for MADRS > 9, treatment versus placebo). Therefore, despite the imbalance in follow-up between the two groups, the evidence presented in favour of a progestogen-associated increase in depressive symptoms is convincing.

7.1.2 NORETHISTERONE ENANTATE AND POSTNATAL DEPRESSION

Our findings suggest that women receiving injectable progestogens after delivery have a two to three time's greater risk of depression in the postnatal period. That this effect had subsided by three months postpartum in this study is probably related to the fact that only a single dose of norethisterone enantate (200mg) was administered. Had the women received another dose, as they would have for contraceptive purposes, it is possible that depressive symptoms may have persisted.

7.1.3 NORETHISTERONE ENANTATE AND HORMONE PARAMETERS

In the postnatal period, lactation, depending on the frequency and duration of breast-feeding, has a profound depressant effect on circulating oestrogen and progesterone levels (Howie et al, 1982). Synthetic progestogens in contraceptive dosages also suppress ovarian hormone secretion by inhibiting pituitary secretion of follicle stimulating hormone and leutinising hormone. There is surprisingly little information available on serum hormone levels following postnatal administration of long-acting progestogen contraceptive agents. Molland et al (1996), in a study on immediate postpartum insertion of long-acting levonorgestrel implants in 14 women formula-feeding their infants reported mean serum 17β-oestradiol levels to be 83.6 pmol/L and mean serum progesterone levels to be 0.95 nmol/L at eight weeks postpartum. To our knowledge, the present study is the only randomised controlled trial comparing serum hormone profiles between women receiving immediate postpartum long-acting progestogen contraception and those receiving placebo. Overall, serum 17β-oestradiol was significantly lower in the progestogen group compared with the placebo group, with the lowest 17β-oestradiol concentration occurring in breast-feeding women receiving the progestogen. Mean serum 17β-oestradiol levels in the group of women comparable to those in the study of Molland et al (that is, those formula-feeding women receiving the progestogen) were twice that found in the their study, although sample sizes are small. Serum progesterone concentrations in the present study were also lower in the progestogen group compared to the placebo

group but reached statistical significance only in formula-feeding women. As in other studies on postnatal depression, hormone parameters failed to correlate with depression scores.

7.1.4 MODE OF INFANT FEEDING, HORMONE PARAMETERS AND POSTNATAL DEPRESSION

In many studies on hormones and postnatal depression the use and/or type (oestrogen and progestogen combined or progestogen only) of hormonal contraception is not mentioned, despite their mood-altering potential. Alder and Cox (1983), in a cohort study, found that women who breast-fed their infants for at least 12 weeks or who used hormonal contraceptive agents had a higher incidence of depression than those who did not do so. On the other hand, Harris et al (1989a), in their cohort study, found that breast-feeding women using hormonal contraceptive agents were less prone to depression at six to eight weeks after delivery than those not using hormonal contraceptive agents. We found a negative association between breast-feeding (exclusive and partial) and depression at six weeks in the placebo group only. However, none of the above (contradictory) associations imply causality as the breast-feeding and formula-feeding groups were not allocated at random, and are likely to differ in many respects.

Depression in the placebo group in our trial was associated with higher levels of serum 17β-oestradiol. This is in keeping with the positive association between

depression and formula-feeding in this group, as formula-feeding women are likely to have higher 17β-oestradiol levels due to earlier resumption of ovarian activity (Howie et al, 1982). It is possible that the depression resulted in an inability to breast-feed rather than the other way around as we know that depressed women may experience more problems with breast-feeding (Tamminen, 1989) and may therefore be less likely to continue breast-feeding.

7.1.5 CONTRACEPTION, SEXUALITY AND POSTNATAL DEPRESSION

Progestogens have been associated with improved sexual functioning compared to a placebo in postmenopausal women (Dennerstein et al, 1980). However, in this trial, norethisterone enantate had no effect on sexuality in the first three months postpartum. As would be expected, depressed women in both the progestogen and placebo groups experienced lower sexual interest and activity.

7.2 OTHER FINDINGS

7.2.1 STRESS AND PREVIOUS DEPRESSION

Psychosocial stressors, associated with an increased risk of depression (Brown et al, 1987), are common in South Africa, with high unemployment rates, high crime

rates, poverty, divorce and many single parent families. Stress and a history of an affective disorder are commonly associated with postnatal depression and our findings support this association.

7.2.2 VAGINAL BLEEDING

Prolonged vaginal bleeding when using depot medroxyprogesterone acetate compared to controls has been described previously (Murphy, 1979) and a comparison between postnatal bleeding has been done between medroxyprogesterone acetate and norethisterone enantate depot preparations (Sapire, 1991). However, to our knowledge, bleeding side effects of depot norethisterone enantate has not been compared to placebo. This trial showed vaginal bleeding to occur for a significantly longer duration in the women receiving norethisterone enantate than placebo. As would be expected, a greater number of women in the former group perceived the bleeding to be troublesome.

7.2.3 SOMATIC COMPLAINTS

In contrast to the view that injectable progestogen contraceptive agents are frequently associated with headaches (Sapire, 1990, Guillebaud, 1994), this side effect was no more common in the progestogen group than in the placebo group in this trial. Exhaustion, however, has not been reported previously and occurred with

significantly greater frequency in the progestogen group than the placebo group. This finding may be due directly to progestogen, which are known to have sedative properties (see Chapter Two). Alternatively, the symptom may be associated with depression or, possibly, anaemia due to the prolonged vaginal bleeding in the progestogen group.

7.3 LIMITATIONS OF THE STUDY

For the purpose of this trial, a broad definition of postnatal depression was used, which ignored the timing of onset of the depression and the possibility of the depression being associated with another disorder e.g. thyroid disease. The reason for this was so as not to exclude from the trial the women who suffered from a lability of mood within 48 hours of delivery. However, this means that some cases of pre-existing depression may have been included. As this was a randomised trial, this inclusion would not alter the conclusions of the study.

This trial addresses the role of a potential risk factor in postnatal depression, rather than the aetiology of the disorder. Dalton (1996) has suggested that only naturally occurring progesterone has mood elevating properties and that the synthetic progestogens as found in contraceptives, by suppressing natural progesterone, possibly cause depression. For this reason, the results of this trial, whilst probably generalisable to other progestogen contraceptive agents, are not generalisable to

progesterone. Progesterone supplementation needs to be evaluated in a separate trial.

7.4 SUMMARY AND RECOMMENDATIONS

7.4.1 FINDINGS NOT TO OUR KNOWLEDGE PREVIOUSLY REPORTED

1. Depot norethisterone enantate (200mg), when given within 48 hours of childbirth significantly increased depressive symptoms at six weeks postpartum, on subjective and objective depression scales. The risk of depression at six weeks postpartum was increased by approximately three-fold.
2. Depot norethisterone enantate given within 48 hours of delivery causes suppression of endogenous 17β-oestradiol secretion at six weeks postpartum below levels induced by lactation.
3. Mean serum progesterone was lower in the progestogen group compared to the placebo group but this reached statistical significance only in the formula-feeding women.
4. There was no significant difference in mean serum testosterone concentrations at six weeks postpartum between women in the progestogen and placebo groups.
5. Postnatal administration of norethisterone enantate was associated with significantly greater fatigue at one week and three months postpartum, irrespective of mode of delivery.

6. Norethisterone enantate was not associated with a change in s .ual interest in the first three months postpartum when compared with placebo.
7. In the placebo group, formula feeding was positively associated with depression at six weeks postpartum.
8. The Edinburgh Postnatal Depression Scale, which has not been validated on an African community previously, was found to be a valid screening instrument in our urban South African community at a threshold of 11/12.

7.4.2 CONFIRMATION OF PREVIOUS FINDINGS

1. Postnatal depression was significantly more common in women with severe psychosocial stressors.
2. A previous history of depression was associated with a greater risk of postnatal depression.
3. There was no significant difference in the serum progesterone, 17β-oestradiol, or 17β-oestradiol:progesterone ratio between the depressed (EPDS and MADRS > 9) and not depressed women at six weeks postpartum.

7.4.3 IMPLICATIONS FOR PRACTICE

Long-acting progestogen contraceptive agents appeal to many groups of women in all walks of life. More than 10 million women worldwide use this form of contraceptive agent (Guillebaud, 1994). Depot progestogen contraceptives constitute an important contraceptive option in the postnatal period due to their negligible effect on lactation. Most contraceptive methods have side effects that need to be weighed against the advantage of avoiding unwanted pregnancy. The potential for mood disturbance is a feature common to hormonal methods of contraception in general. Our findings suggest that, as at other times, caution needs to be exercised when using these agents in the postnatal period or in women with a history of depression. The benefits of these methods may be optimised by careful counselling of clients, inquiry about specific risk factors, such as previous depression, and monitoring for individual adverse responses so that appropriate changes may be made. Furthermore, when a woman is diagnosed as being depressed in the postnatal period, a more holistic approach to her mental health is needed, with collaboration between obstetrician/midwife and psychiatrist. Most importantly, women with postnatal depression who are receiving progestogenic contraception should be counselled about using alternative forms of contraception. The increase in depression in our study was reversed by three months postpartum (one month after the next dose of norethisterone enantate would have been due).

7.4.4 RECOMMENDATIONS FOR FURTHER RESEARCH

As this is the first reported randomised trial of postnatal norethisterone enantate, further research into the effects of progestogen contraceptives on postnatal mood needs to be performed to confirm the findings of this trial. Controlled trials of progesterone and oestrogen are also needed to confirm or refute Dalton's (1985, 1989, 1996) and Gregoire et al's (1996) findings, respectively. Due to an expected large placebo effect, trials should be adequately randomised, double blind and placebo-controlled. Ideally, recruitment should be performed prior to delivery and follow-up extended to six months after delivery. A stricter definition of postnatal depression may improve overall results. Researchers studying the safety of postpartum depot progestogen contraception, with particular reference to the newer agents like Norplant® (Molland et al, 1996, Phemister et al, 1995), should include assessment of mood in their studies.

7.5 CONCLUSIONS

Depot norethisterone enantate given within 48 hours of delivery is associated with an increased risk of developing postnatal depression and causes suppression of endogenous 17β-oestradiol secretion at six weeks postpartum below levels induced by lactation. Norethisterone enantate should be used with caution in the postnatal period and in women with a history of depression. In addition, all progestogen contraceptive

agents should be considered to have potentially depressant effects postnatally until evidence is provided to the contrary. Whilst the mechanism of this norethisterone-associated depression may be a result of a progesterone or oestrogen deficiency (only reduced oestrogen levels were demonstrated in this study), there is no sound evidence at this time to support the use of progesterone or oestrogen in the prevention of postnatal depression.

APPENDIX 1

THE EDINBURGH POSTNATAL DEPRESSION SCALE (including scores)

As you have recently had a baby, we would like to know how you are feeling now. Please underline the answer which comes closest to how you have felt in the past 7 days, not just how you feel today.
Here is an example already completed:
I have felt happy:

Yes, most of the time
Yes, some of the time
No, not very often
No, not at all

Please complete the other questions in the same way.

IN THE PAST SEVEN DAYS:

1. I have been able to laugh and see the funny side of things
   - As much as I always could *0*
   - Not quite so much now *1*
   - Definitely not so much now *2*
   - Not at all *3*

2. I have looked forward with enjoyment to things
   - As much as I ever did *0*
   - Rather less than I used to *1*
   - Definitely less than I used to *2*
   - Hardly at all *3*

3. I have blamed myself unnecessarily when things went wrong
   - Yes, most of the time *3*
   - Yes, some of the time *2*
   - Not very often *1*
   - No, never *0*

4. I have felt worried or anxious for no very good reason
   - No, not at all *0*
   - Hardly ever *1*
   - Yes, sometimes *2*
   - Yes, very often *3*

5. I have felt scared or panicky for no very good reason
   - Yes, quite a lot *3*
   - Yes, sometimes *2*

No, not much	*1*
No, not at all	*0*

6. Things have been getting on top of me

Yes, most of the time I haven't been able to cope at all	*3*
Yes, sometimes I haven't been coping as well as usual	*2*
No, most of the time I have coped quite well	*1*
No, I have been coping as well as ever	*0*

7. I have been so unhappy that I have had difficulty sleeping

Yes, most of the time	*3*
Yes, sometimes	*2*
Not very often	*1*
No, not at all	*0*

8. I have felt sad and miserable

Yes, most of the time	*3*
Yes, quite often	*2*
Not very often	*1*
No, not at all	*0*

9. I have been so unhappy that I have been crying

Yes, most of the time	*3*
Yes, quite often	*2*
Only occasionally	*1*
No, never	*0*

10. The thought of harming myself has occurred to me

Yes, quite often	*3*
Sometimes	*2*
Hardly ever	*1*
Never	*0*

(Cox, JL, Holden, JM & Sagovsky, R. (1987) Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry*, **150**, 782-6.)

APPENDIX 2

EDINBURGH POSTNATAL DEPRESSION SCALE (Modified)

As you have recently had a baby, we would like to know how you are feeling. I am going to read some statements to you and give you a choice of four responses.
For example, I have felt happy:

Yes, all the time
Yes, most of the time
No, not very much
No, not at all

Please choose an answer that comes closest to how you have felt IN THE PAST SEVEN DAYS, not just how you feel today.

IN THE PAST SEVEN DAYS:

1. I have been able to laugh and see the funny side of things
   As much as I always could
   Not quite so much now
   Definitely not so much now
   Not at all

2. I have looked forward with enjoyment to things
   As much as I ever did
   A little less than I used to
   Much less than I used to
   Hardly at all

3. I have blamed myself unnecessarily when things went wrong
   Yes, most of the time
   Yes, some of the time
   Not very much
   No, never

4. I have been worried for no good reason
   No, not at all
   Hardly ever
   Yes, sometimes
   Yes, very much

5. I have felt scared or panicky for no very good reason
   Yes, quite a lot
   Yes, sometimes
   No, not much

No, not at all

6. Things have been getting on top of me
   Yes, most of the time I haven't been managing at all
   Yes, sometimes I haven't been managing as well as usual
   No, most of the time I have managed quite well
   No, I have been managing as well as ever

7. I have been so unhappy that I have had difficulty sleeping (not because of the baby)
   Yes, most of the time
   Yes, sometimes
   Not very much
   No, not at all

8. I have felt sad and miserable
   Yes, most of the time
   Yes, quite a lot
   Not very much
   No, not at all

9. I have been so unhappy that I have been crying
   Yes, most of the time
   Yes, quite a lot
   Only sometimes
   No, never

10. The thought of harming myself has occurred to me
   Yes, quite a lot
   Sometimes
   Hardly ever
   Never

GUIDELINES FOR USE

- The verbal EPDS should be read to the woman in the privacy of a consulting room.
- It may be read by health care workers not specifically trained in psychiatry.
- If the woman's English is poor, the appropriate language translator should translate the questionnaire.
- Responses are scored in the same way as the original EPDS i.e. 0,1,2 and 3 according to increased severity of the symptom.
- If a woman scores 12 or more, she should be referred to a doctor for further psychiatric evaluation.

APPENDIX 3

THE MONTGOMERY-ÅSBERG DEPRESSION RATING SCALE (MADRS).

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms, to more detailed ones, which allow precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or *between them* (1, 3, 5).

---

1. APPARENT SADNESS

Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0 No sadness
1
2 Looks dispirited but does brighten up without difficulty.
3
4 Appears sad and unhappy most of the time.
5
6 Looks miserable all the time. Extremely despondent.

---

2. REPORTED SADNESS

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 Occasional sadness in keeping with circumstances.
1
2 Sad or low but brightens up without difficulty.
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 Continuous or unvarying sadness, misery or despondency.

---

3. INNER TENSION

Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only fleeting inner tension.
1
2 Occasional feelings of edginess and ill-defined discomfort.
3
4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
5
6 Unrelenting dread or anguish. Overwhelming panic.

---

4. REDUCED SLEEP

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 Sleeps as usual.
1
2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
3
4 Sleep reduced or broken by at least two hours.
5
6 Less than two or three hours sleep.

---

5. REDUCED APPETITE

Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite.
1
2 Slightly reduced appetite.
3
4 No appetite. Food is tasteless.
5
6 Needs persuasion to eat at all.

---

6. CONCENTRATION DIFFICULTIES

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties concentrating.
1
2 Occasional difficulties in collecting one's thoughts.

3
4 Difficulties in concentrating which reduces ability to read or hold a conversation.
5
6 Unable to read or converse without great difficulty.

7. LASSITUDE

Representing a difficulty getting started or slowness initiating and performing everyday activities.

0 Hardly any difficulty in getting started. No sluggishness.
1
2 Difficulties in starting activities.
3
4 Difficulty in starting simple routine activities, which are carried out with effort.
5
6 Complete lassitude. Unable to do anything without help.

8. INABILITY TO FEEL

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and other people.
1
2 Reduced ability to enjoy usual interests.
3
4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
5
6 The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. PESSIMISTIC THOUGHTS

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

0 No pessimistic thoughts.
1
2 Fluctuating ideas of failure, self-reproach and self-depreciation.
3
4 Persistent self-accusation, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future
5
6 Delusions of ruin, remorse and irredeemable sin. Self-accusations which are absurd and unshakeable.

10. SUICIDAL THOUGHTS

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and the preparation for suicide. Suicidal attempts should not, in themselves, influence the rating.

0 Enjoys life or takes it as it comes.

1

2 Weary of life. Only fleeting suicidal thoughts.

3

4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.

5

6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

TOTAL SCORE:

APPENDIX 4

CONSENT FORM

You have just delivered your baby and are planning to have a sterilisation or an intra-uterine contraceptive device inserted at your 6 week postnatal check-up to prevent falling pregnant. As many as one in every five women may suffer from depression following childbirth. We are asking you to participate in a study that will help us learn whether an hormonal treatment called Nur-Isterate is helpful in preventing this depression from occurring.

If you participate you will receive an injection once only, now, and you will then need to return to Coronation Hospital for follow up interviews at five days, six weeks and three months after delivery. The injection may be active or inactive. For the purpose of research, neither you nor the hospital staff will know whether you have received the active or inactive injection (although the information will be on file at the study co-ordinating centre and can be made available to your doctor if necessary). A 20ml blood sample, involving a needle prick in the arm, and a small salivary sample will be taken at the six-week visit.

The medicine used in the study will be provided to you free of cost, and your transport costs to and from the hospital will be reimbursed.

This injection will not affect your breast-feeding or harm your baby. It is a commonly used contraception with minimal side effects. However, some women have reported heavy periods or prolonged bleeding after delivery. Other side effects may include depression, the absence of periods, slight weight gain, dizziness, breast tenderness, bloating, headache and a delayed return to fertility (average 5-8 months). The possible benefits of the treatment include lighter periods, less period pains, less chance of infection of the womb and improved breast milk production.

In the time before the sterilisation or loop insertion, you are not safe from falling pregnant so alternative methods i.e. condoms should be used.

Participation in this study is voluntary and you are free to refuse to participate or to withdraw your consent and to discontinue participation at any time. Such refusal will not affect your regular treatments in any way. All information will be strictly confidential.

I have fully explained the above to the patient.

Date: _____ Doctor: _____

I have been fully informed and understand what has been explained to me. I hereby agree to participate in the study.

Date: _____ Patient: _____

APPENDIX 5

POSTNATAL DEPRESSION STUDY QUESTIONNAIRE

INITIAL INTERVIEW

A. General details

Date: | | | | | | |

Study No: | | | |

Name: | | | | | | | | | | | | | | | | |

Birth Date: | | | | | | |

Address: | | | | | | | | | | | | | | | | | |

Telephone: H | | | | | | | | W | | | | | | | |

Language: | | | | | | | | | |

Age: | | Marital Status: | |

Employed: Y/N Details_____Maternity Leave (Wks): | |

Is Partner Employed? Y/N Monthly Household Income: | | | |

B. Delivery details

Gravida: | | Para: | |

Baby's Sex: M/F Gestation At Birth: | | Wks

Birth Weight: | | | | | grams

Mode of delivery: | Nvd | Vacuum | Forceps | Caesarean |

Hours in labour: | |

Companion present: Y/N

Do You Think You Coped Well During Labour? Y/N

Obstetric Complications: Y/N Details _____

Outcome Of Baby: | Good | Nursery | Prem Unit | Icu | Demised |

Give Details If Outcome Not Good _____

Breast Feeding: Y/N

C. Other Details

Medical History: _____

History of Psychiatric Illness: Y/N Details_____

Family History of Psychiatric Illness: Y/N Details_____

Previous Postnatal Depression: Y/N

Previous Blues: Y\N

Premenstrual Syndrome: Y\N

Periods: | Regular | Irregular |

EPDS: | | | MADRS: | | |

DAY 5-10 INTERVIEW

Date: | | | | | | | |

Breast Feeding Y/N

If Not, Why? _____

Other Post-Partum Problems :

Breast Tenderness/Engorgement

No Breast Milk

Backache

Painful Stitches

Exhaustion

Headaches

Other

No. of days in hospital: ☐☐

No. of days in hospital for baby, if different: ☐☐

EPDS: ☐☐ MADRS: ☐☐

SIX-WEEK INTERVIEW

Date: ☐☐☐☐☐☐

Breast feeding Y/N

If Not, Why?_____

Other Post-Partum Problems

Breast Tenderness/Engorgement

No Breast Milk

Backache

Painful Stitches

Exhaustion

Headache

Other

EPDS: ☐☐ MADRS: ☐☐

THREE-MONTH INTERVIEW

Date: | | | | | | |

Breast Feeding Y/N

If Not, Why?_____

Other Post Partum Problems

Breast Tenderness/Engorgement

No Milk

Backache

Painful Stitches

Exhaustion

Headache

Other

EPDS: | | MADRS: | |

OUTCOME

Blues Y/N

Significant Postnatal Depression	No	Minor	Major

Referred to Psychologist Y/N Date _____

Referred to Psychiatrist Y/N Date _____

Referred to Social Worker Y/N Date _____

No. of visits _____

Details_____

Days of PV Bleeding:

Postnatal ☐☐ 6 Weeks ☐☐ 12 Weeks ☐☐

Enough Breast Milk? Y/N

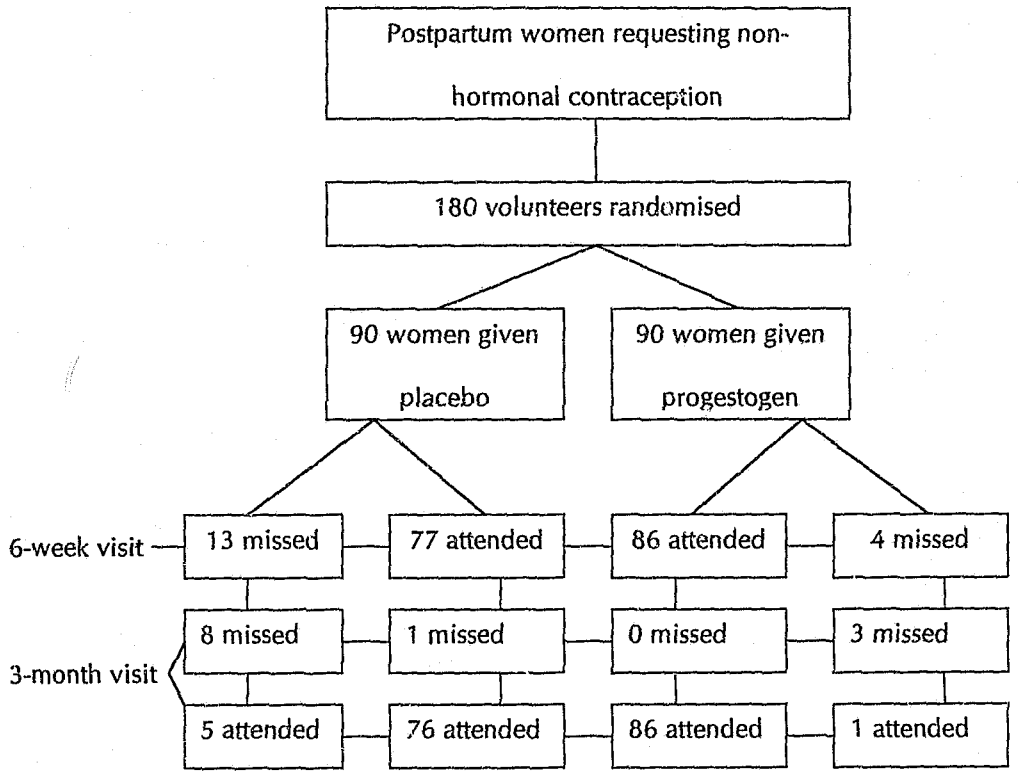
Libido Y/N _____Wks

Other Problems_____

Stressor Score: ☐

APPENDIX 6

TRIAL PROFILE



APPENDIX 7. TABLE1. Baseline, one-week and three month depression scores of the women who missed the six-week visit, compared to those who attended; in the placebo and progestogen group combined, and the placebo group alone expressed as mean score [SD] and total number of women with depressive symptomatology (%) defined by MADRS>18 (major depression), MADRS >9 (major and minor depression) and EPDS >11 (major and minor depression).

	Progestogen and Placebo					Placebo only				
	n	Attended	n	Missed	*p*	n	Attended	n	Missed	*p*
Baseline										
a) Mean MADRS	163	6.05 [6.9]	14	9.29 [6.8]	0.0951	78	5.97 [7.2]	12	9.25 [7.3]	0.1465
b) MADRS>18	163	10 (6.1)	14	1 (7.1)	1.000	78	6 (7.7)	12	1 (8.3)	1.000
c) MADRS>9	163	36 (22.1)	14	8 (57.1)	0.00737*	78	14 (17.9)	12	7 (58.3)	0.00587*
d) Mean EPDS	164	12.8 [5.7]	14	15.4 [3.9]	0.0892	78	12.0 [5.4]	12	15.8 [4.1]	0.0249*
e) EPDS>11	164	92 (56.1)	14	13 (92.9)	0.00868*	78	39 (50.0)	12	11 (91.7)	0.010*
One-week										
a) Mean MADRS		7.02[7.7]	8	7.25 [4.8]	0.9331	72	6.13 [7.8]	8	7.25 [4.8]	0.6940
b) MADRS>18	157	17 (10.8)	8	0 (0.0)	1.000	72	6 (8.3)	8	0 (0.0)	1.000
c) MADRS>9	157	46 (29.3)	8	3 (37.5)	0.696	72	18 (25.0)	8	3 (37.5)	0.426
d) Mean EPDS	158	11.0 [6.0]	10	11.9 [5.7]	0.6428	73	10.27 [5.7]	9	11.11 [5.5]	0.6790
e) EPDS>11	158	76 (48.1)	10	4 (60.0)	0.749	73	31 (42.5)	9	3 (33.3)	0.729
Three-months										
a) Mean MADRS	162	6.25 [7.4]	6	12.33 [10.5]	0.0522	76	5.74 [6.5]	5	13.2 [11.5]	0.0211*
b) MADRS>18	162	13 (8.0)	6	2 (33.3)	0.091	76	5 (6.6)	5	2 (40.0)	0.057
c) MADRS>9	162	44 (27.2)	6	3 (50.0)	0.351	76	20 (26.3)	5	3 (60.0)	0.136
d) Mean EPDS	162	8.82 [6.1]	6	15.0 [5.5]	0.0162*	76	8.15 [5.4]	5	16.2 [5.2]	0.0018*
EPDS>11	162	48 (29.6)	6	4 (66.7)	0.075	76	20 (26.3)	5	4 (80.0)	0.025*

* P<0.05 is considered a statistically significant difference. p-values were calculated for continuous variables by using the U-test of Mann-Whitney and for categorical variables by using Fisher's Exact test.

APPENDIX 8

THE PERSONAL EXPERIENCES QUESTIONAIRE

Please answer the following questions in terms of your current experience by circling the appropriate number.

"Sexual activity" covers behaviours from self stimulation (masturbation), foreplay (arousal with partner) to actual intercourse.

	Not at All				Very Much
1. How enjoyable are sexual activities currently for you?	1	2	3	4	5
2. Are you satisfies with your present sexual frequency?	1	2	3	4	5
3. Do you currently masturbate (stimulation of own genitals)?	1	2	3	4	5
4. How often during sex activities do you feel aroused or excited (heart beating faster/heavier breathing/vaginal wetness/flushing)?	1	2	3	4	5
5. Do you currently experience orgasm (climax) during sex activity?	1	2	3	4	5
6. Do you currently experience any lack of vaginal wetness (lubrication) during sexual activity?	1	2	3	4	5

7a. Give an approximate estimate by circling the answer which best describes how many times you have had sexual thoughts or fantasies (eg daydreams) during the last month?

0 never
1 less than once a week
2 once or twice a week
3 several times a week
4 once a day; sometimes twice
5 several times a day

7b. Give an approximate estimate by circling the answer which

best describes how many times you have had any sexual activities during the last two weeks.

0 never
1 less than once a week
2 once or twice a week
3 several times a week
4 once a day; sometimes twice
5 several times a day

What is your sexual preference (please tick)?

Heterosexual (male partner) ☐
Bisexual (both male and female partner) ☐
Lesbian/gay (female partner) ☐

Do you have a current sexual partner(s)? Yes/No

The rest of the questions relate to sexual partners. If you have no sexual partner you may stop here. If you have one or more sexual partners please continue the questionnaire.

How many current sexual partners do you have? ____

Please answer the following questions in relation to your main sexual partner.

	Not at All				Very Much	N/A
R1 How much companionable love do you feel for your partner?	1	2	3	4	5	6
R2. How much passionate love do you feel for your partner?	1	2	3	4	5	6
R3. How much resentment do you feel towards your partner?	1	2	3	4	5	6
R4. How much hostility do you feel towards your partner?	1	2	3	4	5	6
R5.Are you satisfied with your partner as a friend?	1	2	3	4	5	6
R6.Are you satisfied with your partner as a lover?	1	2	3	4	5	6
R7. Can you discuss openly your sexual wants and desires In your relationship?	1	2	3	4	5	6

R8. Do you currently experience any pain during intercourse?	1	2	3	4	5	6
R9. Do you currently have fears of sexually related infections?	1	2	3	4	5	6
R10. Does your partner(s) experience difficulty in sexual performance?	1	2	3	4	5	6

R11. During the past month how often have you had sexual Intercourse?

0 never
1 less than once a week
2 once or twice a week
3 several times a week
4 once a day; sometimes twice
5 several times a day

ANY FURTHER COMMENTS

APPENDIX 9

PROTOCOL FOR THE COCHRANE LIBRARY:

OESTROGENS AND PROGESTOGENS FOR THE PREVENTION AND TREATMENT OF POSTNATAL DEPRESSION

Oestrogens and progestogens for the prevention and treatment of postnatal depression [protocol]

Lawrie TA, Herxheimer A, Dalton K

Date of most recent substantive amendment : 12 November 1997

Date review expected : 31 May 1998

Background

Postnatal depression, with a prevalence of at least 10%, is probably the most common complication of the puerperium. As symptoms are similar to depression at other times and the aetiology is unclear, controversy surrounds the diagnostic concept of postnatal depression. For this reason, Romito (Romito 1989) suggests that the term 'postnatal depression' constitutes an obstacle to better understanding of unhappiness after childbirth. However, it is important to consider it different from depression at other times for the following reasons (Boyce 1994). Firstly, it has a temporal relationship with childbirth. Secondly, the impact of postnatal depression on a woman's social and personal adjustment is, arguably, greater than depression occurring at a less critical time in a woman's life. Thirdly, postnatal depression may have a detrimental long-term effect on mother-infant bonding and the family as a whole. Infant development has been found in many studies to be adversely affected (eg Murray 1989, Caplan et al 1989, Murray et al 1991, Sharp et al 1995). Marital difficulties are common (Boyce 1994) and the partner may become depressed (Areias et al 1996). Finally, the term 'postnatal depression' is considered a diagnostic term by most women, and for this reason alone, in a user-orientated service it should be included as a category (Cox 1994).

Progesterone and to a lesser extent oestrogen fall precipitously in the days following childbirth. Despite this, no consistent endocrine differences have been found between women who develop postnatal depression and those who do not (Willcox 1985). However, failure to demonstrate systemic evidence of hormone deficiencies does not exclude sex hormones as aetiological factors (O'Brien 1994). Peripheral hormone levels need not correspond with brain levels, nor are they necessarily an index of brain receptor numbers and affinity.

Progesterone, synthetic progestogens and oestrogen all have psychoactive properties (Wieck 1989) and have been shown to modulate serotonergic receptors in the rat brain (Biegon et al 1983). Oestrogen and progestogens may therefore influence brain neurotransmitter function and, hence, behaviour and symptoms.

It is thus conceivable that supplementation with either hormone may prevent postnatal depression, or that hormone therapy may help postnatal depression. Research into hormonal prophylaxis and treatment of postnatal depression is limited. Oestrogen therapy is considered to have mood-elevating properties in the climacteric, and has been used to treat severely depressed hospital inpatients with reported success (Klaiber et al 1979). Progesterone has been reported to elevate mood in the pre-menstruum. For this reason Dalton popularised the use of progesterone for prophylaxis for postnatal depression (Dalton 1985, Dalton 1989a, Dalton 1989b). However, studies in support of this were not adequately controlled. In contrast, synthetic progestogens have been implicated in causing depression amongst women using them for contraception (Wagner 1994, Wagner 1996), and in causing a premenstrual tension-like syndrome in women using combined hormone replacement therapy for the climacteric (Magos et al 1986).

Objectives

1. To evaluate the role of oestrogen supplementation in the prevention of postnatal depression.
2. To evaluate the role of oestrogen therapy in the treatment of postnatal depression.
3. To evaluate the role of progestogen supplementation in the prevention of postnatal depression.
4. To evaluate the role of progestogen therapy in the treatment of postnatal depression.

Criteria for considering studies for this review

Types of participants
Participants will be women who were enrolled into a trial during pregnancy or within six months of giving birth.

Sub-group analyses may include the following groups:
women who have experienced mental illness prior to the pregnancy;
women who have sought help for depressive symptoms, but without symptoms or signs of psychosis;
women who have sought help for depressive symptoms, with symptoms or signs of psychosis;
women who have become depressed but have not sought medical help;
women on concurrent antidepressant medication and/or counselling;
women breastfeeding their infants; and
women not breastfeeding.

Types of intervention
Oestrogens and progestogens of all kinds and in all types of preparation, and placebo, will be considered, alone and in combination with antidepressant medication and/or counselling.

Types of outcome measures
A broad definition of postnatal depression will be used that ignores the timing and onset of the depression, to include women who are clinically depressed during the first six months postpartum. All estimates of depression, by use of screening (eg The Edinburgh postnatal depression scale) or diagnostic (eg DSM-IV) scales, self-report or objective assessment, will be considered. The threshold scores used for respective scales will be those used by the investigators. Where continuous variables for depression have been used, data will be pooled as weighted mean differences. Where possible, continuous variables will also be converted to categorical variables, with the reviewers allocating an appropriate threshold, after examining the relevant literature. Duration and resolution of depression following the intervention will be compared. Use of antidepressant medication after a period of hormone therapy may be taken as a marker for failure of the hormone therapy.

Types of studies
Only adequately randomised trials of suitable methodological quality will be reviewed.

Search strategy for identification of studies
See: Collaborative Review Group search strategy
The search will employ the search strategies developed by the Cochrane Pregnancy and Childbirth Group. Relevant trials will be identified in the Group's Specialised Register of Controlled Trials. Reference lists of identified studies will be examined for additional trials. The Cochrane Controlled Trials register will be searched. Keywords used to identify studies will be: Postnatal depression, postpartum depression, puerperal depression, postnatal psychosis, postpartum psychosis, puerperal psychosis, hormones, progest*, oestr*, estr*, contraception, hormonal contraception.

Methods of the review
Trials under consideration will be assessed for appropriateness of inclusion and methodological quality without regard to their results. Trials in which one of the reviewers has been personally involved, will be assessed for appropriateness by the other reviewers.

Included trial data will be processed as described in: Cochrane Collaboration Handbook [updated 1 March 1997]. In: The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration. Oxford: Update Software; 1996-. Updated quarterly.

Assessment of Methodological Quality:

Details of randomisation, concealment allocation, blinding and exclusion analyses will be recorded and evaluated. Unbiased methods of randomisation that are considered acceptable include random numbers generated by computer or sequentially numbered opaque sealed envelopes containing random allocation. A rating will be assigned to each trial based on the quality categories described in the Cochrane Collaboration Handbook. Where one of the reviewers has been personally involved in a trial, the other reviewers will rate the trial. Only categories A or B will be included in the meta-analysis for this review. Data from other studies

will be described in the 'excluded studies' tables, and may be included in the discussion. Where the reviewers disagree, the matter will be discussed until agreement is reached. Reasons for exclusion of any apparently eligible trial will be clearly described.

Data collection:

Data will be extracted from the trial reports. Missing information will be requested from investigators wherever possible.

Data synthesis:

Trials using different treatments will be analysed separately, and the results combined only if there is no reason to think that they differ in relevant ways.
The relative risk and 95% confidence intervals will be calculated for results using categorical data. Continuous data will be pooled as weighted mean differences.

Potential conflict of interest

None known.

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Coversheet

Title
Oestrogens and progestogens for the prevention and treatment of postnatal depression

Short Title
Sex hormones for postnatal depression

Reviewer(s)
Lawrie TA, Herxheimer A, Dalton K

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For information on the editorial group see:
Cochrane Pregnancy and Childbirth Group

Intramural sources of support to the review

- *None on file*

Extramural sources of support to the review

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Editorial notes
Please note that the 'date next stage expected' is the date by which the reviewer intends to complete the review for submission to the editorial base for editorial approval. It, therefore, does not take account of the time required for the editorial process.

Keywords
CRG Code: HM-PREG

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