**Medicines Q&As**

Q&A 183.5

**Does progesterone or progestogen supplementation prevent postnatal depression?**

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**Background**

Post natal depression occurs in about 10-15% of women within 4 to 6 weeks of childbirth. The signs and symptoms of post natal depression are similar to those experienced during depression at other times and include; low mood, tiredness, insomnia, loss of appetite, apathy, anxiety and feelings of guilt and inadequacy [1, 2].

Without treatment, most women recover spontaneously over 3-6 months, although around 25% still have evidence of depression a year after delivery. Post natal depression may have important adverse effects on the baby’s development as early interactions between the mother and baby may be impaired [1].

The National Institute for Health and Clinical Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) guidance, as well as a Clinical Knowledge Summary, currently recommend that all women are screened for depression and other mental health disorders in the both the antenatal and postnatal period and offered appropriate treatment [3-5]. Current treatment for postnatal depression includes self help approaches and brief psychological treatments including counselling, cognitive behavioural therapy (CBT) and interpersonal psychotherapy (IPT). Antidepressant therapy is used if there is no response to these measures [3-5].

**Answer**

Progesterone is an endogenous steroid hormone, which is necessary for implantation of the ovum and for maintenance of pregnancy [6, 7]. Progestogens are synthetic compounds derived from and with similar actions to progesterone; examples include norethisterone and medroxyprogesterone [6].

Progesterone acts on regions of the brain that are involved in mood control [8]. It has been hypothesized that rapidly falling progesterone levels after birth are linked with the development of postnatal depression [8-10]. Several small, poor quality studies have demonstrated either a weak association or no association between the overall change in plasma progesterone levels and the risk of developing depressive disorders following childbirth [11-14].

In patients with a previous episode of postnatal depression, recurrence has been reduced with a schedule involving daily progesterone 100mg intramuscular injections from the completion of labour for the first seven days, followed by progesterone suppositories 400mg twice daily until the return of normal menstruation, or for two months [15].

In an open label, uncontrolled study, 100 pregnant women who had experienced previous postnatal depression received progesterone prophylaxis by both the intramuscular and rectal routes. Follow up was performed at 6 months following delivery by either direct consultation or postal questionnaire. A response was obtained from 94 women, of which 10% had developed postnatal depression [16]. This was compared with a recurrence rate of 68% in a previous observational study [17].

In a second, open label study, 247 women with previous postnatal depression were encouraged to receive both progesterone 100mg intramuscular injections for 7 days followed by 400mg suppositories twice daily for 8 weeks postpartum or until menstruation after delivery. Follow up at 6 months was achieved in 215 women. Twenty one women, who did not receive progesterone, became the control group and had a recurrence rate of postnatal depression of 67% opposed to 7% in the treated group [18].
A small, double blind, cross over, placebo controlled trial comparing 200mg progesterone suppositories twice daily with placebo suppositories in 10 women with postnatal depression, showed no significant difference in the mean symptom scores [19].

A 36 year old lady with a history of severe postnatal depression following two previous normal deliveries was treated with prophylactic progesterone after the birth of her third child. She received daily intramuscular progesterone 25mg injections for one week and was then commenced on progesterone suppositories 100mg twice daily for 2 months. The dose was then reduced to 100mg daily for one month. No symptoms of postnatal depression or side effects were reported [20].

The effect of norethisterone on postnatal depression was assessed in double blind, randomised, placebo controlled study involving 180 postnatal women using a non-hormonal method of contraception. Participants in the study were randomly allocated to receive either a single dose of norethisterone enanthate 200mg (1ml) or 1ml of normal saline placebo by intramuscular injection, 48 hours post delivery. Depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS) and the Montgomery-Asberg Depression Rating Scale (MADRS). The highest score obtainable on the EPDS is 30 and on the MADRS it is 60. The primary outcome measures were depression scores (as rated by EPDS and MADRS) at 6 weeks and 3 months postpartum [21].

Mean depression scores were significantly higher in the norethisterone group than in the placebo group at six weeks postpartum (mean MADRS score 8.3 vs. 4.9; p=0.0111; mean EPDS score 10.6 vs. 7.5; p=0.0022). Mean serum 17β-oestradiol and progesterone concentrations were significantly lower in the norethisterone group compared with the placebo group. The study authors concluded that long acting norethisterone enanthate given within 48 hours of delivery is associated with an increased risk of developing postnatal depression and causes suppression of endogenous ovarian hormone secretion [21].

A Cochrane review published in 2008 concluded that synthetic progestogens do not have a preventive effect and should be used with significant caution in postnatal depression [22]. The review excluded the studies conducted by Dalton [18] and Van der Meer [19] as the methodological quality was considered to be inadequate. The Cochrane review concluded that the effect of natural progesterone on postnatal depression is unknown and more studies are necessary.

SIGN guidance published in 2012, regarding the management of perinatal mental health states that there is some evidence that progestins may worsen outcome [4]. Current guidance produced by NICE and a Clinical Knowledge Summary, regarding the management of depression in pregnancy, do not include the use of progesterone or progestogens for the prevention of postnatal depression [3, 5].

Summary

- Post natal depression occurs in about 10-15% of women within 4 to 6 weeks of childbirth.
- It has been suggested that rapid changes in plasma progesterone levels at childbirth may be responsible for the development of postnatal depression.
- Several small poor quality studies have demonstrated either a weak association or no association between plasma progesterone levels and the development of depressive disorders following childbirth.
- In a small number of studies, progesterone supplementation (started immediately after the completion of labour) prevented recurrence of postnatal depression.
- The progestogen, norethisterone, may increase the risk of postnatal depression when given within 48 hours of delivery.
- Progesterone supplementation is not included in current NICE guidance for the management of postnatal depression.
- Current SIGN guidance specifically states that there is some evidence that progestins may worsen outcome in postnatal women.
- The effect of progesterone and progestins is currently unknown and more studies are necessary.
Limitations
The use of progesterone for the treatment of other postpartum mental disorders such as mania or postpartum psychosis is not considered.

References
Quality Assurance

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Search strategy
- EMBASE; search terms: [exp PROGESTERONE/ AND exp PUERPERAL DEPRESSION/] AND exp PROPHYLAXIS/, limit to: Publication Year 2014-2016.
- MEDLINE; search terms: [exp PROGESTERONE/ AND exp DEPRESSION, POSTPARTUM/] AND prophylaxis.af, limit to: Publication Year 2014-2016.
- PubMed; search terms: postnatal depression, prophylaxis, progesterone
- Cochrane Library; search terms: progesterone, postnatal depression
- National Institute for Health and Care Excellence (NICE), http://www.nice.org.uk/, search term: postnatal depression
- Scottish Intercollegiate Guidelines Network (SIGN), www.sign.ac.uk, search terms: postnatal depression, progesterone.
- Royal College of Psychiatrists, www.rcpsych.ac.uk, search term: postnatal depression.