

Review Article

Hormonal Changes in the Postpartum and Implications for Postpartum Depression

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The months following childbirth are a time of heightened vulnerability to depressive mood changes. Because of the abrupt and dramatic changes occurring in hormone levels after delivery, many studies have examined the role of hormonal factors in postpartum depression. The authors review the literature on potential hormonal etiologies in postpartum depression, in particular for progesterone, estrogen, prolactin, cortisol, oxytocin, thyroid, and vasopressin. While evidence for an etiologic role is lacking for most hormones, changes in certain hormonal axes may contribute to depressive mood changes in some women following childbirth. (Psychosomatics 1998; 39:93–101)

The weeks following childbirth are a time of vulnerability to depressive symptomatology in women.^{1,2} The literature on postpartum depression has inconsistently defined its time of onset from between 4 weeks and 6 months following delivery. DSM-IV, in an attempt to define the syndrome more rigorously, applies the term “postpartum onset” to depression occurring within 4 weeks of delivery. Most epidemiologic studies have not used this strict criterion. When defined as depression occurring in the first 6 months after delivery, rates are as high as 22%,³ but drop to 12% to 16% if defined more narrowly as occurring in the first 6 to 9 weeks postpartum.^{3,4}

Aside from the postpartum specifier, DSM-IV’s criteria for postpartum depression are no different from those of a major depressive episode. However, in comparison with depression occurring at other times in women’s lives, guilt and agitation appear to occur more frequently in cases of postpartum depression, and suicidality is less common.⁵

Risk factors for postpartum depression include a family history and a personal history of

major depression⁶ and depressive symptomatology during pregnancy.⁷ Marital discord and stressful child care events (e.g., health problems in the baby) also increase the likelihood of postpartum depression.^{6,7} A number of studies have explored whether specific biological characteristics may underlie depression in the postpartum, but with equivocal results. This article reviews the literature on hormonal factors that have been postulated as etiologic in postpartum depression.

HORMONAL EVENTS IN PREGNANCY AND POSTPARTUM

During pregnancy, levels of estrogens (estradiol, estriol, and estrone) and progesterone rise stead-

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ily (see Figure 1 and Figure 2),⁸ in large part as a result of placental production of these hormones. With removal of the placenta at delivery, estrogen and progesterone levels drop sharply, reaching pregravid levels by the fifth postpartum day. Levels of beta-endorphin, human chorionic gonadotrophin, and cortisol also rise across pregnancy, reaching a maximum near term and declining at delivery.

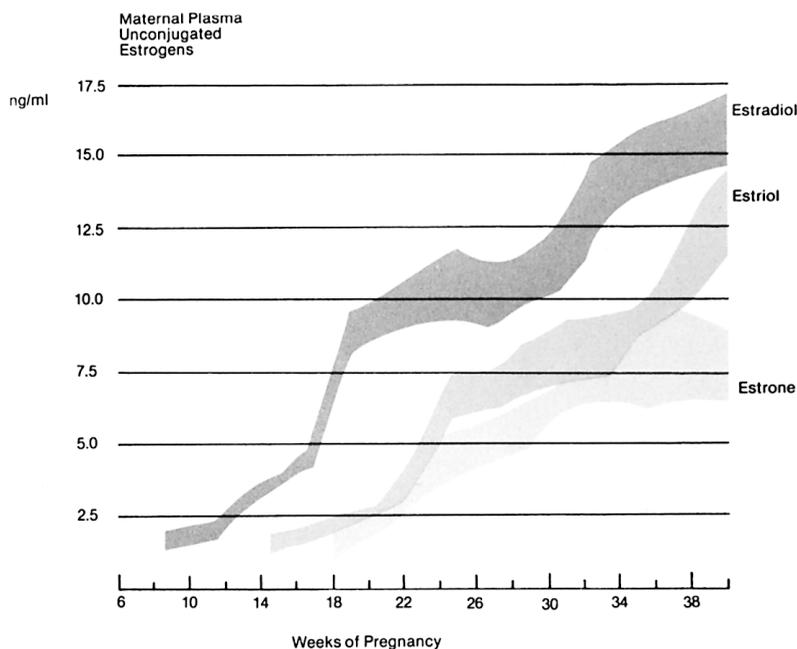
High estrogen levels during pregnancy stimulate production of thyroid hormone-binding globulin, leading to a rise in levels of bound T_3 (triiodothyronine) and T_4 (thyroxine) and a simultaneous drop in levels of free T_3 and T_4 . In consequence, thyroid-stimulating hormone (TSH) increases to compensate for the low free-thyroid hormones, and free T_3 and T_4 thus remain within the normal range.⁹ With the drop in thyroid-binding globulin following delivery, levels of total T_3 and T_4 drop, whereas free T_3

and T_4 remain relatively constant. Prolactin levels rise during pregnancy, peak at delivery and, in nonlactating women, return to pregravid levels within 3 weeks postpartum. By inducing the release of oxytocin, a hormone that stimulates pituitary lactotrophic cells, breast-feeding maintains high prolactin levels. Even in breast-feeding women, however, prolactin levels eventually return to pregravid levels.

GONADAL STEROIDS

Estradiol and estriol are biologically active forms of estrogen that are produced by the placenta and rise during pregnancy by 100-fold and 1,000-fold, respectively. Because synthesis of estriol results from metabolic activity of the fetal liver, it is produced in high concentrations during pregnancy. Animal studies have demonstrated that estradiol enhances neurotransmitter

FIGURE 1. Rise in levels of estrogens during pregnancy



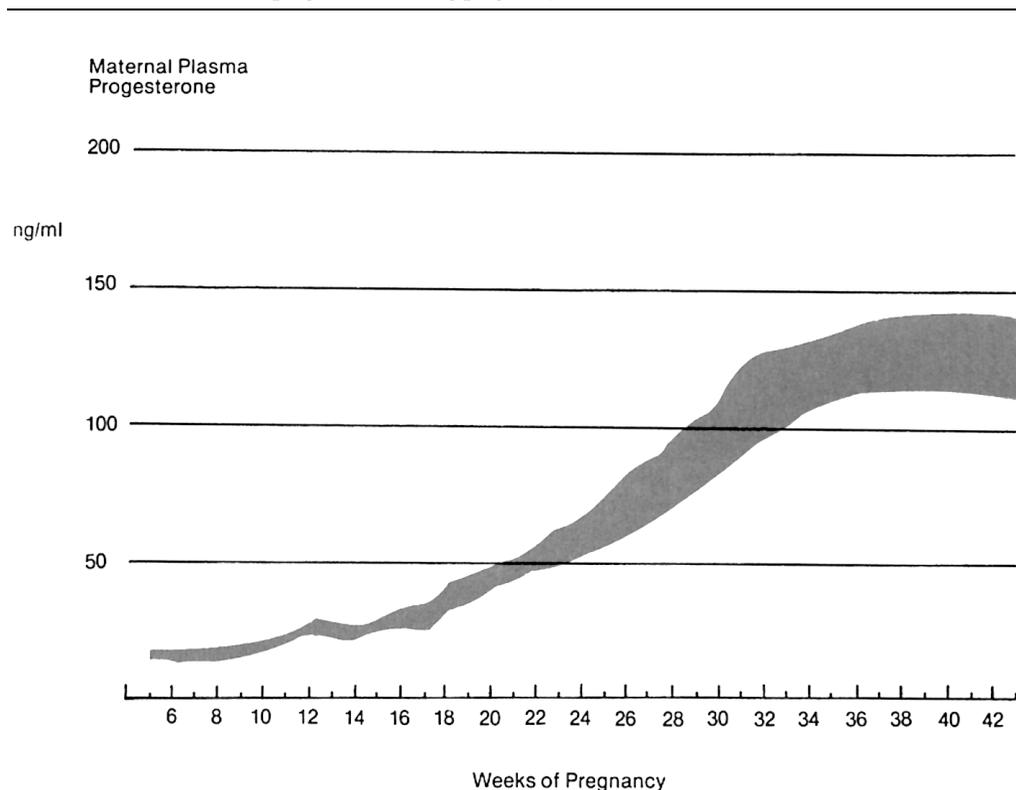
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function through increased synthesis and reduced breakdown of serotonin.¹⁰ The abrupt decrease in estradiol levels following delivery may thus theoretically contribute to postpartum depression. However, a study of 182 childbearing women found no significant difference in the magnitude of change of total estradiol or of free estradiol from late pregnancy to the puerperium in depressed and nondepressed women.¹¹ Total estradiol levels, measured on 9 separate days from Week 34 of gestation to Postpartum Day 8, were no different among the 2 groups of women, with the exception of a single significantly lower level of total estradiol at Week 36 in the women who developed postpartum depression. This finding is of unclear significance, particularly as the lower level was found in an antepartum

rather than a postpartum sample. Other studies of total estradiol levels, obtained at various times between the first day and the eighth week following delivery, have found no difference in women with and without postpartum depression.^{12,13} Levels of unbound (free) estradiol have not been studied in women with postpartum depression but merit examination, as the unbound form is biologically active.

Two recent studies have reported that estrogen supplementation significantly reduced postpartum depressive symptoms. The first was a small open study that included four women with a history of postpartum depression.¹⁴ In the month following delivery the women received up to 10 mg of Premarin (estrogen-replacement therapy) daily, equivalent to about 15 times the

FIGURE 2. Rise in level of progesterone during pregnancy



Source: Speroff L et al: Clinical Gynecologic Endocrinology and Infertility, 4th Edition. Baltimore, MD, Williams & Wilkins, 1983. Reprinted with permission.

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usual dose for estrogen-deficiency symptoms, and thus required heparin (5,000 units bid) to prevent thromboembolic phenomena. Over a 12-month follow-up period, none of these women experienced a recurrence of postpartum depression, despite the expected risk of relapse of 35% to 60%. The small sample size (4 cases of postpartum depression) was a major limitation of the study. In the second, a double-blind placebo-controlled study of 61 women with major depression that developed within 3 months of delivery,¹⁵ 80% of the patients receiving an estrogen patch had Edinburgh Postnatal Depression Scale scores under the threshold for major depression after 3 months of treatment, compared with 31% of the placebo-treated group. However, nearly half of the estrogen-treated patients were also on antidepressant medications, confounding the study results.

The sharp decline in progesterone levels following childbirth has also been implicated in postpartum mood changes, but the data are conflicting. A study of 27 women followed every 3 days for the first 6 weeks after delivery found a weak association between postpartum depression and the magnitude of change of progesterone.¹² Further studies, however, have failed to confirm a relationship between postpartum depression and blood levels of either total^{16,17} or free progesterone.^{11,18}

Salivary levels of progesterone have been examined on the premise that they reflect the free, biologically active, fraction of plasma progesterone concentrations. A study of 147 mothers at 6 to 8 weeks postpartum found that the depressed breast-feeding women had lower levels of salivary progesterone than the euthymic breast-feeding women.¹³ Levels of salivary progesterone were higher, on the other hand, in depressed postpartum women who were bottle feeding. However, nursing may have influenced progesterone levels by suppressing menstrual cycling, confounding the results of the study. A prospective study of 120 women found no association between the levels or the magnitude of change of salivary progesterone and depression at Day 35 postpartum.¹⁹ One report describes prophylactic efficacy of progesterone given

postnatally, but this study lacked a control group.²⁰ No controlled studies exist to date of progesterone in the prophylaxis or treatment of postpartum depression.

THYROID HORMONES

The incidence of abnormal thyroid function rises slightly after childbirth. In the 6 months following delivery, women experience thyroid dysfunction at a rate of up to 7%,²¹⁻²³ compared with a rate of 3% to 4% in the general population.²⁴ Although thyroid dysfunction has not been identified in most women with postpartum depression,²⁵ it may play a role for a subgroup of women.²⁶⁻³¹ In a prospective study of 303 pregnant euthyroid women, 21 women (7%) developed postpartum thyroid disorders.³¹ Depression was identified in 38% of these 21 mothers and resolved with treatment of the thyroid dysfunction.³¹ Thus, in women with symptoms suggesting hypothyroidism (weight gain, cold intolerance, lethargy), measurement of thyroid function is an important part of the evaluation of postpartum depression.

Some postpartum women without overt thyroid dysfunction may nevertheless have thyroid pathology. Thyroid antibodies have been found in up to 11.6% of postpartum women.²⁷ The immunosuppressant effect of high cortisol levels during pregnancy may be followed by a "rebound" immune phenomenon after delivery, producing a high incidence of postpartum thyroid antibodies.⁹ A double-blind study of 145 antibody-positive women and 229 antibody-negative women found a relationship between depression and postpartum antibody status.²⁷ At 6 weeks following delivery, 43% of the antibody-positive women had mild-to-moderate depressive symptoms, compared with 28% of the antibody-negative women. Depression was defined by a score of 17 or higher on the Hamilton Depression scale, a score of 13 or more on the Edinburgh postnatal depression scale, and a score of 11 or more on a hospital anxiety and depression scale. Antibody-positive women should be followed with thyroid function testing beyond the postpartum period, as many patients

with antithyroid antibodies go on to develop overt hypothyroidism within 4 years.³² At this time, however, there does not appear to be a role for thyroid antibody testing in the postpartum, as the relationship between antibodies and depression is weak.

Diminished thyroid function may affect postpartum mood through its association with diminished central 5-HT (5-hydroxytryptamine [serotonin]) activity. Blood levels of 5-HT have been positively correlated with thyroid hormone levels,³³ and the prolactin and cortisol responses to the 5-HT agonist fenfluramine are blunted in hypothyroid patients compared with euthyroid controls, suggesting reduced central 5-HT activity.³⁴

PITUITARY HORMONES

Prolactin rises from pregravid levels of 5–25 ng/ml to 140 ng/ml in late pregnancy and drops in the 3 weeks after delivery in nonlactating women. In breast-feeding mothers, prolactin levels remain high for several months but eventually decline to prepregnancy levels. Prolactin's role in psychopathology has been suggested by the association of anxiety, depression, and hostility in nonpregnant women with pathologic hyperprolactinemia compared with control subjects.³⁵ One study of 147 women at 6–8 weeks postpartum found lower prolactin levels in the depressed breast-feeding women than in the nondepressed breast-feeding women.¹³ However, all levels remained within normal physiological ranges. The study did not control for the relationship between breast-feeding and sampling time. As prolactin levels increase following breast-feeding and nipple stimulation, this is a significant confound. A large prospective study that did control for breast-feeding, in addition to demographic and psychosocial variables, failed to find a relationship between prolactin levels and postpartum mood.¹¹

Oxytocin and vasopressin, two posterior pituitary hormones that undergo changes in levels in the postpartum, have not been assessed for their relationship to postpartum depression. Oxytocin, which rises sharply at delivery and

with breast-feeding, stimulates uterine muscle contraction at labor and promotes release of breast milk. In animal studies, oxytocin also appears to stimulate maternal behavior.

Vasopressin regulates blood pressure and electrolyte balance and has been found lower in urine, but not plasma, of postpartum women compared with the nonpuerperal women in a study that did not assess mood state.³⁶ While negative results have been found in studies of vasopressin levels in women with postpartum blues,^{36,37} no studies have assessed its levels in postpartum depression.

CORTISOL

Cortisol levels peak in late pregnancy as a result of placental production of corticotropin-releasing hormone, and fall abruptly at delivery. A number of studies have failed to find an association between plasma cortisol,^{11,13,38,39} or urinary-free cortisol¹¹ and postpartum depression. One study that did note a positive association between morning serum cortisol levels at 6 weeks postpartum and degree of dysphoria in 26 women²⁹ was confounded by a lack of control for stressful life events and for timing of breast-feeding, factors that may produce an elevation or a reduction, respectively, of cortisol levels.⁴⁰

A prospective study of 182 women followed from the second trimester of pregnancy until Postpartum Week 9 controlled for lactation and for demographic, psychiatric, social, life stress, and other variables. No association was observed between total cortisol, urinary-free cortisol, or dexamethasone-suppression test results and postpartum mood.¹¹ Thus, current data do not support an etiologic role for cortisol in the onset of postpartum depression. A prospective study of 17 healthy euthymic women evaluated in the second trimester of pregnancy and followed to the 12th postpartum week similarly found no relationship between mood and cortisol levels but did observe a significantly greater and longer lasting blunting of adrenocorticotrophic hormone (ACTH) response to corticotropin-releasing hormone in women who developed postpartum blues or postpartum depression

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compared with women who remained euthymic.⁴¹ The authors speculated that the hypercortisolism that characterizes late pregnancy (resulting from placental production of corticotropin-releasing hormone) produces adrenal suppression following delivery that, when sustained and severe, may contribute to depressive mood changes after delivery. This intriguing but small study, consisting of only one case of postpartum depression and seven cases of postpartum blues, merits examination with a larger sample size.

DISCUSSION AND CONCLUSIONS

The dramatic physiological events occurring after delivery have led researchers to speculate that postpartum mood disorders result from a biochemical or hormonal etiology. While certain hormones, such as estradiol and ACTH, merit further exploration, studies have been negative or contradictory for most biological variables thought to be etiologic. Thus, the literature to date does not consistently support any single biological etiology for postpartum depression.

Methodological problems in many studies may have led to the conflicting results. For example, blood sampling in many studies did not control for breast-feeding. Lactation not only influences levels of prolactin, progesterone, estrogen, oxytocin, and cortisol but also has been associated with changes in mood state, both positive⁴² and negative.⁴³ Other variables seldom controlled for in the studies were the time of day when assays were obtained, seasonal variations in hormone levels, extent of sleep deprivation in the mother, and potential medication effects on hormone levels. Many studies assessed total hormone concentration rather than free, biologically active hormone levels. While the majority of studies measured the absolute levels of a biological factor, it may be the degree of change—in particular, the degree of change of free hormone—from pregnancy to the early postpartum that affects psychopathology. Changes in mood may also occur from extreme sensitivity to normal levels of hormones.

A limitation of studies assessing serum lev-

els of hormones and other biological factors is that peripheral levels do not necessarily reflect central activity. For beta-endorphins, for example, the relationship between peripheral and cerebrospinal fluid concentrations is small.⁴⁴ Thyroid hormone measures similarly show little parallel with peripheral indices.^{45,46} Thus, measurement techniques that reliably reflect central neurotransmission are necessary to better establish the relationship between postpartum mood changes and neurotransmitter activity. Central levels of steroid hormones, however, are reported to correlate with plasma levels.⁴⁷

It is possible that no biological etiologies are specific to the postpartum, but rather the birth of a child may represent a major stressful life event that, in vulnerable women, precipitates a depressive episode. Clearly, psychosocial stressors contribute to the syndrome in many women: a lack of support, marital conflict, unemployment, an unplanned pregnancy, single motherhood, and younger age are some factors associated with postpartum depression.^{2,42,48} Infant factors, including high levels of irritability and poor motor behavior, also increase the likelihood of maternal depression.^{49,50} Future research on the biological factors that may underlie postpartum mood disorders should attempt to control for these variables, as they otherwise are likely to confound the data. Measures such as the Neonatal Behavioral Assessment Scale,⁵¹ the Life Events and Difficulties Schedule,⁵² and the Perceived Stress Scale⁵³ can be used for this purpose. Further variables that should be taken into account include personality traits in the mother, length of time and severity of the mother's depression, and qualitative aspects of the depression, including presence of obsessional or anxious features. These are factors that have been shown to predict likelihood of antidepressant response in nonpuerperal major depression but their role in influencing treatment outcome of postpartum depression has not been assessed. The genetic vulnerability that may underlie the development of depression in the postpartum is also worth investigating, for example, through the use of family studies of women with postpartum depression.

A significant problem in research on the etiology of postpartum depression is the heterogeneity of the syndrome. Depression arising 1 week postpartum may be etiologically different from depression developing 3 months after delivery or from depression that had its onset during the pregnancy but continued through the postpartum period. Further, a postpartum depression with anxious and obsessional features may be etiologically different from an anergic postpartum depression. Some authors have postulated that postpartum depressions exist in two distinct categories: cases in which the index episode occurs in the postpartum, and cases in which the postpartum depression represents a recurrence of a previous nonpuerperal depression.⁵⁴ Compared with the former, the latter group appears to have a greater likelihood of nonpuerperal recurrence^{54,55} and thus may require closer long-term follow-up. Other treatment implications, such as differences in treat-

ment outcome between the two groups, are not clear. To our knowledge, no studies have examined biological variables that may distinguish these two potentially distinct populations of postpartum depressed women.

Postpartum depression can produce significant distress to the new mother and her family and may have an adverse impact on the cognitive and emotional development of the child.^{56,57} Further, a postpartum depression predisposes a woman to future psychopathology, particularly following subsequent deliveries. The identification of etiologic factors is therefore of great importance, to allow for better understanding of preventive and treatment strategies. With the increasing tendency for researchers to employ standardized rating instruments (Edinburgh Postnatal Depression Scale, etc.) and to adhere to stringent criteria for postpartum depression, research in the etiology of postpartum depression is likely to advance in coming years.

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