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Biological and Psychosocial Aspects of Postpartum Depression

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Abstract

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Postpartum depression (PPD) is one of the most common complications of childbirth around the world. Despite several studies on the underlying mechanisms, the pathophysiology remains elusive. The aims of this thesis were to assess possible associations between the risk for self reported PPD and serum levels of leptin, the season of delivery, the gender of the newborn, and the history of premenstrual symptoms, respectively.

A population based cohort of 2318 newly delivered women in Sweden were screened five days, six weeks and six months postpartum, using the Edinburgh Postnatal Depression Scale. This cohort comprised 60% of the total population, and the prevalence of self reported PPD was 11.1% six weeks after the delivery.

A negative association between leptin levels at delivery and self reported PPD at six weeks and six months postpartum was evident, even after adjusting for confounding factors.

An increased risk for self reported PPD was noted among women delivering during the last three months of the year, compared to those giving birth in April through June. This is of clinical importance, since women delivering at the end of the year could benefit from a closer follow-up after delivery.

Despite previous varying findings – depending on study population and consequently different cultural settings – in our study, no association between infant gender and self reported PPD could be detected at six weeks or six months postpartum. However, women giving birth to baby boys had a higher risk for postpartum blues.

Lastly, an increased risk for self reported PPD among women with a history of premenstrual symptoms was noted. Interestingly, after stratification for parity, the association between PPD and premenstrual symptoms remained only among multiparas. The association between PPD and premenstrual symptoms might shed light on the many possible routes by which hormonal changes may influence mood in women.

In conclusion, this population based study strengthens the notion that PPD is a complex multifactorial disorder, with biological, social and psychological parameters shaping each individual's risk. Further research is needed in this field, in order to investigate underlying pathophysiological mechanisms, propose more effective diagnostic tests and assess therapeutic interventions.

Keywords: Depression, postpartum, biological, seasonality, gender, premenstrual

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To my family

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Skalkidou A, Sylvén SM, Papadopoulos FC, Olovsson M, Larsson A, Sundström-Poromaa I. Risk of postpartum depression in association with serum leptin and interleukin-6 levels at delivery: a nested case-control study within the UPPSAT cohort. *Psychoneuroendocrinology*. 2009 Oct;34(9):1329-37.
- II Sylvén SM, Papadopoulos FC, Olovsson M, Ekselius L, Poromaa IS, Skalkidou A. Seasonality patterns in postpartum depression. *Am J Obstet and Gynecol*. 2011 May;204(5):413.e1-6.
- III Sylvén SM, Papadopoulos FC, Mpazakidis V, Ekselius L, Sundström-Poromaa I, Skalkidou A. Newborn gender as a predictor of postpartum mood disturbances in a sample of Swedish women. *Arch Womens Ment Health*. 2011 Jun;14(3):195-201.
- IV Sylvén SM, Ekselius L, Sundström Poromaa I, Skalkidou A. Premenstrual syndrome and premenstrual dysphoric disorder as possible risk factors for depressive symptoms postpartum. *Submitted*.

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Abbreviations

ACOG	American College of Obstetricians and Gynecologists
BMI	Body mass index
CBT	Cognitive behavioral therapy
CI	Confidence interval
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DSM	Diagnostic and Statistical manual of Mental disorders
EPDS	Edinburgh Postnatal Depression Scale
HPA	Hypothalamic-pituitary-adrenal axis
IL-6	Interleukin 6
ITP	Interpersonal psychotherapy
IVF	In vitro fertilization
OCs	Oral contraceptives
OR	Odds Ratio
PMDD	Premenstrual dysphoric disorder
PMS	Premenstrual syndrome
PPD	Postpartum depression
SAD	Seasonal Affective Disorder
SPSS	Statistical Package for the Social Sciences
SSRI	Selective serotonin reuptake inhibitor
WHO	World Health Organization

Definitions

Antenatal	Before birth
Gestation	Pregnancy
Perinatal	The time before, during and after delivery.
Postpartum	The period after the birth of a child, historically the first six weeks after childbirth, nowadays most commonly within six months after the delivery
Postnatal	British English term for postpartum
Postpartum depression	A depressive episode occurring within the first year after delivery

Introduction

Depression

Affective disorders in general – and depression in particular – are of great importance, since they have a significant impact not only on the affected patient's life, but also on society as a whole. Major depression is one of the most common diagnoses in western societies, the life time prevalence varying between 10 to 25 % among women and 5 to 12 % among men according to epidemiological studies, while the point prevalence is estimated to about 5-9 % in women and 2-3 % in men (1-3). The variation in prevalence rates may be due to both cultural and socio-economical differences in the societies investigated in the previous studies, variance in co-morbidity, differences in the instruments used for diagnosis, and even treatment seeking factors/behavior may play a role (4-7). In Sweden, the Lundby study, following a population in a community in southern Sweden, found the cumulative probability for developing a depression was 22.5% for men and 30.7% for women (8).

The rising prevalence of mental disorders during recent years has become a growing global concern (9). A WHO report from 2007 states that depression is the leading cause of disability worldwide, and the fourth leading contributor to the global burden of disease (10).

The diagnosis of a major depressive episode is determined based on strict criteria, developed by the American Psychiatric Association as stated in the DSM-IV. The diagnosis is characterized by one or both of the two core symptoms: depressed mood and loss of interest or pleasure in usual activities. In addition to these, symptoms such as changes in appetite or weight, sleep, decreased energy, feelings of guilt and/or worthlessness, difficulty thinking and/or concentrating and difficulty making decisions are frequent. The presence of suicidal thoughts, plans or attempts are also included in the criteria for depression. Five or more of the above symptoms must be present and must persist for most of the day, for at least two consecutive weeks, and the depressive episode must also significantly decrease the patients daily functioning in areas such as social and occupational relations, in order for the patient to meet the criteria for major depression (3).

A reliable biological diagnostic test for depression does not yet exist, despite years of intensive research. Many biomarkers have been investigated and linked to major depressive disorder, but none have been able to provide

us with a test with acceptable sensitivity and specificity. However, recent data, including nine biomarkers and combining them into one diagnostic test, shows some promise in this field (11).

Depression is not only an important issue due to its high prevalence, and the extent to which the above mentioned symptoms significantly decrease the affected patient's functioning and quality of life, but it also affects the patient's entire family, and moreover, increases the risk for several other medical conditions, such as diabetes, cardiovascular disease and cancer (12-14). The co-morbidity with other psychiatric disorders can be as high as 60-70%, the most frequent diagnoses being anxiety disorders, impulse control disorders and substance abuse (4).

Major depression is two to three times more common among women than men (15), and the peak incidence in women occurs during their reproductive years (16). Postpartum depression, affecting 10-20% of all newly delivered women (17-18), can therefore represent a woman's "debut" to a life-time of recurrent depressive episodes (19).

Postpartum depression

Definition and diagnosis

Postpartum depression (PPD) is a condition strictly defined in the psychiatric nomenclature as a major depressive episode beginning within the first four weeks after childbirth (3). However, due to the fact that many women may start experiencing symptoms later in the postpartum period, the definition is often extended to include the entire first year postpartum (20-21). As with other major depressive episodes, the depressive symptoms must be present for at least two consecutive weeks, and in addition to depressed mood or lost of interest in normal activities, sleep and appetite disturbances, loss of energy, feelings of guilt and suicide thoughts may be present. This makes the PPD diagnosis a particularly challenging one since, for example, fatigue and changes in sleep patterns and weight are often observed in the postpartum period.

Postpartum depression must not be confused with postpartum blues, a very common and usually transient condition that is characterized by labile mood, tearfulness and anxiety within the first 10 days after childbirth, and occurs in 15-85% of all women (22-23). This condition is, nevertheless, important to distinguish, since it has been recognized as an important risk factor for the subsequent development of PPD (24-26).

Since PPD is both under diagnosed and inadequately treated (27-28), efforts for detection of the condition are of utmost importance. General practitioners, pediatricians and, in Sweden, midwives or nurses in outpatient clinics, are the ones most often faced with women suffering from mood distur-

bances after childbirth. As an aid for medical workers, several screening tools such as the Edinburgh Postnatal Depression Scale (EPDS), the Beck Depression Inventory (BDI), the General Health Questionnaire (GHQ), the Patient Health Questionnaire (PHQ), the Bromley Postnatal Depression Scale (BPDS), the Center for Epidemiological Studies Depression Scale (CES-D), the Postpartum Depression Screening Scale (PDSS) and the Zung Self-rating Depression Scale (Zung SDS) have been developed (29-30). Of these instruments, the EPDS is the most widely used, studied and validated (31-32). Most screening tools use self reported data, and are short and easy to use. The optimal time to screen for PPD is two weeks to six months after delivery (30), and if a woman screens positive for the condition, a clinical structured psychiatric interview should be performed.

In Sweden, antenatal care is free of charge. There are no private maternity hospitals and home deliveries are rare. Women are followed up six weeks after delivery by their midwife in the antenatal care clinic, and by the nurse taking care of her child in the pediatric outpatient clinic. This program reaches almost 100% of all the new mothers and newborn babies in Sweden. The nurses are recommended to use the EPDS as a screening tool at six to eight weeks postpartum, according to national guidelines (33). However, there are some regional differences as to the compliance to these guidelines. According to a study from 2007 (34) about half of the nurses used the EPDS for screening, and another 7% planned to start using it.

If the nurse in the outpatient clinic detects a case of possible PPD, she/he should take initiative to initiation of treatment. The treatment recommendations are: Supportive sessions with the nurse for mild cases of PPD; cognitive behavioral therapy (CBT), interpersonal therapy (ITP) or psychotherapy for moderate cases; and, antidepressant medication (first choice SSRIs) for (moderate-) severe cases (33, 35-36).

Symptoms and co-morbidity

PPD has a major impact on the woman's life in the critical first year after childbirth. Not only are the depressive symptoms hard to deal with, but they also leave the woman less able to attend to her newborn, which in turn leads to even more extensive feelings of guilt and worthlessness. Development of anxiety, which may persist in the years to come, is a common co-morbid condition (37-38), and may interfere with the woman's relation with both her child and possible partner. Some women with depressive symptoms and anxiety have personality disorders, and these women are at high risk for long-lasting psychiatric illness (39). In the most severe cases of PPD, there is a risk for suicide (40) or even infanticide (41). Five to ten percent of women with PPD present with a high risk of suicide, and suicide is now, in fact, one of the leading causes of maternal death in developed countries (42). In a British study from 1997-1999, suicide was the leading cause of maternal

deaths (specified as deaths occurring after a birth or stillbirth after more than 24 weeks of gestation, up to one year after the delivery), while, in addition, women also die from other complications of psychiatric disorders, including substance abuse (43-44). The high risk of suicide is often linked to puerperal psychosis, a condition that has an incidence of approximately two in 1000 newly delivered women. Women with a previous or family history of bipolar disorder are at increased risk for puerperal psychosis, and in a woman with a psychotic episode after a previous childbirth, the risk of recurrence is 50% (45-46).

Treatment

Treating women with PPD can be somewhat of a delicate matter, since they are sometimes hard to detect, and also to some extent skeptical towards medication (47). It is also difficult to advise the woman to rest and get extra sleep, since she will have to take care of her baby. For mild cases of depression, a shorter period of sick leave is sometimes recommended in Sweden, but for women on maternity leave, this option is not available.

The treatment of PPD is similar to that of major depression. For mild cases, CBT, ITP, psychotherapy or group therapy is the standard (35, 48). In women with more severe PPD, SSRIs are often used with good results, and even hormone supplementations (estrogen and progesterone derivatives) seem to have an effect, though estrogens cannot be administered to breastfeeding women (49-50). In patients who are critically ill, and at risk for suicide or development of postpartum psychosis, electroconvulsive therapy (ECT) has been proven to have a rapid impact and the best results (51). A major challenge in treating pregnant and newly delivered women with depressive symptoms is, however, a widely spread belief that medical interventions may put the child at risk for adverse outcomes (35, 52). However, data suggest that most antidepressants are safe to use during breastfeeding (53).

Antenatal depression

Historically, depression during pregnancy has not received as much attention as PPD. Recent studies from different parts of the world have, nonetheless, suggested that antenatal depression may be as common, or even more common, than PPD, the prevalence ranging from 5 to 50% in different populations (54-62). Antenatal depression is also one of the strongest predictors of PPD (58, 60-61, 63). Exposure to stress during fetal development may be associated with negative outcomes, such as shorter gestational length and low birth weight (54, 61, 64-65). Still, most of the debate continues to be focused on the possible adverse effects antidepressant treatment during pregnancy may have on the child, such as low birth weight, congenital malformations and persistent pulmonary hypertension (66-67). Therefore, use of

antidepressants during pregnancy continues to be a controversial issue, and the decision whether or not to accept treatment is a difficult one for many depressed pregnant women, and their care providers.

Though research states that antenatal and postnatal depression are connected, there are some women who are depressed during pregnancy but not after, and vice versa, while other women seem to enter a depression during pregnancy and continue feeling depressed throughout the postpartum period. This leads us to believe that depressive symptoms during the perinatal period may consist of not one, but two or three different types of affective disorders.

The detection of antenatal depression is, like that of PPD, difficult. However, screening scales like the EPDS have now been validated in Sweden for use during pregnancy, and a cut off of 13 points or more gives a sensitivity of 77% and a specificity of 94% (68). This gives a possibility for midwives working in the antenatal clinics to develop screening procedures for antenatal depression.

Postpartum depression in the partner

PPD affects not only women. The prevalence of depressive symptoms postpartum in men can range from 1-25% (69-74). Among partners of women with PPD, the risk of developing birth-related depressive symptoms can be even higher (72, 75-76). PPD in partners of newly delivered women is a subject which has not been extensively studied, but is of great importance, since depression in the second caregiver, with or without the mother being depressed, can seriously affect parent-infant interactions and child development (77-80). Paternal PPD, if untreated, can also leave the man at risk for suicide (81). Recent evidence suggests that depression in the partner, as well as maternal PPD, should be screened for in the postpartum period, and self report scales such as the EPDS have been validated in men (73, 82).

Significance for the child

Depressive symptoms in the parent may have devastating consequences, not only for him/her but also for his/her newborn child. The depressed parent will have difficulties not only practically, lacking the energy to tend for his/her newborn, but is also at risk for impaired attachment (83-84). Young children are highly sensitive to the quality of care they receive, and even infants respond selectively to social stimuli. This is a problem since depressed parents are typically unresponsive to infant cues, being either withdrawn with flatness of affect or else intrusive and hostile (85).

Previous studies have shown PPD to be associated with cognitive disturbances in the child (86), male children being especially vulnerable (87). The cognitive and emotional disturbances will persist, and studies following

children up to 16 years of age show behavioral problems and impaired patterns of communication, as well as poorer school results, again more prominent in boys than in girls (87-90). PPD has also been implicated as increasing the risk for sudden infant death syndrome (SIDS) (91-92).

Risk factors for postpartum depression

In recent years, PPD has been studied to quite some extent, and the exploration of correlates for the condition has revealed possible risk factors. Many of the risk factors are similar to those of major depression and other psychiatric disorders.

Psychosocial aspects

Previous psychiatric illness is highly associated with PPD, and depression and bipolar disorder, as well as history of somatic illness, all increase the risk for the disorder (59-60, 93-94). A history of PPD after previous pregnancies is, as well, a significant risk factor for PPD (86).

The association between the woman's age and the risk for PPD has been examined to some extent, with some studies showing an increased risk among young mothers (95), while others point to an increased risk for older women (96), and others still find no association between maternal age and risk for PPD (97-98).

Social factors, such as low socio-economic status, low level of education, alcohol and drug abuse, low levels of social or partner support, being single and/or unemployed and even the woman's expectations have been studied and are thought to be associated with PPD (59, 94, 99-100). Stressful life events, for example illness or death in the family, losing one's employment or having to move from one's home, can also increase the risk for PPD (101). Violence and abuse – psychological, physical and sexual – in intimate relationships have been studied, and also increase the risk for PPD (21, 102).

The prevalence of PPD is reportedly different in different parts of the world (103), and also differs between native and immigrant women living in the same country (104). This has led to some studies on cultural differences, and the effect that cultural factors have on PPD. The results of these studies seem to point to the fact that cultural rituals, such as for example “doing the month” (staying inside resting, observing a diet, and other restrictions) can have both negative and positive effects for new mothers (105).

Obesity is another factor often associated with depression and anxiety disorders; however, the subject is still debated and some studies suggest that only a weak level of evidence supports the hypothesis that obesity increases the risk for depressive disorders (106-107). In pregnant and newly delivered women, weight parameters are difficult to assess, since a certain amount of weight gain is both expected and normal during pregnancy, in most cases.

However, if one takes pre-pregnancy obesity into account, recent data suggest that an association between PPD and obesity may, in fact, exist (108).

Another central topic for new mothers, namely gender of the newborn, and its relation to PPD, is somewhat of a controversial subject. Previous studies have reported mixed results, with women giving birth in traditional eastern societies being more prone to PPD if they give birth to a girl (109-113). In contrast, a recent French study points to the fact that mothers giving birth to boys may have an increased risk for PPD, while other studies in western societies seem to support the notion that western parents most commonly have a mixed-gender preference (114-115). Sweden is a country with a high degree of gender equality (116), and therefore, mothers should not be influenced by the possible advantages of having a male offspring, that might be present in other cultures. To our knowledge, there are no previous studies on PPD and the possible association with gender of the newborn conducted in Sweden.

Obstetric and gynecological factors

Factors specific to pregnancy, delivery and the postpartum period have been studied previously in relation to PPD. Having an unplanned pregnancy, experiencing severe nausea during pregnancy or having other pregnancy complications, and/or being delivered by emergency cesarean section are obstetric factors that have been debated as potential risk factors (63, 117-120).

Breastfeeding has long been a topic of much interest to researchers, due to the fact that it affects not only the infant and the mother, but also the bonding between the two, and nursing may even have a possible biological connection with PPD (121). Several studies point to an association between decreased/terminated breastfeeding and increased risk for PPD (122-124), and this has led some researchers to believe that women with breastfeeding difficulties should be screened for PPD. However, it is difficult to determine whether it is the depressive symptoms that cause the cessation of breastfeeding, or vice versa. Another controversial topic related to breastfeeding is the possibility for treatment with antidepressants, and the effects this could have on the child.

Sleep, or lack of it, is another factor all new parents struggle with, and lack of adequate sleep in the first months postpartum is possibly associated with a higher risk for both new onset and recurrence of PPD (125-126). However, one must bear in mind that the assessment of sleep quality in the postpartum period is difficult, since a newborn child is bound to wake its parents several times each night. In addition, the sleeping patterns in patients suffering from depression can be difficult to interpret, since depression can be associated both with insomnia and hypersomnia. The causal relationship is not fully known, and some studies point to a shared neurobiological background between depression and insomnia (127-129).

A gynecological issue that has been investigated in relation to PPD is the history of premenstrual symptoms. Premenstrual symptoms are common among fertile women, and are reported in up to 80% of the population (130-131). Premenstrual disorders are in clinical practice often divided into premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). PMS is a very common condition, affecting approximately 20% of the female population (132-133), and is usually defined as proposed by the ACOG (134). The definition states that at least two symptoms (one of them being affective) must be present in the premenstrual phase, be relieved within 4 days of the onset of menses and occur reproducibly during two cycles of prospective ratings. PMDD, on the other hand, is a more severe and disabling disorder, defined according to the diagnostic criteria in DSM-IV (3). To receive the diagnosis, at least five of eleven mood or physical symptoms must be present in the premenstrual period and interfere with the woman's functioning at home or at work. In addition, symptoms must be confined to the luteal phase of the menstrual cycle and present in at least two consecutive menstrual cycles according to prospective symptom ratings. The symptom criteria for PMS/PMDD are described in detail in the 'Materials and methods'-section. According to these criteria, the prevalence of PMDD is about 3-8% (135).

Women with premenstrual disorders have an increased risk for psychiatric illness (136). Studies have pointed to an association between PPD and a history of premenstrual symptoms, and the prevalence of prior PPD in women diagnosed with PMDD is reportedly between 30-75% (137-139). However, previous studies are often relatively small, do not always apply strict criteria for the diagnosis of PMS/PMDD, and/or use retrospective data. A common pathophysiological mechanism for PPD and PMS/PMDD has been discussed, since they both seem to be disorders of steroid hormone fluctuation and neurosteroid withdrawal (140-141), but no evident association exists to date. Another possible biological connection between the two could be the fact that both respond to treatment with SSRIs (142-144), but the reasons for this are not yet fully understood.

Biological aspects in postpartum depression

Biological theories on the pathophysiology of PPD are to some extent similar to those for other psychiatric disorders. However, pregnant and newly delivered women represent a specific group, with both hormonal and psychosocial events that have no parallel in a woman's life time. Therefore, a direct comparison between depression related to pregnancy and childbirth and depression at other times during a woman's life cannot be made.

Hyper- or hypo-activation of the HPA axis, which is known to have profound effect on immunity, metabolism and reproduction, has previously been associated with depressive states (145). In seasonal affective disorder (SAD),

atypical depression and PPD, the activity of the HPA axis is usually reduced, which could point to a similar pathologic mechanism in these three conditions (146). The activity of the HPA axis can also be influenced by steroid hormones, such as estrogens, which has led to some research using estrogens as antidepressants (147). Estrogens also play a role in depression by increasing serotonergic activity, through regulation of the serotonin receptor, and are in addition neurotrophic, thus promoting neuroplasticity (148). Due to major fluctuations in steroid hormone levels during pregnancy and after delivery, speculations have been made that depression during pregnancy and depression in the postpartum period may have different pathogeneses, the first being melancholic, with hyperactivity in the HPA axis, and the second atypical (149). Following this assumption, one could speculate that PPD would be a good candidate as a model for atypical depression in general.

Corticotropin-Releasing Hormone (CRH), a hormone usually produced in the hypothalamus, but also produced by the placenta, uterus and ovaries during pregnancy, interacts with and regulates the HPA axis (146). Elevated levels of placental CRH are thought to correlate with pre-eclampsia and premature delivery, but also the start of labor in full term pregnancies. This physiological excess production of CRH at the end of the pregnancy leads to a transient down regulation of hypothalamic CRH postpartum, which could possibly lead to an elevated risk for depression (149).

In recent years, evidence that activation of the inflammatory response system may be involved in the pathophysiology of major depression and anxiety states, as well as PPD, has arisen (150). Increased serum concentrations of markers of the inflammatory response – for example Interleukin-6 (IL-6), which is a pro-inflammatory cytokine with a variety of endocrine and metabolic actions – have now been shown to accompany major depression (151-153). IL-6 interacts with the HPA axis, and significantly higher serum levels in women with postpartum depressive symptomatology have been reported (154-155), and, in addition, a recent study has shown that higher cerebrospinal fluid (CSF) IL-6 levels at the time of delivery are associated with higher risk for development of PPD (156).

Thyroid function abnormalities appear to be associated with an increased frequency of psychiatric symptoms, hyperthyroidism being related with anxiety, mania, restlessness, depression and cognitive deficits while hypothyroidism is associated with memory deficits, lack of concentration, psychomotor slowing and depression (157). The mechanism by which thyroid dysfunction might affect the risk of developing depression and vice versa remains to be established, but several theories have been expressed and remain to be evaluated and controlled (158). Hormonal changes and metabolic demands during pregnancy and the puerperium affect thyroid function, and previous studies indicate that thyroid function, or even sub-clinical changes

in thyroid hormone levels, can increase the risk for depressive symptoms postpartum (157, 159).

Leptin, a protein synthesized in the adipose tissue and coded by the *Obese* gene, has been studied recently in regards to depression. Leptin is involved in regulation of food intake and energy expenditure, by binding to specific receptors in the hypothalamus, and is also thought to affect reproductive functions by stimulating the gonadotropin-releasing hormone and luteinizing hormone in healthy women (160-162). Leptin is reported to rise during pregnancy, fall after delivery and subsequently increase during the first six months postpartum in healthy women (163-165). The effects of leptin on depression are inconclusive in previous studies, with leptin levels being unaltered, increased or decreased in different groups of depressed patients (166-168). One study found that high leptin levels are predictive of a new depressive episode during a five-year period in non-smokers only, while others could detect elevated levels of leptin in females with major depression, but not in men (169-171).

Although leptin has received some attention in major depression research, it has not previously been studied in relation to PPD. Since leptin is thought to play a role in reproductive functions, and is affected by pregnancy, it is plausible that it could also influence the risk for PPD.

Effect of season on affective disorders

The seasonal differences in the prevalence of affective disorders are well documented (172-173). Seasonal affective disorder (SAD), for example, affects 1-6% of the general population, and is characterized by major depressive episodes that cycle in response to season (174). SAD is more common among women than men, especially during the childbearing years (175). The underlying mechanisms responsible for the relation between season and psychiatric illness have been speculated upon, and are thought to involve the change in certain climatic variables, such as daylight, which may affect cortical and subcortical serotonergic systems, as well as synthesis of vitamin D in the skin.

Previous studies on season of delivery and its relation to PPD are few, show contradicting results and some use only a small number of patients (176-180). The results of these studies point towards an increased risk for PPD in women delivering in the autumn or winter. The effect of season on PPD is naturally of varying importance depending on the country being studied, with countries near the equator showing little variation in season, while countries such as Sweden have very distinctive seasonal changes in sunlight and temperature (181). Despite this, no previous studies from Sweden on season of delivery and risk for PPD are to be found in the literature.

Genetic polymorphisms

Since many of the psychosocial and biological risk factors for PPD are present for most – if not all – women, the pathophysiology of PPD can likely not be fully explained without accounting for individual (inherited) susceptibility. A number of candidate genes have been studied in relation to affective disorders, such as the brain derived neurotrophic factor (BDNF), the period 2 (PER 2), the serotonin transporter (5-HTT), the catechol-O-methyltransferase (COMT) and the monoamine oxidase-A (MAOA), and these genes have been implicated as key components in the pathophysiology for PPD (182-185). Still, there are few studies investigating the possible heritability of PPD to date, and no evident genetic risk profile has emerged (186).

Aims

The aim of this thesis was to examine correlates of postpartum depression in a large population-based sample from Uppsala, Sweden.

After working in the Maternity ward every day for over a year, I was astonished by the number of new mothers and fathers who develop depression within the first few weeks after delivery. The parents were sometimes so desperate to be admitted that they would call us or just showed up with their infant on our doorstep. These were, of course, extreme cases, but I realized there were a vast number of new parents staying at home, suffering alone, not receiving any treatment, and no one noticing their depression. The idea of possibly contributing in helping these women and men was an inspiration for me, while working with this thesis.

The specific aims of the papers were:

- I To investigate the possible association between the risk for postpartum depression and serum leptin as well as interleukin-6 levels at delivery.
- II To investigate if the season of delivery is associated with an increased risk for postpartum depression in Sweden.
- III To investigate the association between the risk for postpartum depression and gender of the newborn in a population-based sample of Swedish women.
- IV To investigate whether a previous history of premenstrual symptoms could influence the risk for development of postpartum depression.

Materials and methods

Study population and design

This study was undertaken as part of the UPPSAT (Uppsala-Athens) project, a population-based cohort study in the county of Uppsala, Sweden with a sister project in Athens, Greece. The results and papers in this thesis are all based on data from the Uppsala cohort. Uppsala is a medium sized Swedish county with a population of 323 270 inhabitants, and the University Hospital is responsible for all delivering women within the county, as well as high risk pregnancies from nearby counties. In Sweden, maternal health care is free of charge, and over 99% of all women deliver within the public health care system.

After an initial one week long pilot study, all women giving birth at Uppsala University Hospital from May, 2006 to June, 2007, were asked to participate in a longitudinal study on maternal well being. Exclusion criteria were 1) not being able to adequately communicate, write or read in Swedish 2) women with confidentially kept personal data and 3) women with intrauterine demise or with infants immediately admitted in the neonatal intensive care unit. The women were approached by their midwife or midwife's assistant after delivery, and were given oral as well as written information, after which a written consent was obtained. The participating women were given a questionnaire to fill out five days after delivery, containing the Edinburgh Postnatal Depression Scale (EPDS) as well as various questions on life style, medical history, socio-economic factors, partner support, breastfeeding, premenstrual symptoms, and stressful life events (SLEs). The fifth postpartum day was selected as the first screening point, since previous studies have indicated that postpartum blues peaks on day three to five postpartum (23). The majority of the participating women were also discharged from the maternity ward by this time. Two consecutive questionnaires were sent to the women by post, one at six weeks and one at six months postpartum. Data concerning pregnancy, delivery and neonatal outcome were retrieved from the medical records. No reminders were sent, due to administrative reasons. Women with high scores on the EPDS and/or answers indicating suicidal ideation were contacted by a study doctor, assessed and referred when needed.

Six weeks and six months after the delivery, shorter questionnaires were also sent to the woman's partner, if she had one, containing the EPDS and

questions on the delivery experience, the relation with the child's mother, whether the partner was working or not, etcetera. These data were collected to investigate the prevalence and possible correlates of PPD in a cohort of Swedish new fathers/second caregivers.

Blood samples were collected from women delivering from November 2006 until May 2007. The reason blood samples started being collected later than the questionnaires was due to administrative reasons. The blood samples were only taken from women who received an intravenous catheter during their delivery, and the women initially gave oral consent to the blood sampling after oral information by their midwife. After the delivery, all women were approached by medical personnel and informed as stated above. The blood samples from the women who did not give written consent to participate in the UPPSAT study were discarded (40% of all blood samples collected). This procedure was used in order to minimize selection bias and to avoid unnecessary extra blood sampling after the women received written information following delivery. Coded blood samples were stored at 4° C for a maximum of 24 hours and then centrifuged. The sera were stored at -70° C.

The study protocol was approved by the Regional Research and Ethics Committee of Uppsala.

Outcome measures

Self reported postpartum depression

The woman's score on the Swedish version of the EPDS (31) was used as the primary outcome measure. The EPDS is a screening instrument for postnatal depression, which consists of 10 questions, and can usually be completed in less than 5 minutes. The responses are scored 0, 1, 2 or 3 according to increased severity of the symptoms, and the total score is determined by adding together the scores for each of the 10 items. The EPDS has been validated in Sweden and has a cut-off of 12 or more points, after which a mother is considered being at high risk of postpartum depression (32). Please see the appendix for the full version of the EPDS.

The EPDS is a self-administered instrument, which was used instead of a psychiatric interview for the classification of PPD cases, for methodological reasons (due to the large study sample). In the Swedish validation, the EPDS displayed a sensitivity of 96%, a specificity of 49% and a positive predictive value of 59% (32). The EPDS has been validated in a large number of countries, and the cut-off scores vary between countries.

For the studies in this thesis, we used the EPDS score either as a continuous variable or as a dichotomous one. After a logarithmic transformation (to

account for non-normality) the EPDS score could be used as a continuous variable in the linear regression models. For the dichotomous variable, the women scoring 12 or more on the EPDS were considered cases of self reported PPD, while women scoring below 12 served as controls.

Analyses of leptin and high sensitivity IL-6

Samples were analyzed using commercially available ELISA kits (Leptin kit DY398 and high sensitivity IL-6 kit HS600B, R&D Systems, Minneapolis, MN, USA). The assays employ the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for IL-6 or leptin has been pre-coated onto a micro plate. Standards and samples are pipetted into the wells and any IL-6 or leptin present is bound by the immobilized antibody. After washing away any unbound substances, a specific detection antibody is added to the wells. Following a wash to remove unbound antibody-enzyme reagent, a substrate solution is added to the wells. (For the IL-6 assay, an amplifier solution had to be added to the substrate to achieve a proper color development). The color develops in proportion to the amount of antigen bound in the initial step. The concentration of IL-6 and leptin in the samples are calculated using the standard curve. The immunoassays are calibrated against highly purified E. coli-expressed recombinant human IL-6 and leptin. The assays have a total coefficient of variation (CV) of approximately 7%.

Definition of maternity stressors

For Paper II, previous psychiatric history, breastfeeding, reported partner support, maternal education, stressful life events (SLEs) and whether the current pregnancy was planned or not were treated as potential confounders and were included in the logistic regression analyses. In order not to compromise the power of the study by including 6 different variables in the logistic regression model, a score of “maternity stressors” was constructed from among the possible confounders. Mothers received one point for each one of the following: not breastfeeding, not considering their partner as supportive, having low educational status, having experienced at least one stressful life event in the past months, having an unplanned pregnancy. The sum of these points equals the “maternity stressors score”.

The division of the year into quartiles

For the binary logistic regression models in Paper II, we used year quartiles as the predictor variable, with EPDS-status as the outcome variable. The first quartile included January, February and March, the second one April, May and June, the third one July, August and September and the fourth one Octo-

ber, November and December. The second quartile of the year was considered as baseline, since June was the month with the lowest mean reported EPDS score over a six month period, and also due to the fact that June is the brightest month in Sweden (181).

Diagnostic criteria for PMS/PMDD diagnosis

The assessment of PMS/PMDD was made retrospectively, in the five days postpartum questionnaire, and was based on the DSM-IV criteria of PMDD. The specific questions used are presented in Box 1. Women were considered as cases of PMS if they reported more than two symptoms in the (A) category and answered yes in the (B) as well as (C) category question, according to the criteria established by the American College of Obstetricians and Gynecologists (134). A woman was considered a PMDD case if she reported five or more of the symptoms 1-11 in the (A) category, of which at least one had to be 1, 2, 3, or 4. The fulfilment of (B) as well as (C) category criteria were also required for the diagnosis (3).

Box 1. *Questionnaire used for the diagnosis of PMS and PMDD*

- A. Before this pregnancy, did you ever experience mood swings or other symptoms, increasing before menses and remitting within a week after onset of menses?

Yes

No

If your answer was Yes, please tell us which symptoms (more than one symptom can be chosen).

1. Depressed mood or dysphoria
 2. Anxiety
 3. Mood swings
 4. Irritability
 5. Decreased interest in normal activities
 6. Concentration difficulties
 7. Marked lack of energy
 8. Marked lack in appetite, overeating or food cravings
 9. Hypersomnia
 10. Feeling overwhelmed
 11. Other physical symptoms (e.g. breast tenderness, headache, bloating)
-

- B. Did you experience these symptoms each menstrual cycle?

- C. Did the symptoms interfere with work, school, usual activities or relationships?
-

Statistical analyses

Paper I

Differences in the study variables among cases and controls were assessed with the Mann-Whitney U-test, or the Fisher's exact test. Correlations between leptin and the possible confounders were assessed with the Spearman correlation coefficient and the Mann-Whitney U-test. A multivariate linear regression model was performed, with the logarithm of the EPDS score as the outcome variable and leptin, IL-6 and possible confounders as predictor variables.

SPSS version 15.0 was used for the analysis, and the significance level was set at a p-value of <0.05 .

Paper II

The data were modelled through multiple logistic regression, using self reported PPD status at five days, six weeks and six months as the outcome variable and year quartile as well as "maternity stressor score" as predictor variables.

SPSS version 17.0 was used for the analysis, and the significance level was set at a p-value of <0.05 .

Paper III

The data were modelled through multiple logistic regressions, using self reported PPD status at five days, six weeks and six months as the outcome variables and baby gender as well as potential confounders as predictor variables. Logistic regression models were repeated after stratification for previous contact with a psychiatrist or psychologist.

SPSS version 18.0 was used for the analysis, and the significance level was set at a p-value of <0.05 .

Paper IV

A multiple logistic regression model was used, with self reported PPD status as the outcome variable and PMS/PMDD as well as the possible confounders as predictor variables. Separate logistic regression models for EPDS screening status at five days, six weeks and six months after delivery were performed, and the regression models were repeated after stratification for parity.

SPSS version 18.0 was used for the analysis, and the significance level was set at a p-value of <0.05 .

Results

General results

For the whole of the UPPSAT cohort, 2318 women filled out at least one of the three questionnaires (93% among those who consented to participate in the study, 60% of all eligible delivering women). There were 52 women who moved without leaving a new address, and thus were lost to follow up. The response rate was 73.7% for the first questionnaire (1838/2493), 73.2% for the second one (1812/2475) and 63.7% for the third questionnaire (1554/2441) (See Figure 1). Answers to the EPDS in women who filled out the questionnaires significantly later than the required time points were excluded from the analyses, in order to minimize recall bias. One thousand three hundred and eight women answered all three questionnaires.

A non-response analysis was conducted, using anonymized data from the medical records of all women delivering in Uppsala University Hospital during the study period. Comparing the women participating in the study with the ones not participating, no significant differences could be found regarding maternal age, time of delivery (season and time of day), pregnancy complications, delivery outcome, gender of the baby, weight of the baby or area of residence. There was, however, a difference in parity, the study population having slightly more primiparas.

Table 1. *The prevalence of self reported depressive symptoms*

	Control N (%)	Case N (%)
Five days postpartum	1504 (88.9)	187 (11.1)
Six weeks postpartum	1536 (88.9)	191 (11.1)
Six months postpartum	1398 (90.5)	146 (9.5)

Out of the 2318 women in our cohort, 15.5% had self reported depressive symptoms at one or more points during the study period. The prevalence of depressive symptoms at five days, six weeks and six months postpartum are displayed in Table 1. The outcome regarding screening status among the 1308 women answering all three questionnaires is displayed in Figure 2.

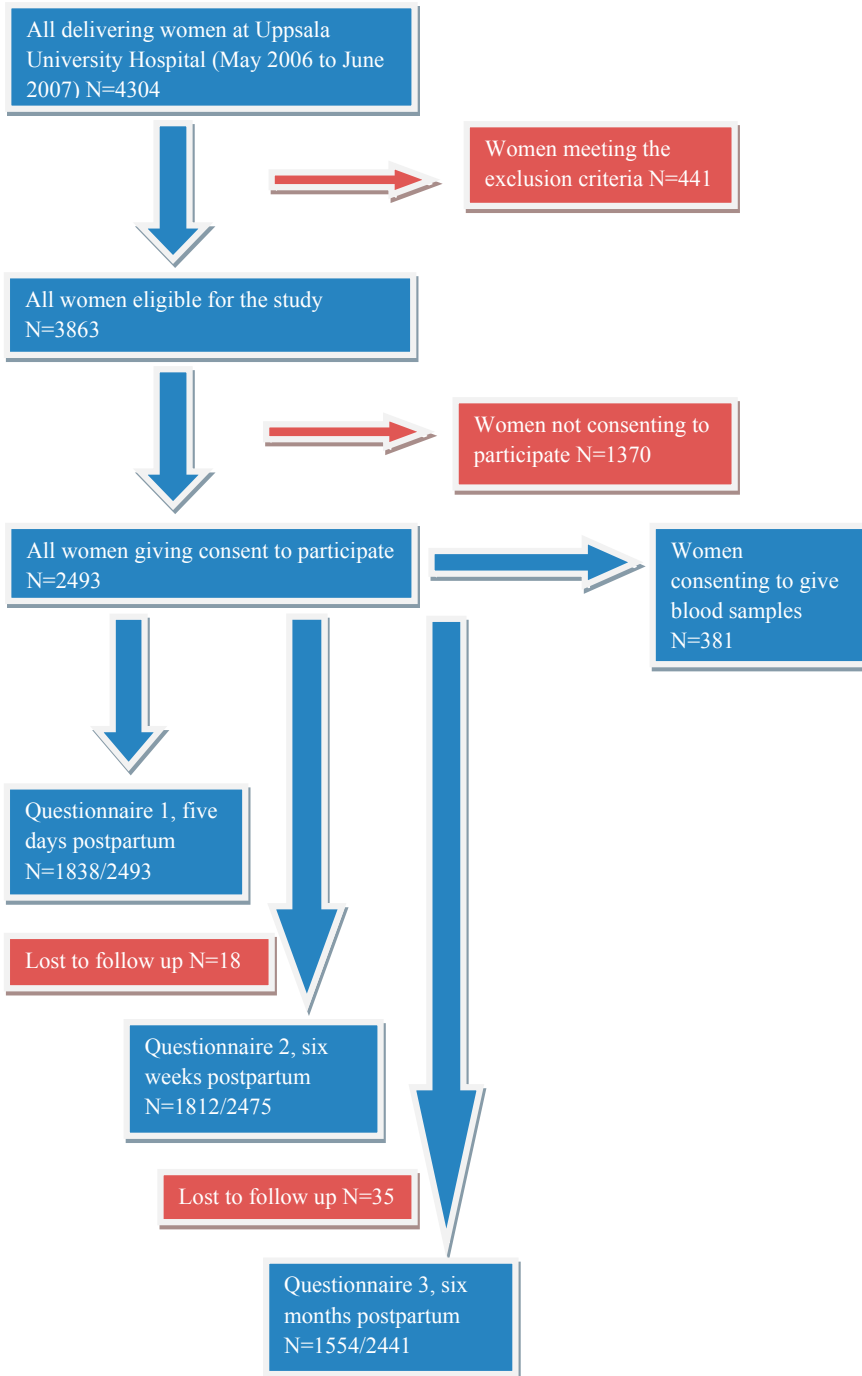


Figure 1. Flow chart of participants

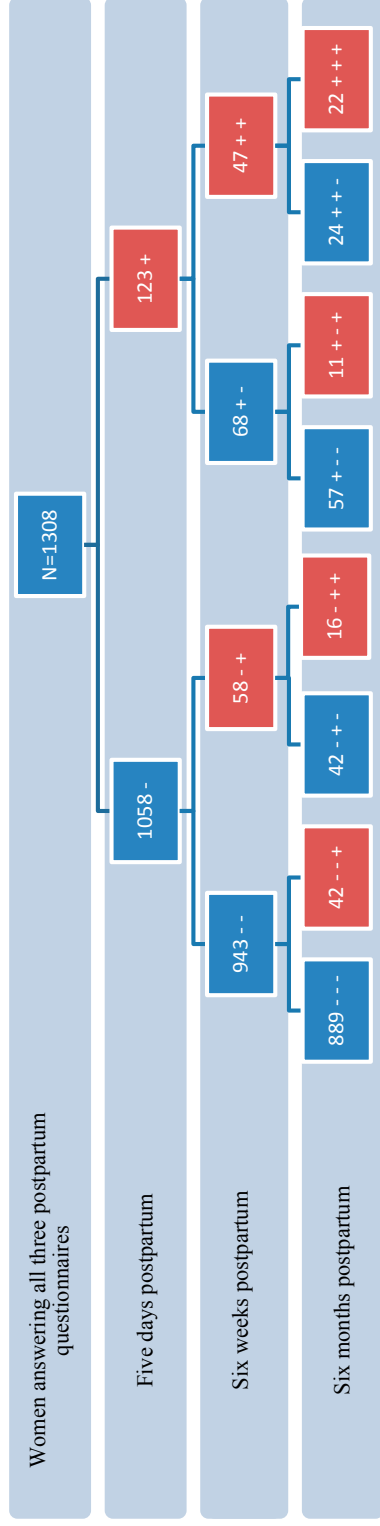


Figure 2. EPDS case/control status at five days, six weeks and six months after delivery among the 1308 women who answered all three postpartum questionnaires (+ stands for case of self reported PPD, - for control)

The mean age of the women participating in the UPPSAT study was 30.8 years (S.D. 4.6 years). Among the participating women, 45.4% had a qualified occupation, whereas 54.6% were students, unemployed or had an unqualified occupation. Ninety-eight point five percent of the women were married or living with a partner, and 46.2% of these women perceived their partner as being supportive six weeks after delivery. Seventy-five point three percent of the women had a vaginal delivery, whereas 24.7% required assisted delivery (vacuum extraction or caesarean delivery). Eighty-eight point seven percent of the women were exclusively breastfeeding their infant five days after delivery, 80.4% were breastfeeding six weeks after the delivery and six months postpartum, 39.8% were still breastfeeding. The mean duration of gestation in this sample was 278 days (S.D. 12.8 days). Seventy-six percent of the women in our cohort had never had contact with a psychiatrist or psychologist prior to or during the current pregnancy. Seventeen percent of the women had not planned the current pregnancy and 46% were first time mothers.

In table 2, factors possibly associated with self reported PPD are displayed. For the purpose of this table, a woman was considered a case of self reported PPD if she had screened positive at least one time during the study period.

Table 2. *Potential risk factors and their possible association with self reported PPD status within the first six months postpartum*

		OR (95% CI)
History of psychiatric illness	No	-*
	Yes	3.8 (2.9-5.0)
Maternal age	One year increments	0.97 (0.95-1.0)
Maternal age (groups)	22-35 years	-
	36-46 years	0.8 (0.5-1.2)
	15-21 years	1.2 (0.6-2.6)
Maternal BMI	One kilogram increments	1.05 (1.02-1.08)
Maternal BMI (groups)	Normal (18.5-25)	-
	Underweight (<18)	1.5 (0.7-3.4)
	Overweight (25-30)	1.6 (1.1-2.2)
	Obese (>30)	1.8 (1.2-2.9)
Maternal occupation	Qualified	-
	Unqualified	1.4 (1.0-1.8)
	Unemployed	2.0 (1.4-2.9)
Maternal place of birth	Sweden	-
	Other	1.0 (0.6-1.7)
Smoking during pregnancy	No	-
	Yes	1.9 (1.1-3.4)
Family status	Married/living with partner	-
	Single	3.7 (1.7-8.1)
Support from the father	Adequate	-
	Low	2.1 (1.5-2.8)
SLE ^a during last six months	No	-
	Yes	2.7 (2.0-3.5)
Duration of gestation	One day increments	0.99 (0.99-1.0)
Duration of gestation (groups)	Normal	-
	Premature	0.97 (0.4-2.3)
	Postterm	0.48 (0.2-1.4)
Delivery	Vaginal	-
	Cesarean	1.5 (1.1-2.0)
Breastfeeding at six weeks	Yes	-
	No	2.0 (1.5-2.6)
Hours sleep at six weeks	More than six hours/night	-
	Less than six hours/night	2.9 (2.2-3.7)
Severe nausea during pregnancy	No	-
	Yes	1.5 (1.0-2.2)
Use of assisted reproduction (IVF)	No	-
	Yes	0.8 (0.5-1.3)
Mood swings when using OCs	No	-
	Yes	2.0 (1.5-2.6)
Previous miscarriage(s)	No	-
	Yes	1.1 (0.8-1.5)
Previous abortion(s)	No	-
	Yes	1.2 (0.9-1.7)
Parity	Primipara	-
	Multipara	0.8 (0.7-1.1)

*considered as baseline

^a Stressful life event

Table 3. *Linear regression models for variables associated with depressive symptoms six weeks and six months after delivery*

Variables	EPDS six weeks postpartum	EPDS six months postpartum
	B ¹	B ¹
Leptin	0.82*	0.82*
IL-6	1.10	1.06
BMI	1.03	1.02
Age	1.00	0.99
Duration of gestation	0.99	0.99
Newborn gender	0.95	0.94
Smoking	0.87	0.80

¹ B is the coefficient from the linear regression model

* p- value <0.05

Paper I

In total, one blood sample, written consent, as well as at least one completed questionnaire were available for 365 women. Eighteen women who reported alcohol use during pregnancy were excluded from the analysis because of the reported significant alterations in leptin levels among alcohol consumers, leaving 347 to be included in the final analyses.

The results of the linear regression models, with EPDS score as the outcome variable and leptin, IL-6 and possible confounders as predictor variables, show lower maternal serum leptin levels at delivery to be associated with higher risk for depressive symptoms five days ($p=0.082$), six weeks ($p=0.009$) and six months after delivery ($p=0.026$). More specifically, leptin levels higher by one standard deviation among controls, which corresponds to 34.06 ng/mL, were associated with an EPDS score lowered by 18% six weeks and at six months after delivery. The EPDS score was introduced as the outcome variable after logarithmic transformation in order to account for non-normality. In the analyses, adjustments were made for maternal BMI at six weeks postpartum, maternal age, duration of gestation, offspring gender, as well as maternal smoking status during pregnancy.

No association between depressive symptoms during the first six months postpartum and IL-6 levels at delivery could be found.

Paper II

When studying seasonal effects on depressive symptoms, we investigated the entire UPPSAT cohort (2318 women).

The point prevalence of self reported PPD is displayed in Figure 3. This graph was constructed using a moving average procedure. Women giving birth during October, November and December had a higher prevalence of

self reported PPD compared to those giving birth in June, at all three postpartum assessment points.

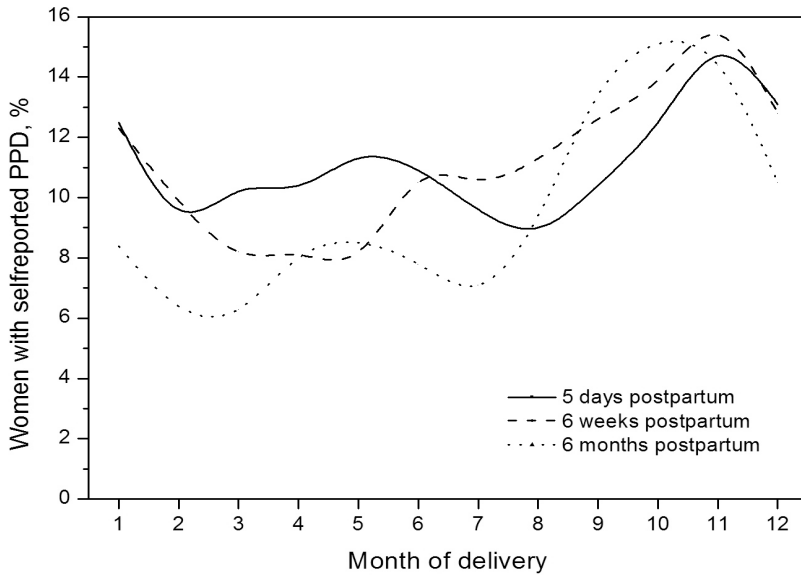


Figure 3. The point prevalence of self reported PPD in relation to month of delivery

After dividing the year into quartiles, the multiple regression analyses including the entire cohort showed significant associations between self reported PPD status at six weeks and six months postpartum and delivery during the fourth quartile of the year, even after adjusting for confounders. When investigating only the women without previous psychiatric contact, significant associations were observed between self reported PPD at six weeks postpartum and the fourth quartile, both before and after adjustment for possible confounders. Six months after delivery, the crude association was significant, but after adjusting for maternity stressors the results were borderline significant. Among women with previous psychiatric contact, no significant associations between quartile of delivery and self reported depression were observed. In Table 4, the results of the regression analyses for the entire cohort, with EPDS case/control status at six weeks and six months postpartum, are displayed.

There were no significant associations between self reported PPD at five days postpartum and quartile of delivery.

Table 4. Multiple logistic regression models displaying the risk for self reported PPD in relation to season of delivery and confounding factors

Variables	EPDS six weeks postpartum OR (95% CI)	EPDS six months postpartum OR (95% CI)
Season of delivery		
Quartile 1	1.65 (0.89-3.08)	0.85 (0.44-1.64)
Quartile 2	-	-
Quartile 3	1.46 (0.79-2.72)	1.22 (0.67-2.19)
Quartile 4	2.83 (1.57-5.10)	1.83 (1.02-3.29)
Previous psychiatric history		
No	-	-
Yes	3.66 (2.44-5.48)	4.05 (2.65-6.19)
Maternity stressors		
None	-	-
One or more	4.24 (1.53-11.78)	2.64 (1.19-5.85)

Paper III

For this study, only the women with singleton births were included (2267 women). The variables that could act as potential confounders and were used in the logistic regression model were maternal age, level of employment, duration of gestation, delivery mode, breastfeeding and partner support.

Results from the multiple logistic regression analysis, with self reported depression at five days after delivery as the outcome variable and baby gender as well as possible confounders as the predictor variables, show a significantly higher risk for postpartum blues among women who gave birth to boys (OR = 1.38, $p < 0.05$). The association remained significant after adjusting for maternal age, maternal level of employment, duration of gestation, delivery mode, breastfeeding and partner support (OR = 1.42, $p < 0.05$). These results are displayed in Table 5. Among women without previous psychiatric contact, the respective adjusted OR was 1.53 ($p = 0.057$), controlling for possible confounders, while among women who have had a previous psychiatric contact, the association was non-significant.

No significant associations between self reported depression and baby gender could be detected at six weeks (OR=1.16, $p=0.51$) or six months postpartum (OR=1.40, $p=0.145$), not even after controlling for possible confounders or after stratification according to previous psychiatric contact.

When investigating primiparas separately, no association between gender of the newborn and risk for self reported PPD could be detected, at five days, six weeks or six months postpartum.

Among the twenty-eight women in our cohort born outside Europe, a tendency towards a higher risk for depressive symptomatology five days after delivery among those who gave birth to female offspring could be detected – of

the 11 women giving birth to boys, not one scored high on the EPDS, while 4 out of the 17 women giving birth to a girl had self-reported depression five days postpartum. Women from the United States, Canada and Australia were excluded from this analysis due to cultural similarities with Sweden.

Table 5. *Multiple logistic regression displaying the risk for self reported postpartum blues in relation to baby gender and confounding factors*

Variables		EPDS five days postpartum OR
Newborn gender	Girl	-
	Boy	1.42*
Maternal age	One year increments	0.98
Duration of gestation	One day increments	0.99
Maternal level of employment	High	-
	Low/unemployed	1.49**
Breastfeeding five days postpartum	Exclusive	-
	Non-exclusive/none	2.48*
Partner support five days postpartum	High	-
	Low	1.64

*p-value <0.05

**p-value <0.10

Paper IV

For this paper, the entire cohort (2318 women) was included. The variables that could possibly act as confounders, and were therefore included in the multiple regression models, were: previous psychiatric contact, maternal age, a history of mood swings while taking oral contraceptives (OCs), nausea during current pregnancy, inadequate sleep and breastfeeding. Parity was strongly associated with PMS/PMDD, but not with PPD, and was therefore treated as an effect modifier instead of a confounder. Thus, the multiple logistic regression models were repeated after stratification for parity.

The prevalence of self reported PMS and PMDD was 7.1 % (128 women) and 2.9% (53 women), respectively. When investigating primiparas and multiparas separately, the prevalence of PMS was 5.0% in primiparas and 8.8% in multiparas. The criteria for PMDD were met in 2.1% of the primiparas and 3.6% of the multiparas.

PPD was significantly associated with PMS and PMDD, respectively, at all three postpartum measurements. When investigating the entire cohort, these associations remained significant after adjusting for confounding factors at five days and six weeks, but not at six months postpartum (Table 6).

Table 6. *Multiple logistic regression models displaying the risk for self reported PPD in the entire cohort, in relation to PMS/PMDD status, and after adjustment for confounding factors¹*

Variable	EPDS five days postpartum OR (95% CI)	EPDS six weeks postpartum OR (95% CI)	EPDS six months postpartum OR (95% CI)
PMS	3.40 (1.99-5.82)	3.35 (1.72-6.51)	1.59 (0.73-3.45)
PMDD	6.78 (3.20-14.38)	4.20 (1.57-11.26)	2.48 (0.92-6.70)

¹ Adjusted for previous psychiatric contact, maternal age, mood swings from OCs, nausea during pregnancy, sleep and breastfeeding

When stratifying for parity, however, primiparas displayed no significant association between PMS/PMDD status and postpartum depressive symptoms, except in the unadjusted models for 5 days postpartum, and for the PMS cases at 6 months postpartum. Multiparas with previous PMS/PMDD had an increased risk of self reported postpartum depression at five days and six weeks postpartum, but the respective associations six months postpartum were not significant after adjustment for confounders (Table 7).

Table 7. *Multiple logistic regression models displaying the risk for self reported PPD among multiparas, in relation to PMS/PMDD status, and after adjustment for confounding factors¹*

Variable	EPDS five days postpartum OR (95% CI)	EPDS six weeks postpartum OR (95% CI)	EPDS six months postpartum OR (95% CI)
PMS	4.58 (2.29-9.15)	6.15 (2.80-13.52)	1.50 (0.57-3.94)
PMDD	8.40 (3.24-21.75)	9.82 (3.24-29.74)	2.81 (0.83-9.48)

¹ Adjusted for previous psychiatric contact, maternal age, mood swings from OCs, nausea during pregnancy, sleep and breastfeeding

Discussion

Methodological considerations

The UPPSAT study has several strengths. Its population based design, the large study sample, and the substantial information on possible confounding factors (on an individual basis) are all factors that increase the generalizability of the findings presented in the papers. There are, nevertheless, many limitations that one must consider.

The exclusion criteria were a methodological limitation. Excluding all women who were not fluent in Swedish was necessary for practical reasons, however, it led to the study population being almost exclusively native Swedish women. As a consequence of this, it is plausible that the results from the study cannot be extrapolated to women in cultures that substantially differ from Sweden. This limitation is perhaps most explicit in Paper III, since several previous studies suggest that the gender of the infant and the risk for PPD is a subject sensitive to cultural influences. The mental health of immigrant women is of great importance, and it would be interesting to study if cultural perceptions continue to burden women after coming to Sweden.

The response frequency for the UPPSAT study was 60% of the entire eligible population, and 93% of all women giving written consent to participate. Response rates for academic studies are usually between 50 and 60%, and a response rate of 60% must be considered acceptable (187-188). We also conducted a non-response analysis, which detected no differences between the groups regarding maternal age, time of delivery (season and time of day), pregnancy complications, delivery outcome, gender of the baby, weight of the baby or residence area. For parity, there was a difference between the participating and non-participating women, the study population consisting of slightly more primiparas. The likely explanation as to why more primiparas accepted to participate in the current study can only be speculated, but would plausibly have more to do with time issues than rates of PPD. We could not perform an attrition analysis, since we had no data on depression rates in the women not consenting to participate in the study. However, previous studies indicate that psychiatric illness is more common in people not consenting to participate in research, and inclusion of the women not consenting to participate would probably thus have led to strengthening of the associations reported in this thesis (189). The participation

rates of only 60% of all eligible delivering women could be considered a potential problem in Paper II. One could hypothesize that if season was to have an effect on depression rates, this might have led to an increased drop-out rate for depressed women during a certain period of the year. Still, this would probably have led to an underestimation of the association. Moreover, when we controlled the drop-out rates throughout the year, they were stable.

In the UPPSAT study, we did not have the opportunity to send reminders, for administrative reasons. This might have negatively affected the number of depressed mothers participating, since one could imagine that depressed mothers possibly would not have the energy to fill out the questionnaires, or remember to return them. Nonetheless, this limitation would probably have led to an underestimation of the factors associated with PPD, rather than an overestimation.

Although the EPDS is a validated instrument for the detection of women at risk for suffering from PPD, one must take into consideration that it does not provide us with a clinical diagnosis. The scale is a self administered instrument, which was used in the current studies instead of a psychiatric interview for the classification of postpartum depression cases, for methodological reasons (due to the large study sample). In the Swedish validation, the EPDS displayed a sensitivity of 96%, a specificity of 49% and a positive predictive value of 59% (32). This could result in misclassification of non-cases as cases (false positives) but this would, on the other hand, underestimate possible associations. The Swedish validation of the EPDS is based on comparison with interviews using the Montgomery Åsberg Depression Rating Scale (MADRS) and assessment according to DSM-III-R criteria for major depression. Validations in Norway and Spain, among others, have displayed sensitivities and specificities similar to the Swedish validation when using the Mini International Neuropsychiatric Interview for DSM-IV major and minor depressive disorders (MINI) and the Structured Clinical Interview for DSM-IV, non-patient (SCID NP) (190-192). A recent Swedish meta-analysis conducted by the *Swedish Council on Health Technology Assessment* (currently in press) states that the EPDS has a sensitivity of 72% and specificity of 88% (using a cut off of 12/13), and thus only detects about two thirds of all cases of postpartum depression (193). This must be taken into consideration when interpreting the results in this thesis, since it has probably led to an underestimation of the detected associations. It is also in line with previous results from Sweden, indicating that the health care system fails to identify many of the women suffering from PPD (28).

The blood samples used in this study were taken during delivery, in conjunction with routine intravenous catheterization. The blood samples were only available from women who gave birth from November 2006 to May 2007, for administrative reasons. This was unfortunate, since blood samples from all the months of the year would have been optimal, to investigate sea-

sonal differences in biological parameters. Labor represents an extremely stressful situation, and usually occurs unplanned throughout the day, which could affect the results as well as the timing of the blood samples. The timing of blood samples could, in turn, affect the hormone levels assessed, since many hormones, such as for example leptin, exhibit a diurnal variation and is also affected by fasting (194-195). No such tendencies were observed in our samples, however. Repeated blood samples in the first few weeks postpartum could have provided us with a better understanding of the hormonal pathophysiology behind PPD, but were not possible to obtain, unfortunately.

Measuring levels of hormones such as leptin and IL-6 in serum is not optimal. The hormone levels in cerebrospinal fluid (CSF) are thought to correlate much more intimately with pathological processes in the brain, for example depression, and one study has even shown an association between CSF levels of IL-6 at delivery and PPD (156). In the current study, we had no possibility to obtain CSF samples, for obvious reasons.

Antenatal depression is, as stated earlier, a strong risk factor for PPD. The design of the UPPSAT study did not enable us to collect information on the presence of depressive symptoms during pregnancy, which would have been useful in the analyses. For example, the presence of antenatal depression is thought to be associated with high cortisol levels (149), which could influence leptin synthesis and secretion. However, we did have the possibility to collect substantial information on a large number of other potential risk factors, on an individual level, and include them in the analyses. The selection of possible confounding factors was made after thorough literature studies and, also, after assessing the correlations between the potential confounder and the risk factor and primary outcome measure, respectively.

A major limitation of this study is the use of retrospective measurements for the diagnosis of PMS/PMDD. This method is not as reliable as using prospective daily ratings for several menstrual cycles; however, prospective measurements were not possible in the current study. Instead we used strict criteria for PMS/PMDD, based on the DSM-IV, and a woman was considered a case only if all the criteria were met, to reduce the risk of memory bias. Even so, one should consider the fact that memory bias will most likely not lead to overestimation, but underestimation of symptoms. A study from New Zealand indicates that the prevalence of lifetime mental disorders to age 32 was approximately doubled in prospective as compared to retrospective data (196). A memory bias effect might even explain the discrepancy in PMS symptom reporting between first time mothers and multiparas, since the primiparas are possibly more overwhelmed by the delivery experience and having to take care of their newborn that they are more likely to under-report previous premenstrual symptoms.

Ethics

There are some ethical considerations that must be addressed in a study such as UPPSAT. First, one must consider the burden we put on the women when asking them a number of personal questions, which may leave them feeling more vulnerable than before entering the study. Some women might have experienced depressive symptoms, but never considered harming themselves, before encountering respective questions in the structured questionnaires. We tried to address these issues by first conducting a pilot study during one week, asking participants to comment on the length of the questionnaires and quality and nature of the questions. A very high participation rate was achieved during the pilot study (80%), and small adjustments were made to the questionnaires, which were otherwise considered appropriate by the participants. During the course of the study, we were on a weekly basis calculating the total EPDS score and directly assessing the individual answers when the women sent back the questionnaires. The women with a high EPDS score and/or answers indicating suicidal thoughts or plans were contacted by one of the study doctors. A clinical assessment was made, and depending on the severity of the woman's depressive symptoms, she was referred to a psychologist or a psychiatrist or, if the symptoms were mild, was given clinical guidance and practical advice from the study doctor.

Beside these considerations, we believe that participation in the study had many positive aspects for the participants. Several of the participants expressed their joy in being able to contribute in this field of research. Furthermore, studies show that PPD is both under diagnosed and inadequately treated. The reasons for this are thought to be due to the fact that health care providers do not detect all cases, but also because women do not seek medical attention, although they desperately need to. When participating in a study like UPPSAT, the women were followed up as described above. This actually led to the prompt detection and referral of PPD cases that would otherwise possibly never have been diagnosed or treated.

Paper I

This nested case-control study demonstrates that lower serum leptin levels at delivery are associated with higher risk for the development of postpartum depressive symptomatology. This is, to our knowledge, the first time such an association has been reported in the literature. If this finding can be replicated by other studies, leptin could possibly be included in a biological test for PPD in the future. Bearing in mind the several similarities between postpartum depression and atypical depression, these results might even contribute in the efforts to unravel the complex pathophysiological mechanisms involved in that condition as well.

Previous studies have investigated leptin levels in depressed patients, with mixed results (166-168, 197-199). This may partly be explained by the inclusion of different depression subtypes. Since melancholic and atypical depression have differences in the HPA-axis function and leptin levels are induced by cortisol, the difference in leptin levels are not unlikely, on a basic pathophysiological level (200). Also, not controlling for confounding factors, differences in inclusion criteria and presence of co-morbidity may contribute to the inconclusive results on the association between leptin and major depression.

The limitations of this study have been mentioned above. Nonetheless, in spite of these limitations, the negative association between leptin and depressive symptoms was still present, and thus the potential predictive value of serum leptin levels at delivery cannot be considered compromised.

Paper II

This study shows an association between development of self reported postpartum depression and season of delivery, the darker autumn months giving new mothers a significantly higher risk for depressive symptoms six weeks and six months postpartum, even after adjustment for confounding factors. These results point in the same direction as previous studies, and are of clinical importance, since mothers delivering during the last three months of the year could benefit from a closer follow up after birth.

When stratifying for previous psychiatric contact, the women with a history of psychiatric illness did not follow the same pattern as previously healthy women. One reason for this could be that delivery could act as a potential trigger for a depressive episode, regardless of when it takes place, and for especially vulnerable women with a history of depression this might be enough to “tip the scales”. Another explanation could be that women with an ongoing affective illness already have contact with public health services, and thereby might have received support and treatment early in the puerperium, or during pregnancy.

As to the possible explanations of the association between PPD and season of delivery, one can only speculate. The serotonergic activity in the brain is thought to contribute to the development of mood disorders, and a seasonal variation of the major serotonin metabolite 5-hydroxyindoleacetic acid has been found in normal volunteers (201). Studies have also shown seasonal variation in brain turnover in healthy men, with the highest values during spring and summer, as well as lower serotonin concentrations in the hypothalamus during winter in post-mortem brains (202-203). Thus, one may hypothesize that decreased serotonergic activity in fall and winter in healthy individuals may give women who deliver during this period a predisposition for developing PPD. A recent genetic study also point to an asso-

ciation between a polymorphism in the brain-derived neurotrophic factor (BDNF), season of birth and PPD. In that study, a significant association between BDNF Met66 carrier status and development of PPD symptoms at six weeks postpartum, even when controlling for relevant risk factors, was evident among women delivering during autumn/winter (182).

Sweden is a country with very varying seasons, the summer being bright – the sun sets for only a few hours every night – and the winters cold and dark, with only a few hours sunshine each day. The effect of light on depression has been discussed for some time, and attempts have even been made using light therapy as a treatment for PPD (204). Vitamin D is a substance that has received some attention recently, and has been implicated in the pathophysiology of affective disorders (205). Since vitamin D is, for the most part, synthesized in the skin with the help of sunlight, one could speculate that, through lack of sunlight, this might be a contributing factor in the association between PPD and season of delivery.

Paper III

This longitudinal study demonstrates that the birth of a male offspring in Sweden is associated with a higher risk for postpartum blues five days after delivery, even after adjusting for potential confounding factors. The association is no longer evident at 6 weeks or 6 months postpartum.

Previous studies from traditional eastern societies such as India and China have suggested an association that was in contrast with the one in our study, namely that giving birth to a baby girl will render the mother not only more prone to depression postpartum, but also more likely to be subjected to physical violence from her partner (109-110, 112-113, 206). The reasons for this are thought to be solely cultural, since the preference for male children is deeply rooted in some societies, due to for example dowry payments. In China, the one child-policy has led to a preference for boys over girls, since the son is presumed to take over the family farm or business, while a daughter will “belong” to the groom’s family after marriage.

To our knowledge, there is only one study from a traditional western society that points in the same direction as our study (115). However, in the study by de Tyche et al., the association between offspring gender and PPD was still evident two months after the delivery, while in our study it was only present five days postpartum. Another study conducted in European societies demonstrates that a mixed-gender preference is most common (114). Mixed-gender preference, however, should not have influenced our results, since disappointment of not fulfilling such a preference would affect women with female offspring as well. When investigating primiparas separately, we found no differences in gender preference, which would support this notion.

An interesting biological explanation for the association between postpartum blues and gender of the newborn could be in line with the results from Paper I of this thesis. Higher plasma leptin concentrations have been reported in mothers carrying female offspring (165), and in Paper I we presented our finding of a negative association between leptin levels at delivery and PPD. One hypothesis could thus be that mothers carrying male fetuses have lower leptin levels at delivery, and thus are at greater risk of developing postpartum blues.

Paper IV

In line with previous work, this study confirms the previously reported association between PPD and premenstrual symptoms. However, the introduction of parity as a potential effect modifier is, to our knowledge, a new finding which may help shed some light on the discrepancies of previous studies.

The association between PMS/PMDD and PDD has been debated in previous studies. A biological explanation is not too unlikely, since PMDD is thought to be – at least in part – a disorder of steroid hormone fluctuations and neurosteroid withdrawal, with symptoms most pronounced during the late luteal phase when progesterone and neurosteroids are rapidly decreasing (141). The postpartum period is also a period characterized by low sex steroid hormones, and the rapid decrease in steroids after parturition may mimic that of the luteal phase for women sensitive to hormone fluctuations (140). This would even explain the fact that the association between PPD and PMS/PMDD in our study was more pronounced at five days and six weeks postpartum, and disappeared after adjustment for confounding factors in the measurement at six months after delivery.

Another biological association between PPD and PMS/PMDD could be the possible dysregulation of the serotonin system, which has been discussed recently. SSRIs are one of the standard treatments for PPD, as for other affective disorders, and SSRIs also are increasingly used in the treatment of PMDD (133, 143-142). According to a recent review (144), they are highly effective in treating behavioral, functional and physical symptoms of the disorder. The mechanisms behind this “serotonin hypothesis” are not fully understood, but recent studies have provided evidence that estrogen regulates the serotonin pathways in different ways, for example through inhibition of monoamine oxidases (MAOs) and up regulation of serotonin receptors, leading to an increase in serotonin availability and neurotransmission (207).

The modifying effect of parity could in part be explained, at least from a clinical perspective. A woman with one or more small children in her care will likely find the presence of premenstrual symptoms more disturbing than a woman without any children. Also, premenstrual symptoms have been

reported to increase with increasing parity, even though it seems that some symptoms worsen (such as irritability, decreased interest and hypersomnia) while others may remain unchanged or even decrease (e.g. anxiety, mood swings, and physical symptoms), both in our study and a recent one by Dennerstein et al. (2008). Increasing age, on the other hand, seemed to decrease most of the premenstrual symptoms for the women in our study, save symptoms of depressed mood, feeling overwhelmed and physical symptoms. In our study, we noted that the effect of parity on premenstrual symptoms remained after controlling for age in the stratified analyses, which is also in accordance with our clinical experience.

Conclusion and clinical relevance

In this large population based sample, we have been able to investigate both factors previously implicated in PPD pathophysiology, and potential biological biomarkers for the disease. Although season of delivery, gender of the newborn and a previous history of premenstrual disorders have been discussed in relation to PPD to some extent in the literature, we believe that our sample is large enough to shed some light on the discrepancies of previous studies. Season of delivery, gender of the newborn and a history of PMS/PMDD also have the advantage that they are all variables that can easily be obtained by a caregiver, either by asking the woman directly or by studying the medical records. Thus, we believe that women who have a history of PMS or PMDD, deliver in the autumn, and give birth to a baby boy might benefit from a closer follow up during the first few months postpartum.

As to the finding of the association between PPD and leptin levels, this is, as discussed before, a very interesting one. The possibility of a biological diagnostic test for the detection of PPD is tempting to consider, and we hope that future studies will be able to replicate our results, and bring us one step closer to possibly predicting PPD.

Future work

The UPPSAT study

Many of the pieces in the puzzle that is PPD pathophysiology have started to unravel themselves in recent years, and our hope is that this thesis will contribute in this direction. Nonetheless, there is still a vast amount of work to be done before we can even begin to understand the underlying mechanisms and start to develop convenient screening tools and biological diagnostic tests.

In order to investigate the prevalence and the correlates of PPD in a population of previously healthy primiparas, we have chosen to include only the first time mothers without any previous psychiatric contact in a sub-cohort of the UPPSAT study. Since we have a large amount of data on an individual basis for these women, it will be most interesting to note if there is a difference in risk factors in this group, compared to the entire cohort.

The effect of thyroid disturbances on PPD and other affective disorders is well known. In UPPSAT, we have blood samples from 367 women, and have now started to analyze these, in order to evaluate if one of the hormones of the thyroid axis could act as a potential biomarker for PPD.

As a follow up study to the work we did on seasonality in PPD, we have collected data from the *Swedish Meteorological Institute* (SMHI), to investigate whether the presence or absence of sunlight is in fact the reason behind the association between PPD and season of delivery. In accordance with this, we have the intention to analyze vitamin D in the women of the UPPSAT study, to determine whether the levels of this vitamin will differ depending on season of birth, and, also, if vitamin D levels at delivery have an association with the risk for self-reported PPD.

The prevalence and correlates of PPD in men have not been extensively studied. In the UPPSAT study, we had the opportunity to approach the partners of the participating women, and have received answers from approximately 1500 men. This gives us a unique chance to investigate the prevalence and correlates of PPD in this population, and the possible association PPD in the father may have with PPD in the mother. This is an important subject, not only for the affected men and their partner, but also certainly for the children in these families. It is well known that depression in one or both of the caregivers will have an impact on the child, and it can be speculated that depression in both parents will affect the child to an even greater extent.

As stated in the introduction, genetic studies on PPD are few. However, the UPPSAT study has already contributed to this area with two studies. In the first one, we investigated the gene-environment interaction between genetic variations in the monoaminergic system (COMT, MAOA and 5HTT), SLEs, maternity stressors and previous psychiatric contact and the possible contribution these might have in the risk for PPD (183). Three functional polymorphisms were genotyped. The COMT-Val¹⁵⁸Met was found to be significantly associated with self reported PPD at six weeks, but not at six months postpartum, while a significant gene-gene interaction effect was present between COMT-Val¹⁵⁸Met and MAOA-uVNTR. Following this, a gene-environment model displayed significant associations between PPD symptoms and COMT-Val¹⁵⁸Met, psychiatric contact and maternity stressors. Among the women with a history of psychiatric contact, the COMT-Val¹⁵⁸Met and 5HTT-LPR risk variants were associated with self reported PPD, whereas in the women without psychiatric contact only maternity stressors were associated with self reported PPD.

The results from our study replicated the results from a previous study (184), which is always important when investigating genetic associations. In addition, we found the association even after adjusting for possible confounding factors. Our conclusion from this study is that PPD is most likely a result of several complex interactions between multiple factors, including genes, environment, hormones and other factors. The results from our study also point to the contribution of a dysfunction in the monoaminergic system in the etiology of PPD.

In the second genetic study from UPPSAT, we aimed to investigate whether the functional polymorphisms BDNFVal66Met, 5HTT-LPR and PER2 SNP10870 were associated with PPD symptoms, and, in addition, if these polymorphisms interact with season of delivery in predicting PPD. The results revealed no overall association between self reported PPD and the studied polymorphisms. However, a significant association between self reported PPD and BDNF Met66 carrier status was found in women delivering during fall/winter, after controlling for environmental risk factors. No gene-gene interactions were found, but a cumulative effect was detected in carriers with a greater number of 5HTT-LPR S and BDNFVal66Met Met alleles reporting higher EPDS scores, if delivered during fall/winter. These findings lead us to believe that the BDNF gene could play a role in the development of PPD, and that this association is potentially mediated by season of delivery.

The BASIC study

When working with the UPPSAT study, many new questions were raised. The need for data on depressive symptoms during pregnancy, as well as

personality traits and anxiety, would be interesting to relate to PPD. As mentioned above, the biological and genetic research on PPD is somewhat sparse, and the collection of a population-based bio bank seemed to us the best way to enable extensive biologic research in the PPD field.

Considering this, a new study was started in 2009. BASIC stands for Biology, Affection, Stress, Imaging and Cognition, and the study is based on a population of pregnant women followed in Uppsala University Hospital. The women are approached before their routine ultrasound, which takes place in gestational week 17-18, and are given extensive written information about the study. If they give written consent, an email is sent to them soon after the routine ultrasound, containing a link to the web based questionnaires that are the basis for the BASIC study. Additional questionnaires are sent to the women at gestational week 32, as well as six weeks and six months postpartum. The questionnaires contain the EPDS, as well as more extensive scales designed to evaluate psychiatric illness (depression, bipolar disorder, and etcetera), personality traits, anxiety traits, posttraumatic stress, stressful life events and sleep disturbances. In addition, the questionnaires contain multiple questions on social parameters, expectations concerning the delivery, relation with the partner and the baby, among other things. Because of the web based design, it is easy to approach the women with reminders if they have forgotten to answer one of the questionnaires, which is a factor we hope will raise the response rates.

To evaluate biological parameters possibly related to PPD, an extensive blood and tissue sampling procedure has been established. After the women give informed consent to do so, they donate the following biological material: Blood samples, amniotic fluid, placenta biopsy, and a blood and tissue sample from the umbilical cord. The women who are delivered via cesarean, and receive spinal anesthesia, will donate spinal fluid and a biopsy from the uterus, in addition to the biological material mentioned above.

A random sample of the women participating in the BASIC study are asked to come in to the clinic for a more extensive psychiatric and psychological evaluation, at gestational week 36 and six weeks postpartum. During these psychological assessments, blood, urine and saliva samples are collected. In addition, a number of cases (women who screened positive on the EPDS, and subsequently were diagnosed with depression after a psychiatric interview) and controls are asked to participate in an imaging study, using functional magnetic resonance imaging to study the brain.

By collecting and analyzing of the data within the BASIC study, we hope to contribute in unraveling the underlying mechanisms of postpartum depression pathophysiology.

Summary in Swedish

Sammanfattning på svenska

Min avhandling studerar postpartumdepression, vilket är en åkomma som drabbar cirka 10-20 % av alla nyförlösta kvinnor. Tillståndet definieras som en depressiv episod, där kvinnan insjuknar med depressiva symptom under det första året efter förlossningen. Alla fyra delarbeten i avhandlingen bygger på en studie, UPPSAT, där samtliga kvinnor som förlöstes och vårdades vid förlossningsavdelningen/BB på Akademiska sjukhuset från och med maj 2006 till och med juni 2007 tillfrågades om de ville delta i en studie om psykisk hälsa och välmående efter förlossningen. Kvinnorna fick fylla i enkäter med frågor om tidigare sjukdomar inklusive psykiatrisk hälsa, premenstruella symptom, tidigare gynekologiska händelser (missfall, aborter, infertilitet etc.), barnets hälsa, förlossningsupplevelse, relation till partnern, socialt stöd, med mera. I enkäterna ingick även Edinburgh Postnatal Depression Scale (EPDS) vilket är ett etablerat screeninginstrument för postpartumdepression, i Sverige och internationellt. I Sverige har EPDS validerats och man har funnit att en cut-off på 12 poäng (av 30) ger högst sensitivitet och specificitet, varför vi i de studier som ingår i avhandlingen räknar alla kvinnor med 12 poäng eller mer på EPDS som egenrapporterade fall av postpartumdepression. Kvinnorna fyllde i en enkät inom den första veckan efter förlossningen, en efter cirka sex veckor och en efter sex månader. Vi hade även möjlighet att ta blodprover på 367 kvinnor, för analys av hormoner och gener.

I delarbete I ville vi undersöka en möjlig biologisk förklaringsmodell till postpartumdepression, och valde att studera nivåer av Leptin och Interleukin-6 i serum vid förlossningen. Leptin syntetiseras i fettväv och är involverat i bland annat reglering av matintag, medan Interleukin-6 är en immunmodulerande cytokin som bland annat stimulerar HPA-axeln. Båda dessa proteiner har i tidigare studier visat sig vara involverade i patogenesen för affektiva sjukdomar. Blodprover från 347 kvinnor analyserades, och det visade sig att Leptin var negativt korrelerat till postpartumdepression, det vill säga höga Leptinnivåer verkar minska risken för att insjukna med depressiva symptom både sex veckor och sex månader efter förlossningen. Detta samband kvarstod även efter justering för kvinnans ålder, BMI, rökning, Interleukin-6-nivåer, graviditetslängd och barnets kön. Så vitt vi vet är detta första

gången som sambandet mellan Leptin och postpartumdepression har studerats. Fyndet är därför en viktig länk för att öka förståelsen för de patofysiologiska mekanismer som ligger bakom detta vanliga sjukdomstillstånd. Inget samband mellan depressiva symptom och serumnivåer av Interleukin-6 kunde påvisas.

I det andra delarbetet ville vi studera hur årstiden då förlossningen äger rum påverkar risken för depressiva symptom hos nyförlösta kvinnor. Vi använde oss här av hela kohorten (2318 kvinnor), och jämförde andelen screeningpositiva kvinnor per månad vid sex veckor och sex månader postpartum. Därefter delade vi in året i kvartal, och jämförde första, tredje och fjärde kvartalet med kvartal två (april-juni), som visade sig vara den tidsperiod då risken för att insjukna i postpartumdepression var som lägst. Kvinnor som födde barn i oktober-december visade sig ha högst risk att insjukna i postpartumdepression, både sex veckor och sex månader efter förlossningen. Efter justering för tidigare psykiatrisk ohälsa, samt för troliga interagerande riskfaktorer (amning, dåligt stöd av partner, låg utbildning, oplanerad graviditet och/eller omvälvande livshändelser de senaste sex månaderna), kvarstod detta samband. Således kan vi dra slutsatsen att kvinnor som föder barn i Sverige påverkas i sitt mående av den årstid då förlossningen infaller, och att denna påverkan sträcker sig så långt som sex månader efter förlossningen. Detta har klinisk betydelse, då sjukvårdspersonal som följer upp kvinnor postpartum torde vara särskilt uppmärksamma på depressiva symptom hos kvinnor som fött barn sent på året. Dessutom kan även detta fynd vara intressant för att komma närmare förklaringen till de patofysiologiska mekanismerna bakom postpartumdepression.

Efter att ha studerat den internationella litteraturen ville vi i delarbete III studera hur barnets kön påverkar risken för depression hos modern. Studier från samhällen med traditionell ”österländsk” kultur och låg status för kvinnor/låg jämställdhet (t.ex. Indien, Kina, Nigeria) har visat att kvinnor löper högre risk för både depressiva symptom och partnerrelaterat våld, om de föder en flicka. En studie från Frankrike år 2008 visade istället på ökad psykisk ohälsa hos kvinnor som födde en pojke. För denna delstudie använde vi oss av alla kvinnor med singelgraviditet (N=2267), och undersökte depressionsprevalensen fem dagar, sex veckor och sex månader postpartum. Ingen skillnad i depressionsprevalens hos flick- respektive pojkmammor kunde ses vid sex veckor och sex månader postpartum. Dock noterades en signifikant ökad risk för depressiva symptom fem dagar efter förlossningen, så kallad ”postpartum blues”. Sambandet kvarstod efter justering för kvinnans ålder, utbildningsnivå, graviditetstid, förlossningsätt, partnerstöd och amning.

I delarbete IV har vi undersökt risken för postpartumdepression i förhållande till tidigare premenstruella symptom. Premenstruella symptom är mycket

vanligt hos fertila kvinnor, och varierar mellan lättare fysiska symptom, såsom bröstspänningar och illamående, till regelrätt PMS och PMDS (premenstruellt dysforiskt syndrom), där det senare definieras enligt kriterier i DSM-IV. Även i denna delstudie använde vi oss av hela UPPSAT-kohorten. Diagnoserna PMS och PMDS baserades på strikta kriterier från American College of Obstetricians and Gynecologists (PMS) och DSM-IV (PMDS) och erhöles via retrospektiva skattningar som kvinnorna utförde fem dagar efter förlossningen. Statistiskt signifikanta associationer mellan PMS/PMDS och postpartumdepression noterades vid alla de tre uppföljningarna efter förlossningen. Då paritet i vårt material var starkt associerat med ökande premenstruella symptom, valde vi att stratifiera för denna variabel. Efterföljande regressionsanalys visade att endast omföderskor med tidigare PMS/PMDS hade en kvarstående ökad risk för depressiva symptom postpartum, medan förstföderskor med PMS/PMDS ej hade någon sådan risk. Paritetens roll som "effektmodifierare" i associationen mellan PMS och PPD bör därför sannolikt studeras vidare.

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Appendix

EPDS – English

How are you feeling?

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

This would mean: ‘I have felt happy some of the time during the past week’. Please complete the other questions in the same way.

In the past 7 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
Rather less than I used to
Definitely 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 often
No, never
4. I have been anxious or worried for no good reason:
No, not at all
Hardly ever
Yes, sometimes
Yes, very often

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

7. I have been so unhappy that I have had difficulty sleeping:
Yes, most of the time
Yes, sometimes
Not very often
No, not at all

8. I have felt sad or miserable:
Yes, most of the time
Yes, quite often
Not very often
No, not at all

9. I have been so unhappy that I have been crying:
Yes, most of the time
Yes, quite often
Only occasionally
No, never

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

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EPDS – Svenska

Eftersom du nyligen har fått barn, skulle vi vilja veta hur du mår. Var snäll och stryk under det svar, som bäst stammer överens med hur du känt dig de senaste 7 dagarna, inte bara hur du mår idag. Här är ett exempel, som redan är ifyllt:

Jag har känt mig lycklig:

Ja, hela tiden

Ja, för det mesta

Nej, inte särskilt ofta

Nej, inte alls

Detta betyder: “Jag har känt mig lycklig mest hela tiden under veckan som har gått”. Var snäll och fyll i de andra frågorna på samma sätt.

Under de senaste 7 dagarna

1. Jag har kunnat skratta och se tillvaron från den ljusa sidan:
Lika bra som vanligt
Nästan lika bra som vanligt
Mycket mindre än vanligt
Inte alls
2. Jag har glatt mig åt saker som ska hända:
Lika mycket som vanligt
Något mindre än vanligt
Mycket mindre än vanligt
Inte alls
3. Jag har lagt skulden på mig själv onödigt mycket när något har gått snett:
Ja, för det mesta
Ja, ibland
Nej, inte så ofta
Nej, inte alls
4. Jag har känt mig rädd och orolig utan egentlig anledning:
Nej, inte alls
Nej, knappast alls
Ja, ibland
Ja, mycket ofta

5. Jag har känt mig skrämmd eller panikslagen utan speciell anledning:
Ja, mycket ofta
Ja, ibland
Nej, ganska sällan
Nej, inte alls

6. Det har kört ihop sig för mig och blivit för mycket:
Ja, mesta tiden har jag inte kunnat ta itu med något alls
Ja, ibland har jag inte kunnat ta itu med saker lika bra som vanligt
Nej, för det mesta har jag kunnat ta itu med saker ganska bra
Nej, jag har kunnat ta itu med saker precis som vanligt

7. Jag har känt mig så olycklig att jag har haft svårt att sova:
Ja, för det mesta
Ja, rätt ofta
Nej, sällan
Nej, aldrig

8. Jag har känt mig ledsen och nere:
Ja, för det mesta
Ja, ganska ofta
Nej, sällan
Nej, aldrig

9. Jag har känt mig så olycklig att jag har gråtit:
Ja, nästan jämt
Ja, ganska ofta
Bara någon gång
Nej, aldrig

10. Tankar på att göra mig själv illa har förekommit:
Ja, rätt så ofta
Ja, då och då
Knappast alls
Aldrig

Cox J.L., Holden J.M & Sagovsky R. (1987) Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry*, 150, 782-786.

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