Postpartum Depression –

Epidemiological and Biological Aspects

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Contents

Abstract

Postpartum depression is by definition a major depression with an onset during the first weeks after delivery. In practice, however, the term, postpartum depression is used to characterize all kinds of depressive symptoms after childbirth. The aims of this thesis were to investigate the prevalence of depressive symptoms during late pregnancy, in the puerperium and four years after delivery, and to analyze the mothers' estimation of personal health and their children's behavior at the age of four. Additional goals were to test the predictive power of potential associated factors of postpartum depression during pregnancy and the puerperium and finally, to elucidate possible genetic or neuropeptidergic explanatory variables behind the development of postpartum depression.

A population-based sample of 1489 women was screened with the Edinburgh Postnatal Depression Scale and the prevalence of depressive symptoms was 17% in late pregnancy and 13% postpartum. Antenatal depressed mood was related to postpartum depression. In a cross-sectional study we later found that postpartum depression was associated with subsequent depressive symptoms and current health problems four years after childbirth. Four-year-old boys of postpartum depressed mothers and children of mothers with a subsequent depressive status had more behavior problems than children of non-symptomatic mothers did, according to the mothers' opinion.

The strongest associated factors for postpartum depression, in a case-control study, were sick leave during pregnancy mainly due to pregnancy complications, e.g. hyperemesis and premature contractions and a high number of visits to the antenatal care clinic. There was no association between delivery complications or complications in the perinatal period and postpartum depression. The theory that depressive symptoms in late pregnancy or postpartum are connected with CYP2D6 genotype could not be confirmed.

In a rat model, we found that pregnancy and parturition influence the concentrations of neuropeptide Y, cholecystokinin, substance P and galanin in the rat brain. This result supports the hypothesis that neuropeptidergic systems in the brain influence the mood changes around childbirth. In conclusion, postpartum depression is a common feature with influence on both maternal and child well being.

List of original papers

This thesis is based on the following papers, which are referred to by their Roman numerals I - V.

I. Josefsson A, Berg G, Nordin C, Sydsjö G. Prevalence of depressive symptoms in late pregnancy and postpartum. Acta Obstet Gynecol Scand Gyn 2001; 80: 251-255.

II. Josefsson A, Angelsiöö L, Berg G, Ekström CM, Gunnervik C, Nordin C, Sydsjö G. Obstetric, somatic, and demographic risk factors for postpartum depressive symptoms. Obstetrics & Gynecology 2002; 99: 223-228.

III. Josefsson A, Gunnarsson T, Sydsjö G. A follow-up study of postnatal depressed women: Recurrent maternal depressive symptoms and child behaviour after four years. Submitted.

IV. Josefsson A, Sydsjö G, Berg G, Dahl ML, Wadelius M, Nordin C. CYP2D6 genotypes and depressive symptoms during late pregnancy and postpartum. Accepted for publication in Nordic Journal of Psychiatry, 17 October 2002.

V. Josefsson A, Berg G, Gunnarsson T, Rugarn O, Sydsjö G, Theodorsson E. Pregnancy and parturition influence neuropeptide concentrations in the rat brain. Manuscript.

Statement

Description of contribution

Study I

Design: Josefsson A, Sydsjö G, Berg G, Nordin C
Data collection and analysis: Josefsson A, Sydsjö G, Angelsiöö L, Ekström CM, Gunnervik C
Manuscript writing: Josefsson A, Sydsjö G
Manuscript revision: Nordin C, Berg G

Study II

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Study III

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Data collection and analysis: Josefsson A, Sydsjö G
Manuscript writing: Josefsson A
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Study IV

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Data collection and analysis: Josefsson A, Wadelius M, Dahl ML
Manuscript writing: Josefsson A
Manuscript revision: Sydsjö G, Nordin C, Berg G, Wadelius M, Dahl ML

Study V

Design: Josefsson A, Rugarn O, Theodorson E, Berg G
Laboratory work and analysis: Josefsson A, Theodorsson E
Manuscript writing: Josefsson A, Rugarn O
Manuscript revision: Berg G, Gunnarsson T, Sydsjö G, Theodorsson E

Abbreviations

ACTH: Adrenocorticotropic hormone

ANC: Antenatal Care

CCK: Cholecystokinin

CI: Confidence Interval

CNS: Central Nervous System

CRH: Corticotropin-releasing hormone

CYP2D6: Cytochrome P4502D6

DSM-IV: Diagnostic and Statistic Manual of Mental Disorders, fourth edition, American Psychiatric Association, 1994

EPDS: Edinburgh Postnatal Depression Scale

FSH: Follicle-stimulating hormone

GAL: Galanin

HCG: Human chorionic gonadotropin

HPA: Hypothalamic-pituitary-adrenal

ICD-10: International Classification of Diseases, WHO 1992

LH: Luteinizing hormone

mRNA: messenger ribonucleic acid

NPY: Neuropeptide Y

OR: Odds ratio

PBCL: Pre-School Behaviour Checklist

SP: Substance P

Definitions

Depression: defined as ≥ 10 on the EPDS in this study.

Major Depression: a period of at least 2 weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities. At least 5 out of 9 stated symptoms have to be fulfilled, see DSM-IV for complete criteria.

Minor Depression: a period of at least 2 weeks of depressive symptoms but with fewer than the five items required for Major Depression, see DSM-IV.

Postnatal: British English term for postpartum.

Postpartum Depression: A major depression with onset within 4 weeks after delivery (DSM-IV) or within 6 weeks after delivery (ICD-10).

The postpartum period: in this context to some degree arbitrary, but a time limit of 6 months after delivery is the most prevailing definition in the literature.

Introduction

Pregnancy and childbirth are complex events, packed with physical and psychological incidents as well as a profound biological, social and emotional transition. Although reactions of anxiety and sadness are common during pregnancy, most women navigate this transition without major psychopathology. Mental disturbance following childbirth was first mentioned by Hippocrates (approx. 400 BC), but the first good description of postpartum mental illness was written by a French psychiatrist, Louis Marcé, in 1858.

Becoming a mother is a major life event and has great importance not only for the individual family but also for the society and the survival of mankind. Pregnancy and childbirth have always been surrounded by magical and mythical thinking. In the old days a pregnant woman was considered to have magical power and vulnerability. Different experiences that she had were thought to affect the fetus, e.g. an unpleasant event could make her fetus malformed and a burn wound could cause the fetus to acquire a nasty birthmark. The woman's experiences and behavior during pregnancy could also influence the delivery outcome. After childbirth the mother and her baby were considered to be impure heathens during the period of time before the child was christened and the woman was reassembled in the parish. Meanwhile, there were a lot of rules that had to be followed. For instance the woman was not allowed to do any kind of work in the household, she could not have sexual intercourse and somebody had to watch over her baby in case she had to go outside. This ritual had a twofold purpose; it would protect the surroundings from the impure woman and her child and would also make it possible for the mother to devote her time to the baby (Tillhagen 1983).

Similar rituals can still be found in other cultures and countries, e.g. Nigeria and China. In today's Swedish society these myths have disappeared and antenatal care clinics (ANC-clinics) have replaced many of these protective rituals.

The Swedish antenatal health care system reaches almost 100% of all pregnant women (Swedish National Board of Health and Welfare). The ANC-clinics provide regular check-ups on the physical and psychological health during pregnancy and puerperium. During the last two decades the staffs of the ANC-clinics have become more aware of and skilled in handling psychosocial risk factors interfering with the outcome of childbearing. The clinical impression is that mental illnesses have become more frequent lately – but this may not be true. It is possible that there has been no real increase in prevalence but rather a change in the pregnant women's attitudes in revealing personal feelings, mood or a history of psychiatric illness.

Background

Postpartum mood disorders

In the literature, three categories of puerperal mental disturbances are described in order of ascending severity: maternity blues, postpartum depression and postpartum psychosis (Brockington 1996).

Maternity Blues

Maternity blues is a common, benign, transitory condition occurring in the first days after delivery. Its incidence ranges from 30 – 80 %. Maternity blues typically begins 3-4 days after delivery and peaks on days 4-5. Characteristic symptoms are crying, confusion, anxiety, mood lability, insomnia and dysphoria. The symptoms last from a few hours to a couple of days, have few negative sequelae and do not require treatment. Biological and hormonal factors are the most likely major contributors (Beck 1991, O'Hara 1994, Brockington 1996).

Postpartum Depression

Is described in detail on the following pages.

Postpartum Psychosis

Postpartum psychosis is a severe and rare disorder with an acute onset after a symptom-free phase. Most postpartum psychoses begin within the first 3 weeks after delivery. Its incidence is 0.1 – 0.2 %. Prodromal symptoms are often seen as sleep disturbances, hypomania and irritability. Symptoms include delusions, hallucinations and gross impairment in functioning. Affective symptoms are most prominent. The prevailing view is that this disorder is biologically mediated (Boyce 1994, Brockington 1996).

Postpartum Depression

Classification

Postpartum depression refers to a non-psychotic depressive episode that begins in or extends into the postpartum period (Cox, Murray & Chapman 1993). It is a disorder lasting more than 2 weeks, the severity of which meets criteria for a major depression. The longitudinal specifiers of postpartum depression in DSM-IV (four weeks) and in ICD-10 (six weeks) are under current discussion. The Marcé Society, an international organization for the study of psychiatric illness related to childbearing, recognizes the time of vulnerability for postpartum depression as one year after delivery (Parry & Haynes 2000). In Anglo-American literature the definition postpartum depression is often used in a wider concept including both major and minor depressions, as a minor depression may be a potentially severe disorder when occurring in the postpartum period.

Prevalence

A meta-analysis of numerous studies found the average prevalence rate of postpartum depression to be 13 % (O´Hara & Swain 1996). Two Swedish studies have been performed in urban populations with a relatively high degree of multi-ethnic and socially disadvantaged postpartum women (Wickberg & Hwang1996a, Bågedahl-Strindlund & Monsen-Börjesson 1998). The prevalence rates were in accordance with O'Hara and Swain (1996). There is a three-fold increase in the risk of depression during the first months after delivery. Except for that time-period it has not been demonstrated that depression is more common during the first year after childbirth than at other times during the female reproductive period (Kumar & Robson 1984, O'Hara et al. 1991, Cox, Murray & Chapman 1993).

Etiology and causal factors

In 1995 Cooper and Murray suggested a specific nosologic reference for the concept of postnatal depression. They implied that the population of women who develop a depression after childbirth might comprise two different subgroups: the first consists of women for whom the experience of having a child constitutes a specific causative factor, and the second of women for whom the birth is an unspecific stressor. Accordingly, the latter subgroup of women has a general vulnerability to depression at any time during life, while the former group of women is more likely to become depressed during times of childbearing. This

finding is important as it may provide some clues about a distinctive depression that develops in response to childbirth for some women.

Several studies have investigated sociodemographic variables and background factors as a possible risk but most of them found no relation to postpartum depression (Cox et al. 1982, O'Hara & Swain 1996, O'Hara 1997).

Many hypotheses accounting for the biological basis of postpartum depression have been investigated. One of them, the hormonal dysfunction hypothesis, is similar to that proposed for mood disturbances in the premenstrual period and during menopause (Yalom et al. 1968, Dalton 1980, Birkhäuser 2002). Progesterone withdrawal has been hypothesized as a causal factor (Dalton 1980) but the studies are inconclusive (O'Hara 1997). The same hypothesis has been postulated for estradiol and at least three studies have investigated a possible relation between estradiol levels and postpartum depression. Two of the studies produced negative findings (Gard et al. 1986, Harris et al. 1989a). However, O'Hara et al. (1991), found significantly lower levels of estradiol in postpartum depressed women compared to non-depressed women at 36 weeks gestation and 2 days postpartum. Bloch et al. (2000) investigated the possible role of changes in gonadal steroid levels in postpartum depression by simulating the hormonal conditions related to pregnancy and parturition in euthymic women with and without a history of postpartum depression. The women with a history of postpartum depression were more likely to develop depression after withdrawal of estrogen and progesterone. The maternal hypercortisolism in the third trimester of pregnancy causes a transient adrenal suppression after delivery, which together with the estrogen withdrawal, has been suggested as a possible causative factor (Chrousos et al. 1998). Harris showed in 1996 a minor association of postpartum depression and thyroid dysfunction in thyroid antibody-positive women. Other hormones, e.g. prolactin, have also been investigated without any conclusive findings (Altshuler et al. 1998).

Pregnancy or delivery complications have been inconsistently related to postpartum depression, with some studies documenting less frequent mood disturbances in women with more stress or delivery complications (Nielsen Forman et al. 2000, Saisto et al. 2001). The findings in these studies do suggest that a third variable, such as a history of psychiatric illness, may mediate a relation between obstetric stress and postpartum depression (Murray & Cartwright 1993).

In several studies, higher levels of stressful life events during pregnancy and after delivery were associated with an increased risk of postpartum depression (O'Hara 1997). Depression during pregnancy, a previous history of affective disorder or of

other psychiatric illnesses was also closely linked to postpartum depression (O'Hara 1997).

A poor marital relationship and/or lack of social support have also been found to be associated with postpartum depression (Gotlib et al. 1991, Kumar & Robson 1984, Robinson et al. 1989).

In summary, various explanatory models on the etiology and causal factors of postpartum depression have been proposed and it is probable that the illness is ordinarily a result of an interaction between genetic vulnerability, hormonal changes, environmental stress and major life events (Hendrick et al. 1998).

Consequences

Postpartum depression usually resolves spontaneously after a couple of months but may persist in up to 25% percent of cases one year after delivery if untreated (Brockington, 1996). There is also a 30-50 % risk of relapse in a future pregnancy (Cooper & Murray 1995, Weissman & Olfson, 1995).

Postpartum depression may have a deleterious effect on the woman's social and personal adjustment, the marital and the mother-infant relationships.
Postpartum or maternal depression has been considered a risk factor for the child's cognitive and emotional development (Cogill et al. 1986, Cummings et al. 1994, Sharp et al. 1995, Murray et al. 1996). There are different suggestions concerning how an emotional disorder affecting the mother might adversely influence the child. The most common proposal is that the symptoms of depression interfere with the ability to establish a relationship, and to communicate and interact well with the child (Murray 1992). Cognitive problems have been observed among children to postpartum depressed mothers in three English population samples (Cogill et al. 1986, Murray et al. 1996, Hay et al. 2001) where a longitudinal follow-up has been performed. The duration and intensity of the problems vary between the groups, which is most likely explained by the social differences between the samples.

In a review, Weinberg & Tronick (1998) summarized findings about the effects of maternal depression on infant cognitive, behavioral, and emotional functioning, showing compromised development in all three domains. These effects lasted beyond the mother's resumption of normal interaction with the child. The data also suggested that male infants might be more vulnerable to maternal depression than female infants.

Finally, it has been shown that adverse social experiences in early life affect brain development, perceptual and memory abilities, as well as social adjustment. These effects are partly mediated by hormonal factors, in particular the adrenocortical reaction to stress. Studies of a number of mammalian species have shown that high levels of cortisol produce persistent hyperresponsivity in the hypothalmic-pituitary-adrenal (HPA) axis, and affect the function of the hippocampus with consequences for memory, attention, and effortful control of behavior (Glaser 2000, Goodyer 2001, Newport et al. 2002).

Treatment

There is little systematic information on the clinical management of postpartum depression. Possible explanations to this lack of research might be that postpartum depression commonly goes undetected and that this disorder, in psychiatric terms, represents a relatively minor disturbance which eventually will remit spontaneously (Cooper & Murray 1997). On the objectives to evaluate the effectiveness of different kind of treatment strategies there are three available Cochrane reviews.

In the first review, Ray & Hodnett (2002) assessed the effect of caregiver support for postpartum depression. Two studies involving 137 women were included. The results showed that professional and/or social support was associated with a reduction in depression at 25 weeks after delivery (OR 0.34, 95% CI 0.17-0.69). However, the reviewers highlighted the possibility of bias due to large numbers of women who refused to take part in the studies as well as significant losses to follow-up.

In the second review, Hoffbrand et al. (2002) evaluated antidepressant treatment for postnatal depression. The review could only include a single trial with 87 (of 188 eligible) women by Appleby et al. (1997). They showed that Fluoxetine was significantly more effective than placebo, and after an initial session of counseling, as effective as a full course of cognitive-behavioral counseling in the treatment of postpartum depression. However, the trial excluded women with drug misuse, chronic or resistant depression and breastfeeding women. The reviewers concluded that more trials with a longer follow-up period are needed to compare different antidepressants, and to compare antidepressants with psychosocial interventions.

In the third Cochrane review, Lawrie et al. (2002) investigated the role of estrogens and progestogens for preventing and treating postnatal depression. Two randomized placebo controlled trials were included. Lawrie et al. (1998) randomized 180 postpartum women to either depot norethisterone enanthate or

saline within 48 hours after delivery in an effort to prevent postpartum depression. The women who received the active substance had higher depression scores after 6 weeks than the placebo group. The other randomized trial in this review evaluated high-dose transdermal estrogen terapy for the treatment of severe postnatal depression (Gregoire et al. 1996). Sixty-one women were included in the study. Estrogen therapy was associated with a greater improvement than placebo. However, the treatment and placebo groups may not have been sufficiently comparable as more women in the active treatment group received conventional antidepressant therapy as well. The reviewers summarized that there is no place for synthetic progestogens in the prevention or treatment of postpartum depression. They also stated that the role of progesterone for prevention and/or treatment has to be evaluated in a randomized placebo-controlled trial and that estrogen may be of modest value at a late stage of severe postpartum depression.

In Sweden, Wickberg & Hwang (1996b) studied the effect of non-directive counseling on postpartum depression in 41 women. After a diagnostic interview, women with major depression were randomly allocated to a study and a control group. The women in the study group received 6 counseling sessions by Child Health Clinic nurses. The results were encouraging as 80% of the women with a major depression in the counseling group were fully recovered after the intervention compared to 25% of the women in the control group. The study did not include any long-term follow-up. During the late 1990s quite a few projects around Sweden have started, where nurses working in Child Health Clinics screen for postpartum depression and provide support. No evaluation studies have been published so far.

Prophylaxis

In a double-blind, randomized study Wisner et al. (2001) tested the efficacy of nortriptyline in prevention of recurrent postpartum depression. They found no difference between the two treatment groups. One fourth of the women in both treatment groups suffered recurrences. Harris et al. (2002) tested the potency of thyroxine to prevent postpartum depression in thyroid-antibody-positive women in a randomized double-blind study. They concluded that the excess of depression in thyroid-antibody-positive women postpartum was not corrected by daily administration of thyroxine.

Pregnancy and postpartum endocrinology – an overview

The endocrine changes following childbirth are unmatched by any other biological event in terms of rapidity and magnitude. Endocrine changes through pregnancy are, in the main, the direct or indirect consequence of placental activity (Speroff et al. 1999).

Gonadotrophic hormones

During pregnancy, the pituitary-ovarian axis is suppressed. The placenta takes over from the pituitary, producing human gonadotrophic hormone (HCG), which is similar to luteinizing hormone (LH), but has a different beta-chain. After the delivery of the placenta, HCG is rapidly cleared. In the second week postpartum, the pituitary resumes its gonadotrophic function and the normal cycle is re-established in 6-8 weeks. Follicle-stimulating hormone (FSH) returns to normal between 7 and 18 days postpartum, and, in breast-feeding women, is high during the period of hyperprolactinemia. LH remains below the normal cyclic range for at least 28 days (Speroff et al. 1999).

Estrogen

Estrogen concentrations increase constantly during pregnancy. Near term there is a daily production of 15-20 mg estradiol and 50-100 mg of estriol. Most of the precursors are formed by the fetal adrenal gland. One enzyme responsible for estrogen synthesis is the placental cytochrome P450 aromatase enzyme, the product of the CYP19 gene. After delivery, placental estrogen is fully cleared in seven days. In spite of high FSH secretion, estrogen remains low during hyperprolactinemia, then increases as LH secretion is resumed. There is a difference between lactating and non-lactating mothers: after 14 days, non-lactating mothers have significantly higher levels of estrogen, and they are much higher at six weeks (Speroff et al. 1999). There is evidence of estrogen's interaction with neurotransmitter systems (Joffe & Cohen 1998). Some data indicate that estradiol may affect transmitter systems implicated in cognitive and emotional processes. Estrogen receptors are widespread in the brain, both in humans (Österlund et al. 2000a, 2000b) and in rats (Österlund et al. 1998, Laflamme et al. 1998). In particular, both estrogen receptor α mRNA and estrogen receptor β mRNA are expressed in human hippocampus and cortex, whereas estrogen receptor α mRNA is also abundant in amygdala (Österlund et al. 2000 a,b). The best-established effects of estrogen are its interaction with dopaminergic receptors, especially its dopamine-blocking actions. Estrogen also exerts an effect on norepinephrine,

adrenaline and serotonin receptors. The latter interaction may be related to the supposed antidepressant action of estrogen (Joffe & Cohen 1998).

Progesterone

In late pregnancy the placenta produces at least 250 mg of progesterone per day. The placental progesterone is fully cleared within 7 days postpartum, and the blood level falls 100-fold during this time. It then remains low until about 20 days postpartum, even in mothers whose lactation has been suppressed (Speroff et al. 1999). Progesterone and some of its metabolites are sedative and anaesthetic in high doses. It may well account for the relative euphoria of pregnancy and removal of this euphoric effect could possibly be associated with depression (O'Brien & Pitt 1994).

Prolactin

Prolactin levels rise progressively during pregnancy. After delivery they fall in both lactating and non-lactating mothers, but more steeply in the latter. Although prolactin is affected by dopamine, which inhibits its release, there is little evidence that the blood level of this hormone affects mental functioning (O'Hara 1997, Hendrick et al. 1998).

Neuropeptides

Biologically active peptides that are produced in neurons and have neuromodulatory or neuroendocrine actions are classified as neuropeptides. Neuropeptides are phylogenetically the oldest neurotransmitters, modulators and growth factors. They are found throughout the central nervous system (CNS), as well as in various peripheral organs. Neuropeptides have been implicated in a variety of physiological and behavioral functions in the CNS (Strand 1999). Synthesis and transport of neuropeptides are slow processes compared to that of classical neurotransmitters, such as dopamine, noradrenaline, acetylcholine and serotonin. Neuropeptides are assumed to exert their main action when the nervous system is stressed, dysfunctional or afflicted by disease (Hökfelt et al. 2000). Differences in sex steroid exposure are related to changes in the concentrations of neuropeptides in extra-hypothalamic areas of the rat brain, areas involved in control of mood and cognitive function (Rugarn 2001). The neuropeptides cholecystokinin (CCK), neuropeptide Y (NPY), substance P (SP) and galanin (GAL) are related to control of mood and coexist with classical neurotransmitters that are supposed to have a role in the pathogenesis of depression (Strand 1999, Redrobe et al. 2002, Nemeroff 2002).

Corticotrophin releasing hormone (CRH) and cortisol

The third trimester of pregnancy is characterized by a hyperactive HPA axis. This is the result of progressively increasing levels of circulating CRH of placental origin and decreasing levels of CRH-binding protein, both phenomena contributing to elevated levels of CRH and, thus, hypersecretion of ACTH and cortisol. Steroids, prostaglandins and several neuropeptides, e.g. NPY, regulate the production of CRH during pregnancy.

Just before delivery, morning levels of free cortisol double, peak during labor and decrease within 4 hours postpartum. The down-regulation of the hypothalamic CRH neuron together with the postnatal estrogen deficiency leads to a state of hypoactivation of the HPA axis, which may last from a few weeks to several months (Chrousos et al. 1998, Speroff et al. 1999).

Cytochrome P4502D6 (CYP2D6)

Cytochrome P450s are key enzymes in the metabolism of cholesterol, fatty acids and their derivatives. The enzymes are involved in steroid hormone synthesis and various metabolic processes. CYP2D6 is also expressed in the brain where it is assumed to be involved in the dopamine neurotransmission. Evidence of a relationship between CYP2D6 phenotype and personality traits has been presented (Bertilsson et al. 1989, Llerena et al. 1993). It suggests that this polymorphic enzyme might have an endogenous neuroactive substrate or product, although not yet known. The expression of CYP2D6 is predominantly under genetic control and enzyme-inducing drugs have only a minor influence on CYP2D6 enzyme activity. Nevertheless pregnancy enhances the CYP2D6 catalyzed metabolism of metoprolol and dextromethorphan in man (Wadelius et al. 1997). This finding is the first example of a physiological condition that markedly affects the activity of human CYP2D6. A possible metabolic contribution from the placenta and fetal organs have been discussed but the CYP2D6 enzyme is usually neither expressed in fetal liver nor in term placenta (Hakkola et al. 1994, Hakkola et al. 1996).

A rationale for using a rat model

To further investigate the possibility of a hormonal background to the mood changes around parturition it is, for obvious reasons, necessary to choose an animal model. As described in the previous pages there are similarities between the CNS of rats and humans. The estrous cycle and the duration of pregnancy are also much shorter in a female rat than in women. Thus, an understanding of the hormonal background to possible mood changes in humans can be developed by studying female rats.

The female rat shows 4- or 5-day estrous cycles. A cycle consists of proestrus, estrus and diestrus. The level of estrogen increases together with follicular development in early proestrus and the preovulatory surge of 17β-estradiol begins in the morning of proestrus, terminating in the late afternoon. Estrus takes place during late night/early morning the day after.

The rat ovary continues to produce estrogen throughout pregnancy. In the second half of pregnancy the placenta supplies androgens. They are converted to estradiol in the granulosa cells. Parturition occurs on day 21-22 of pregnancy.

The use of rating scales as a method of screening

As to methods of screening for depression, besides self-report questionnaires there are three types of assessment. First, a full clinical interview with a psychiatrist, second, a structured clinical interview and, third, observer-rated scales. Self- and observer-rated scales correlate but do so incompletely as they often measure somewhat different variables (Harris et al. 1989b). A screening instrument requires high sensitivity and specificity. Sensitivity is an index of the number correctly diagnosed as suffering from depression, and specificity is the number correctly identified as normal. Sensitivity is the more important, because a screening instrument must not miss cases. Once a possible case has been identified, an interview can eliminate the false positives.

Often primary health care workers, midwives and child health nurses fail to identify depressed women in the puerperium (Cox et al. 1982, Wickberg-Johansson et al. 1996, Bågedahl-Strindlund & Monsen-Börjesson 1998). In order to screen for depression in childbearing women several authors have recognized serious limitations in previously existing self-rating scales that proved to be less valid (Cox et al. 1983, Whiffen 1988a, Harris et al. 1989b). Especially the widely used Beck Depression Inventory lacked specificity (Whiffen 1988a, Harris et al. 1989b, O'Hara et al. 1991). In one study the Beck Depression Inventory also appeared to be insensitive to minor postpartum depression (Whiffen 1988b). In an attempt to overcome these deficiencies Cox et al. (1987) developed the Edinburgh Postnatal Depression Scale (EPDS). Its main feature is the exclusion of items that might reflect physical discomfort and confuse depression with the somatic effects of childbirth.

The Edinburgh Postnatal Depression Scale

The Edinburgh Postnatal Depression Scale (EPDS) is a 10-item self-report scale, specifically designed to screen for postnatal depression in community samples (Cox et al. 1987). Each item is scored on a 4 point scale (0 to 3), the minimum and maximum total score ranging from 0 to 30 respectively. The scale rates the intensity of depressive symptoms present within the previous 7 days. Five of the items are concerned with dysphoric mood itself, two with anxiety, and one each with guilt, suicidal ideas and "not coping". The EPDS is widely used in the world and has been translated into at least 11 languages, including Swedish (Lund & Gyllang 1993).

The EPDS cannot by itself confirm a diagnosis of depressive illness. However, when using >12 as a cut-off level Cox et al. (1987) showed a sensitivity of 86%, a specificity of 78%, and a positive predictive value of 73% for major depressive illness. Another validation of EPDS on a large community sample (n=702), using the same cut-off, showed a sensitivity of 68%, a specificity of 96% and a positive predictive value of 67% for both major and minor depressive illness (Murray & Carothers 1990). As it is important in some clinical or research settings to find all actual major depressions, a cut-off level of ten (≥10) was proposed to reduce detection failure (Cox et al. 1987). When selecting this threshold the sensitivity for the detection of major depression increased to almost 100% and the specificity to 82% (Harris et al. 1989b). It is important to know that when interpreting results for specificity, there is error in the interview assessment of depression, so that specificity of 90% is about the maximum that can be achieved (Brockington 1996). Validity of the Swedish version of EPDS has been tested and the findings were identical or similar to earlier studies (Wickberg & Hwang 1996a, Bågedahl-Strindlund & Monsen-Börjesson 1998).

The EPDS has been validated for use in pregnancy (Murray & Cox 1990). At the cut-off >12 the sensitivity for major depression was 100%, specificity 87% and positive predictive value 33%. One fourth of the false positives had a minor depression. For major depression the cut-off >14 was optimal as the sensitivity was 100%, false positive rate 4% and positive predictive value 60%.

In addition to the clinical applications for which it was designed, the EPDS has much potential as a research tool (Green & Murray 1994). There are two main ways in which it can be used. One is as a screening tool for case finding in an intervention study or epidemiological study. The other way is to regard scores not simply as a possible marker of a psychiatric diagnosis, but as a valid measure in their own right of what Kendall et al. (1987) have termed "dysphoria". Used in this way it becomes an economical means of tracking dysphoria in large samples through the various stages of pregnancy and the puerperium. Although lacking the rigor of clinical diagnosis, it is possible in this way to illuminate some of the relationships between antenatal and postpartum symptoms and other associated factors, although based solely on self-reported symptoms (Green & Murray 1994).

Validation of the EPDS in non-postpartum women (Cox et al. 1996) showed similar validity as for postpartum women at the cut-off >12. Consequently, the EPDS can be used to screen for depression in pregnancy and postpartum, and to follow women beyond this period in longitudinal studies, and clinically to screen for depression in mothers with older children (Cox et al. 1996).

Richman's Pre-School Behaviour Checklist

Preschool children render special difficulties in assessment of their behavior. In these ages the children are not emotionally and cognitively mature enough to be interviewed. Thus, observational studies of the child are often the only way to collect information and, as such, are very time consuming. Another time-consuming and expensive method is a semi-structured interview with the parent. Screening instruments for preschool children's behavior are sparse. Richman's PBCL is a short and user-friendly instrument which can be used for parental assessment of 4 year old children. Parents have a thorough knowledge about their own child and experience the child in its natural environment. On the other hand, parents might be less objective in their assessments, so this has to be taken into consideration (Field 1995).

In order to screen for emotional and behavioral problems Richman's Pre-School Behaviour Checklist (PBCL) was originally developed to be used by staff working in group settings with preschool children. The scale was also meant to provide the basis of a working plan, for those children who did have problems (McGuire & Richman 1986). The PBCL describes behaviors as specifically as possible, asking the rater to choose between several alternatives rather than saying how applicable one statement is to a child. Inter-rater reliability ($r=0.68$) and internal consistency was established (Cronbach's alpha=0.83), and its validity was shown using a variety of methods with good correlation ($r=0.83$) (McGuire & Richman 1986).

The translated and slightly modified version of Richman's PBCL was validated on a pre-school sample using a semi-structured diagnostic behavior symptom interview with a correlation of $r = 0.75$ (Gustafsson, 1995). In the Swedish version of the PBCL 25 items are included, in which the last question is open. Each item is scored on a 3 point scale (0 to 2), and the scale can give a total sum of 50 points. A cut-off level of 14 was used to distinguish between children with and without behavior problems according to Gustafsson (1995). The PBCL measures the dimensions of behavior and can be grouped as 3 factors; out-acting, isolated/immature and anxious.

Aims of the study

To examine the prevalence of depressive symptoms in an unselected population during late pregnancy and the postpartum period

To determine whether there is an association between antenatal and postpartum depressive symptoms

To investigate if complications during pregnancy, delivery and the perinatal period are associated with an increased risk of postpartum depression

To investigate the prevalence of depressive symptoms and personal opinion about health four years after childbirth

To examine the behavior of four-year-old children in relation to maternal depressive symptoms

To explore if CYP2D6 genotype plays a role in the etiology of depressive symptoms in late pregnancy and/or postpartum

To study the effect of pregnancy and puerperium, as well as estradiol, on the concentrations of NPY, CCK, SP and galanin in the rat striatum, hippocampus and cortex

Subjects and methods

Study I

The sample comprises all pregnant women consecutively registered at the ANC-clinics in four communities in the southeast region of Sweden. Enrolment took place in separate three-month periods for each of the four communities during 1997-1999. A total of 1558 women were approached. Sixty-nine (4.4 %) women declined to participate.

The participating women were asked to complete the Edinburgh Postnatal Depression Scale (EPDS) at the ANC-clinic in gestational week 35-36, at the maternity ward in average 3 days after delivery, at the ANC-clinic in connection with the routine check-up 6-8 weeks postpartum and at home 6 months after delivery. At 6 months after delivery the EPDS was sent to the participants together with a prestamped envelope and a reminding information letter. In this study the cut-off level of 10 of the EPDS was used as the dependent variable for reasons previously described (see page 24).

Study II

From the original sample in study I, all women with depressive symptoms on the EPDS at 6-8 weeks and/or 6 months postpartum, from two of the four communities (Värnamo and Linköping), were selected as an index group (n=132). As control group 264 women without depressive symptoms on the EPDS, were randomly chosen from all four communities. Records from three index women and two control women were not found. One woman in the control group delivered a dead infant and was therefore excluded.

All data related to the pregnancy, delivery and the puerperium were registered in the standardized and identical Swedish antenatal, delivery and neonatal records. The data were manually extracted from the records by the author and are thus prospectively related to the development of depressive symptoms. In multiparas, medical records from earlier deliveries were also scrutinized. The following data were collected; age, parity, marital status, occupation, and number of induced abortions, miscarriages or extrauterine pregnancies. Any history of infertility, psychiatric disorder or obstetric complications, actual chronic medical diseases, number of visits at the antenatal care clinics before delivery (midwife and physician), pregnancy complications, sick-leave during pregnancy and perinatal events were obtained.

The dependent variables were depressed or non-depressed. The explanatory variables were sociodemographic data, medical, gynecological and obstetric history, pregnancy, delivery and neonatal data.

Study III

From the original sample in study I, all women who had depressive symptoms on the EPDS at 6-8 weeks and/or 6 months postpartum were selected as an index group (n = 251). A control group was created by randomly choosing twice as many women without postnatal depressive symptoms on the EPDS (n = 502) after a matching procedure based on gender and age of the children.

In total, 753 women received a personal letter in which they were asked to participate in this follow-up study. The letter also contained an EPDS to screen for present depressive symptoms and a Richman's PBCL (McGuire & Richman 1986, Gustafsson 1995) to appraise the mother's view of her child's behavior. A short questionnaire asking the woman about age, ongoing illness, pharmacological medication, pregnancy and if she had a baby ≤ 6 months old was included. Four women in the index group declined to participate or could not be reached. There were 25 non-responders in the index group and 48 in the control group. One woman was excluded since her child had a diagnosis of cerebral palsy. Thus 675 women took part in the study, 221 (88 %) in the index group and 454 (90 %) in the control group. Fourteen women had not completed the EPDS (2.1 %) and 7 women had incomplete answers on the Richman's PBCL scale (1 %). They were therefore partially excluded in the results.

A cut-off at 14 was used for the Richman's PBCL to distinguish between children with and without behavior problems. A cut-off level of 10 of the EPDS was used to screen for depressive symptoms.

Study IV

From the original sample in study I, all Caucasian women with depressive symptoms in gestational week 35-36, at 6-8 weeks postpartum and 6 months after delivery (n = 177) were selected from two of the four communities. Twenty-six women refrained from participating, mainly due to practical reasons or fear of pain related to the blood-sampling procedure. Six women were excluded due to incomplete answers in the EPDS on any one of the three occasions. Finally, venous blood samples were taken from 145 (82%) women.

DNA was extracted from leukocytes according to standard procedures. Genotyping was performed by polymerase chain reaction (PCR) followed by digestion with restriction enzymes and polyacrylamide electrophoresis. The genotyping procedures are published (Gough et al. 1990, Wolf et al. 1990, Smith et al. 1992, Steijns & van der Weide 1998) and further described in paper IV. Individuals carrying the duplicated/multiduplicated CYP2D6 alleles were classified as ultrarapid metabolizers. A comparison between the study population and previously genotyped Caucasian females from the general population (Mattsson et al. 2000) was performed.

Study V

A total number of 36 rats were used. The experimental groups consisted of 22 rats. The control group comprised 14 non-pregnant rats.
Group 1 (n = 10): the pregnant group. The animals were sacrificed after 17 – 18 days of pregnancy. Pregnancy was verified by autopsy.
Group 2 (n = 12): the puerperal group. The animals were sacrificed 2 days after delivery.
Group 3 (n = 14): the estrus group. The animals were examined with vaginal smear on a daily basis at the same time every morning. A few drops of water were installed in the vagina and re-aspirated. The smear was then examined in a microscope to identify the phase of the estrous cycle (Maeda et al. 2000). The animals were sacrificed at estrus.

Blood-samples for the analysis of estradiol from all animals were taken from the femoral vein under general anesthesia just before sacrifice. The anesthesia was achieved with inhalation of isoflurane by means of an inhalation mask. The rats were sacrificed using a guillotine and the brains dissected (Glowinski & Iversen 1996) with particular reference to cortex, hippocampus and striatum regions of the brain. The hippocampus, cortex and striatum were removed and immediately weighed and frozen on dry ice.

The radioimmunoassays used to measure immunoreactivity of SP (Brodin et al. 1986), galanin (Theodorsson & Rugarn 2000) and NPY (Theodorsson et al. 1985) are published. CCK was analyzed using a commercial radioimmunoassay kit. The assays are briefly described in paper V. Samples for 17ß-estradiol were determined by a ^{125}I radioimmunoassay (Sirois & Fortune 1990).

Statistics

The statistical analyses were done using the statistical programs SPSS and MINITAB. Significance was defined as two-sided *P* values lower than or equal to 5%. Normality was tested with the Kolmogorov-Smirnov's test. When the assumptions of normality could not be met, non-parametric tests like the Mann-Whitney U test, Spearman's rank correlation test and Kruskal-Wallis one-way analysis of variance were used instead of the corresponding parametric methods, i.e. the t-test, Pearson's correlation test and one-way analysis of variance (Theodorsson-Norheim 1986, Siegel et al. 1988).

The categorical variables were tested with the Chi2-test and by computing the 95% exact confidence intervals for proportions (i.e. the Binomial test). The odds ratios, also presented with 95% confidence intervals, were calculated for the categorical variables in study II. Logistic regression analysis with conditional stepwise backward elimination was used when multiple variables were considered simultaneously in study II and III. In study V, medians and quartiles were used to display the central tendency and variation respectively.

Ethical considerations

In study I-IV, we questioned ourselves whether it would create increased anxiety to ask the eligible women personal questions about mental and physical health and later on about their children's behavior. However, we concluded that the positive effects would outweigh the negative effects and that the attendance rate would reflect the women's opinions in this matter. Verbal and written information was given to all participants and it was made clear that participation was voluntary. Individual informed consent was obtained from all women. The studies I – IV were approved by the Regional Ethics Committee for Human Research of the Faculty of Health Sciences, Linköping University and conducted in accordance with the Declaration of Helsinki.

Study V was approved by the local animal research ethics committee. The rats were treated in accordance with the guidelines issued by the Central Committee for Animal Research in Sweden.

Results and Discussion

Prevalence of depressive symptoms in late pregnancy and postpartum (paper I)

The mean age of the women was 29.3 years (range 16-46 years, SD 4.70). The age was normally distributed and did not differ between the 4 communities. The distribution of the EPDS scores and the prevalence of depressive symptoms did not differ between the study areas within each assessment (Kruskal-Wallis tests N.S). Partial dropouts were 12.5% at the maternity ward, 19.9% at 6-8 weeks postpartum and 17.7% after 6 months. In one of the communities (Kalmar) the partial dropout rate was significantly higher than in the other three communities (p< 0.001).

The percentage of women with an EPDS score of 10 or more was higher antenatally compared to the assessments at 6-8 weeks and 6 months postnatally (CI, 16-19 vs. CI, 11-15 and CI, 11-15). There was no age-related difference within each assessment. The frequencies of women with depressive symptoms were 13% in the total population at the two latter postpartum assessments.

There was an obvious relationship between antenatal and postpartum scores (antenatal vs. 6-8 weeks postpartum). Out of the 209 women who scored above cut-off antenatally, 68 (33%) also scored above cut-off postpartum, compared with 83 (8%) of 983 women who scored below antenatally and above postpartum. Alternatively, it may be noted that 68 (45 %) of the 151 women who scored above cut-off postpartum had high antenatal scores. Seventeen women (1.1 %) scored 0 on all four assessments and an equal number of women (1.1 %) scored 10 or more on all four assessments.

EPDS is a screening instrument and high scores do not in themselves confirm depressive illness. Nevertheless evaluation of the EPDS has shown that it provides a valid measurement of affective morbidity and it has previously been used alone in assessing maternal mood (Hannah et al. 1992, Warner et al. 1996).

In this study women from various social backgrounds were included. Very few women (4.4 %) refrained from participation. The partial dropout was acceptable in this longitudinal study considering the size of the study population and the repetitive assessments. A possible explanation to the dropouts at the maternity ward (12.6 %) might be that some women preferred early discharge and were never given an opportunity to fill in the scale. General experience with Swedish populations of delivered women is also that around 20% never attend any postpartum check-up, which is in accordance with the dropout at that time. In the group of women with depressive symptoms antenatally, 2.1 % dropped out from

the further assessments. Thus, the rates of postpartum depressive symptoms might be slightly underestimated. As the distribution of the EPDS scores for each assessment did not differ between the communities, we concluded that there was neither a seasonal difference nor any other difference between rural and urban areas regarding the frequency of depressive symptoms. In general, the frequencies of depressive symptoms were higher during late pregnancy and at the maternity ward than at the latter two postpartum assessments. The relatively high scores at the maternity ward have to be interpreted with caution, as this is a time where the common symptoms of the maternity blues occur.

It seems that antenatal high scores do have a predictive power for postpartum depressive symptoms, even though over half of antenatal high-scorers do not score above cut-off postpartum. The fact that there seems to be a continuity for some women and not for others supports the theory of different etiologies. For some women the antenatal depressive symptoms could reflect a higher proportion of general anxiety for the delivery and becoming a mother. British studies using self-report symptom rating scales have also shown a pattern of higher depressive scores in late pregnancy than postpartum (Cox & Holden 1994). These and our results indicate that detection of depressive symptoms and some of the women at risk for developing postpartum depression can be done during late pregnancy.

Obstetric, somatic, and demographic risk factors for postpartum depressive symptoms (paper II)

The main issue with this population based case-control study was to explore possible associations with postpartum depression and complications during pregnancy, childbirth and the perinatal period. We found no association between postpartum depression and sociodemographic variables like age, parity, marital status or socioeconomic status. Women with an earlier history of two or more abortions and with a history of earlier obstetric complications, mainly acute cesarean section and instrumental delivery, were significantly more prone to develop depressive symptoms postpartum.

Complications during the present pregnancy such as hyperemesis, premature contractions and psychiatric disorder were more common in the postpartum depressed group of women. Number of visits at the antenatal care clinics and number of women on sick leave were also more frequent in this group.

Concerning delivery data, no differences were found, except from intrapartal analgesia with morphine analogues. As the women included in this study were

enrolled in pregnancy week 35-36 there were no premature deliveries in the sample. Women with postpartum depressive symptoms stayed longer at the hospital after delivery but did not have a higher frequency of complicated puerperium than non-depressed women. Women who gave birth to babies with congenital major malformations were also more depressed.

A subsequent multivariable analysis showed that sick leave during pregnancy and the number of visits at the antenatal care clinic were the variables with the strongest association to postpartum depressive symptoms for all women. To facilitate comparisons multivariable analyses were performed for multiparas and primiparas respectively but no further information was gained.

An advantage of this study is that all data were extracted from standardized medical records in which data were collected prior to knowledge of postpartum mood. This made it possible to minimize maternal recall bias. To our knowledge this is the only study that includes earlier medical, gynecologic and obstetric history.
Most of the predictors found were obvious already during pregnancy, which could facilitate planning of prevention and intervention in the future. The strongest risk factors for postpartum depressive symptoms were sick leave during pregnancy and a high number of visits to the antenatal care clinic. The reasons for sick leave were mainly pregnancy related complications and psychiatric disorders. However, a potential weakness in this study might have been an underestimation of earlier or ongoing psychiatric condition influencing the results. Hyperemesis and premature contractions were more common in the postpartum depressed group of women. Explanatory models for these symptoms might be somatization of pregnancy related anxiety or depression but might also be an effect of hormonal changes in the pregnant woman. Antenatal depressive symptoms and postpartum depression are correlated, whether this is on a psychosocial basis or due to a hormonal and genetic vulnerability remains to be investigated. The absence of correlation between sociodemographic variables and depressive symptoms is in line with some previous studies (Kumar & Robson 1984, Watson et al. 1984). The risk factors identified in the gynecologic and obstetric history were two induced abortions or more and among multiparas a history of acute cesarean section or instrumental delivery in the past. However, these risk factors did not remain significant on the multivariable level. We found no association between delivery complications and the development of depressive symptoms. This is consistent with the findings in two recent studies (Nielsen et al. 2000, Saisto et al. 2001) but not with two earlier studies which have reported a strong link between cesarean section and postpartum depression (Hannah et al. 1992, Boyce & Todd 1992).

Our results show that women at risk for postpartum depression can be identified during pregnancy. The strongest predictors, sick leave and a high number of visits at the antenatal care clinics, are not etiological and might be of either behavioral or biologic origin.

A follow-up study of postpartum depressed women: Recurrent maternal depressive symptoms and child behavior after four years (paper III)

Almost 90% of the eligible women participated in this cross-sectional follow-up study. The multivariable analyses showed that subsequent depressive symptoms were related to depressive symptoms postpartum and ongoing illness. The variables that influenced the child's behavior were gender, maternal postpartum and recurrent depressive symptoms.

The women who had experienced depressive symptoms postpartum were four times more likely than the controls to be depressed at the follow-up and they suffered from some kind of illness more than twice as often. Stated illness was divided into three groups: chronic disease (hypertension, autoimmune disorders, diabetes mellitus, thrombophilia etc.), affective disorder and minor illness (infections, temporary pain, allergy etc.). Reported medication was defined as a prescribed medicine taken on a daily basis with the exception of vitamins and oral contraceptives. Women who had been depressed postpartum used more antidepressants four years after childbirth than did the controls (p= <0.001). Women who considered themselves not healthy were more often currently depressed than healthy women (p=0.008).

The mothers' views of their children's emotional and behavioral status showed that behavior problems were more common among the sons of postpartum depressed women than among the sons of the controls. No differences were observed between daughters of the mothers in the two groups. Both boys and girls of the mothers with recurrent depressive symptoms had a higher frequency of behavioral problems than did the children of the non-symptomatic group.

It is noteworthy that this study did not separate between minor and major depressions, which might be a limitation. Another possible weakness is that the results on the children's behavior are based on a self-estimation by the mothers and not on observations or diagnostic interviews. However, this is a common approach in a number of studies concerning emotional and behavioral problems in children (Caplan et al. 1989, Philipps & O'Hara 1991, Murray 1992, Sharp et al. 1995,

Luoma et al. 2001). Raised levels of maternal hostility and a failure to acknowledge infant autonomy characterize early mother-infant relationship in the context of postpartum depression (Field 1992). It seems possible that, despite the mother's subsequent recovery from depression, these initial attitudes to the infant may set up a cycle of particularly marked difficulties that come to influence the subsequent behavior of the child (Murray et al. 1999). This is consistent with some findings that report postpartum depressed mothers' early perceptions of their infants to be more negative than those of independent observers, and to show considerable continuity throughout the preschool years (Field et al. 1993, Bendell et al. 1993). Postpartum depression is supposedly more likely to have prolonged effects on the infant when the depression is chronic and severe. In low-risk samples like the women in our study one could expect the depression to be short-lived and the effects on the child to be negligible. Nevertheless, the differences are significant between the groups of women, which means that women with depressive symptoms postpartum constitute a risk group for future depressive episodes and negative influence of child behavior no matter of major or minor depression. Other longitudinal studies have shown a lower prevalence of subsequent depression in women with an earlier depression postpartum (Cogill et al. 1986, Cummings & Davies 1994, Luoma et al. 2001). In these studies different methods and measurements were used to detect depression and the samples were fairly small. We found that the four-year-old boys of women who had postpartum depressive symptoms or who displayed subsequent depressive symptoms seem to have behavioral problems more frequently and to be more vulnerable than the daughters do. Gender-linked differences in children to depressed mothers are unclear and there are no consistent findings in earlier literature (Cummings & Davies, 1994).

Our results suggest that there is a great need to recognize these mothers as early as possible, preferably already during the postnatal check-up visit at the ANC-clinics. Future research must focus on strategies for treatment of postnatal depression and prospective evaluation of maternal and child health. This task requires a close collaboration between midwives, obstetricians and consultants with special interest in perinatal psychiatry.

CYP2D6 genotypes and depressive symptoms during late pregnancy and postpartum (paper IV)

The aim of this exploratory study was to investigate whether there is a relation between CYP2D6 genotype and depressive symptoms in late pregnancy and/or postpartum. Among all the 145 women, 4.8% were genotyped as poor metabolizers and 2.1% as ultrarapid metabolizers. Forty-five women had depressive symptoms

only during late pregnancy, and in this group one woman was a poor metabolizer. Fifty-six women had depressive symptoms only during the postpartum period, and in this group two women were poor metabolizers. Among the 44 women with depressive symptoms both in late pregnancy and after delivery there were four (9.1%) poor metabolizers and three (6.8%) ultrarapid metabolizers. There were no differences in extensive and poor CYP2D6 genotypes between the three groups of women, χ^2 – test 2.598, p = 0.273. The frequencies of extensive and poor metabolizers in the study were in agreement not only with results from an earlier Swedish study by Mattsson et al (2000) but also with other European studies (Smith et al. 1992, Perrett et al. 1995, Wadelius et al. 1997).

However, we found that the frequency of ultrarapid CYP2D6 metabolizers among women who are depressed both during late pregnancy and postpartum was higher than expected in a general population. This finding was not significant, which may be due to a type-2 error, as a power analysis could not be carried out due to the exploratory character of the study.

Thus, we could neither confirm nor rule out the theory that depressive symptoms in late pregnancy and postpartum are connected with CYP2D6 genotype. Cytochrome P450s are important enzymes in the synthesis and metabolism of gonadal hormones and if an increased frequency of ultrarapid metabolizers can be confirmed, an explanatory model might be that this CYP2D6 genotype is more vulnerable to the changes of metabolism in the period of time around parturition.

Pregnancy and parturition influence neuropeptide concentrations in the rat brain (paperV)

Study V was undertaken to investigate the role of neuropeptidergic systems in the brain as a possible trigger of the mood changes observed around parturition.

The tissue concentrations of neuropeptide Y *in the striatum* were 53% higher in near term pregnancy compared to the estrus phase (p<0.05). It decreased by 54% (p<0.01) from the pregnant state to 2 days postpartum. Similarly the tissue concentrations of cholecystokinin in the striatum were 29% higher in late pregnancy compared to estrus (p<0.05) and decreased by 23% (p<0.01) from the pregnant state to 2 days postpartum. On the contrary, the tissue concentrations of substance P in the striatum were 32% higher two days postpartum compared to estrus (p<0.01) and 33% (p=0.06) higher two days postpartum compared to 17-18 days into the pregnancy. No significant differences were found for galanin in the striatum.

In the cortex, the tissue concentrations of cholecystokinin were 40% higher during pregnancy compared to estrus (p<0.05) and decreased by 26% (p<0.05) from the pregnant state to 2 days postpartum. In contrast the tissue concentrations of substance P were 27% lower in pregnancy compared to estrus (p<0.05) and 48% (p<0.05) higher two days postpartum compared to late pregnancy. The tissue concentrations of galanin were 24% higher two days postpartum compared to estrus (p<0.05) and 38% (p<0.05) higher two days postpartum compared to near term gestation. We found no changes for neuropeptide Y.

No significant changes in neuropeptide concentrations were found *in the hippocampus*.

The concentrations of *estradiol* in plasma were 41% higher in late pregnancy compared to estrus (p<0.001). They decreased by 35% from the pregnant state to postpartum (p<0.001). There were no significant differences in estradiol concentration between estrus and postpartum (p=0.068).

The concentrations of neuropeptides varied markedly between the brain regions, which is in accordance with previous findings (Stenfors et al. 1989, Rugarn et al. 1999).

Pathogenic mechanisms of depression involve dysfunction in the monoaminergic systems of the brain, especially those containing norepinephrine and serotonin (Nemeroff & Owens 2002). The mechanisms of the effects of antidepressants targeting the monoaminergic systems have been elucidated; these include changes in the protein macromolecules and the effects of such changes. The effects on the protein macromolecules occur within days but the clinical effects on depression take place 2-5 weeks after these changes. Among the explanations suggested for this delay is that antidepressants affect the concentrations of neuropeptides, e.g. increase the concentrations of neuropeptide Y, and that the time frame for this increase is in the order of weeks (Heilig et al. 1988). Estrogenic regulation of cholecystokinin and its receptors is correlated with the initiation and termination of the lordosis reflex in the female rat (Micevych et al. 1996). Furthermore, cholecystokinin-B receptor antagonists have been shown to have antidepressant-like effects in mouse models of depression (Shlik et al. 1997).

Despite the obvious temporal relation, earlier studies have failed to explain the correlation between the great changes in the plasma concentrations of gonadal hormones around parturition and the onset of postpartum depression (O'Hara & Swain 1996, Hendrick et al. 1998). Nevertheless, two recent studies have reported results supporting the hypothesis of a role for gonadal steroids in the etiology of postpartum depression. The results imply that the decrease from chronic high levels of pregnancy-associated hormones (estradiol and progesterone) to lower levels – a kind of withdrawal - can produce depressive symptoms both in humans (Bloch et

al. 2000) and in rodents (Galea et al. 2001). Earlier studies have shown that estrogen changes the concentrations of neuropeptides in the female rat brain, particularly in the hippocampus and we expected to find major changes in neuropeptide concentrations in the hippocampus in late pregnancy as well (Rugarn 2001). Thus, it is likely that neuronal systems in the central nervous system may exhibit differential sensitivity to the complex changes of hormones in response to pregnancy and parturition compared with estrogen alone (Magiakou et al. 1996, Bloch et al. 2000). Neuropeptides are likely to play a major role in fine-tuning the response of neuronal systems to internal and external conditions including pregnancy and the period of time around delivery. This study has shown that pregnancy and puerperium are temporally linked to changes in neuropeptide concentrations in the rat brain. Such changes may be important to consider when assessing the impact of gonadal steroid withdrawal upon mood changes postpartum.

Conclusions

Postpartum depression is a common feature that affects both maternal and child well being

We found the prevalence of depressive symptoms to be 17% in late pregnancy and 13% at 6-8 weeks as well as 6 months postpartum

Postpartum depression is correlated with antenatal depressed mood, and screening in late pregnancy might therefore be used to a certain extent to detect women at risk

The strongest predictors for postpartum depression were sick leave during pregnancy related mainly due to pregnancy complications, e.g. hyperemesis and premature contractions and a high number of visits to the ANC-clinic

We found no association between delivery complications or complications in the perinatal period and postpartum depression

Subsequent depressive symptoms and current health problems four years after delivery were correlated with postpartum depressed mood

Four-year-old boys of postpartum depressed mothers and children of mothers with a subsequent depressive status have more behavior problems than children of non-symptomatic mothers do

We could neither confirm nor rule out the theory that depressive symptoms in late pregnancy and postpartum are connected with CYP2D6 genotype. The hypothesis has to be tested in a larger sample

The complex hormonal adjustments occurring during pregnancy and in the puerperium change the concentrations of several neuropeptides in regions of the rat brain that are involved in the control of mood

Future Perspectives

During pregnancy the midwives at the ANC-clinics usually manage to establish a strong and trustful relation with the mother-to-be. Women are likely to feel their care has been personal and sensitive where there is a continuous relationship with a small number of professionals as in the antenatal care. At the postpartum check-up the focus is on maternal wellbeing, which means that it is permissible for the woman herself to discuss all sorts of personal problems with the midwife or doctor. We have shown that the ANC-clinics are useful settings in screening for depression both antenatally and postpartum. Thus, it is appropriate to further develop routines that aim to provide the knowledge, skills and resources necessary for detection of maternal mental illness at the ANC-clinics. Furthermore, a strategy with effective treatment has to be outlined and developed according to local conditions at the ANC-clinic, in cooperation with psychiatric competence and the staff at the Child Health Clinics.

In Great Britain specialized perinatal psychiatric units have been developed to treat women with psychiatric disorders after delivery. In accordance with their experience it is evident that a critical mass of knowledge is required to maintain skills and to ensure understanding of this group of patients. Therefore it is probably crucial to establish a limited group of interested and skilled professionals dealing with this matter.

In cooperation with the Division of Psychiatry in Linköping, we are conducting a randomized controlled treatment study. In addition we also investigate personality, self-image and possible changes in some hormone and neuropeptide levels in peripheral blood. A follow-up on child well being will be performed together with the department of Child and Adolescent Psychiatry.

A preliminary protocol with guidelines on the provision of service and treatment is under way and will be evaluated.

Swedish summary – Sammanfattning på svenska

Bakgrund

Den svenska mödrahälsovården är unik då nästan 100% av alla gravida följer programmet för graviditetsövervakning. Mödravårdens övergripande mål är att värna om en god reproduktiv och sexuell hälsa. Kvinnor erbjudes regelbundna kontroller avseende framförallt den fysiska men även den psykiska hälsan under graviditet och efter förlossning. Under de senaste årtiondena har personalen inom mödravården blivit allt skickligare att identifiera och hantera psykosociala riskfaktorer som kan påverka förlossningsutfall och föräldraskap. Den kliniska erfarenheten är att psykisk ohälsa ökat under senare tid. Huruvida detta är en reell ökning eller en spegling av kvinnors benägenhet att tala om denna typ av problem är okänd.

Depression i samband med barnafödande har fått allt större uppmärksamhet internationellt och i Sverige. Förekomsten av depressivitet i en svensk, oselekterad gravid och nyförlöst population har varit delvis okänd. Vi valde därför att genomföra en populationsbaserad prevalensstudie i sydöstra sjukvårdsregionen. Tidigare forskning har varit inriktad på att finna eventuella samband mellan uppkomst av depression postpartum och psykosociala bakgrundsfaktorer. Vi undersökte eventuella orsakssamband mellan depression efter förlossning och obstetriska, somatiska och demografiska variabler.

I framför allt engelska studier har man följt barnen till kvinnor som haft depression postpartum avseende beteende och funnit varierande resultat. Dessa studier har varit relativt små och har utförts i populationer som varit selekterade avseende socialgruppstillhörighet. Det har inte heller funnits någon aktuell svensk forskning där man följt upp kvinnor som varit deprimerade efter förlossning beträffande deras psykiska och fysiska hälsa i ett längre perspektiv. Med en tvärsnittsstudie fyra år efter förlossningen undersökte vi kvinnors aktuella psykiska och fysiska hälsa samt barnens beteende.

Kvinnor drabbas av depression i dubbelt så stor utsträckning som män. Orsakerna till en ökad förekomst av nyinsjuknande i depression efter förlossning är tämligen oklara. I litteraturen menar man att orsaken sannolikt är dels beroende av psykosocial pålagring och dels av biologisk, hormonell karaktär. I två hypotesgenererande arbeten prövade vi olika infallsvinklar avseende biologiska faktorers möjliga påverkan på utvecklingen av depression i en del av livet när enorma hormonella omställningar sker i kvinnokroppen.

Arbete I – Förekomst av depressiva symptom under sen graviditet och efter förlossning

En prospektiv kohortstudie där 1489 kvinnor från samtliga mödravårdscentraler i Norrköping, Värnamo, Kalmar och Linköping deltog. Dessa rekryterades konsekutivt under en tremånaders period. Kvinnorna följdes från graviditetsvecka 36 till 6 månader efter förlossningen. Med hjälp av Edinburgh Postnatal Depression Scale, som är en väletablerad, validerad och enkel självskattningsskala, undersöktes dessa kvinnor vid fyra tillfällen. I sen graviditet hade 17 % av kvinnorna depressiva symptom, 6-8 veckor efter förlossningen samt sex månader efter förlossningen förelåg depression hos 13 % av kvinnorna. Det fanns även ett samband mellan depressivitet i sen graviditet samt postpartum (p<0.0001). Prevalenssiffrorna postpartum överensstämmer väl med resultatet från två tidigare svenska studier. Dessa är dock genomförda i storstadsregioner till skillnad från detta arbete som omfattar både städer och landsbygd.

Arbete II – Obstetriska, somatiska och demografiska riskfaktorer för depressiva symptom efter förlossning

Flera olika förklaringsmodeller till uppkomsten av depression postpartum har föreslagits genom åren. Vad beträffar predisponerande faktorer för att utveckla depression postpartum har man tidigare framförallt fokuserat på psykosociala riskfaktorer. Däremot var eventuella obstetriska, somatiska och demografiska riskfaktorer sparsamt undersökta. Den gravida populationen av idag skiljer sig också kraftigt från tidigare då allt fler kvinnor med bakomliggande sjukdom nu kan bli gravida och fullfölja en graviditet. I denna fall-kontroll studie studerades olika tänkbara riskfaktorers betydelse för att utveckla depressiva symptom postpartum. 132 kvinnor med depressiva symptom postpartum utgjorde indexgrupp medan 264 kvinnor utan depression postpartum utgjorde kontrollgrupp. Data relaterades till sociodemografiskt status, medicinsk, gynekologisk och obstetrisk anamnes, förlossningens utfall och perinatala händelser. Oberoende variabler utgjordes av paritet, spontana aborter, legala aborter, utomkvedshavandeskap, infertilitet, civilstånd, rökning, yrke, kroniska sjukdomar, psykiatrisk anamnes, tidigare och aktuella obstetriska komplikationer, antal besök på MVC hos barnmorska respektive läkare, förlossningsförlopp (förlossningslängd, blödningsmängd, anestesi, instrumentell förlossning, sectio), prematuritet, vård på neonatalavdelning, antal dagar på BB och amning. Graviditetsavvikelser såsom kraftigt illamående, smärtsamma förvärkar, sjukskrivning och ett stort antal besök på mödravårdscentralen visade ökat samband med depression postpartum. Vi fann även ett tydligt samband mellan tidigare eller aktuell psykiatrisk anamnes och

depressivitet postpartum men inga samband med ålder, civilstånd, yrke eller paritet, kronisk sjukdom, långvarig tidigare infertilitetsproblematik eller tidigare gynekologisk problematik. Aktuella komplikationer under förlossning eller puerperium utgjorde inte heller riskfaktorer. Efter att en logistisk regressionsanalys gjorts kvarstod endast sjukskrivning och stort antal besök på mödravårdscentralen som samvarierande faktorer.

Arbete III – Kvinnors psykiska och fysiska hälsa samt deras barns beteende 4 år efter förlossning

I en tvärsnittsstudie fyra år efter förlossning undersökte vi en grupp kvinnors aktuella psykiska och fysiska hälsa samt hur dessa kvinnor uppfattar sina barns beteende och emotionella utveckling. Samtliga kvinnor med depressivitet postpartum (n=251) från delarbete I ombads deltaga. Kontroller bestod av kvinnor som i ursprungsstudien ej hade några depressiva symptom postpartum (n= 502). Kvinnorna matchades avseende barnets ålder och kön. Totalt ombads 753 kvinnor att deltaga i studien och 675 kvinnor deltog. Barnen undersöktes med Richman's PBCL, en enkel, väletablerad och validerad skattningsskala som ifylldes av modern. Kvinnor som uppvisat symptom på depression postpartum hade en ökad förekomst av depression samt upplevde en ökad sjuklighet i somatiska åkommor fyra år efter barnets födelse. Sönerna till de kvinnor som varit deprimerade postpartum hade en ökad förekomst av beteendeproblem jämfört med barnen till de kvinnor som ej varit deprimerade postpartum. Både pojkarna och flickorna till de kvinnor som uppvisade depressiva symtom när barnen var 4 år gamla hade signifikant mera problem av beteendekaraktär.

Arbete IV – CYP2D6 genotyp och depressiva symptom i sen graviditet och efter förlossning

I denna hypotesgenererande pilot-studie var målsättningen att kartlägga om genotyp för CYP2D6 är relaterat till utvecklingen av depressiva symptom i sen graviditet och postpartum. Etthundra fyrtiofem kvinnor med depressiva symptom i sen graviditet och/eller postpartum från delarbete I undersöktes med PCR avseende genotyp för CYP2D6. Jämförelser gjordes med tidigare publicerade svenska och europeiska populationsstudier.
Studien kunde inte påvisa något signifikant samband mellan CYP2D6 genotyp och förekomst av depressiva symptom i anslutning till förlossning. Vi fann dock att frekvensen av ultrasnabb CYP2D6 genotyp var vanligare i gruppen av kvinnor som var deprimerade både under sen graviditet och efter förlossning jämfört med förekomsten i andra populationsstudier. Fyndet är så pass intressant att vidare

undersökningar bör göras både på gravida samt nyblivna mammor och kanske även i en allmän grupp av patienter med egentlig depression.

Arbete V – Graviditet och förlossning påverkar koncentrationer av neuropeptider i råtthjärna.

Man har tidigare i några studier funnit ett visst samband mellan depression efter förlossning och ett kraftigt fall av östrogenkoncentration i blod. Östrogen har i djurstudier visat sig kunna påverka koncentrationen av galanin och vissa andra neuropeptider i flera hjärnregioner. Tidigare data har även visat att förändringar i dessa neuropeptiders koncentration kan ha samband med depression.

I ett försök att kartlägga möjliga uppkomstmekanismer till depression postpartum genomförde vi en experimentell djurstudie för att på så vis öka kunskapen om eventuella förändringar i koncentrationen av galanin, NPY, CCK samt substans P i samband med dräktighet och förlossning samt därmed också varierande estradiolkoncentrationer. Trettiosex honråttor undersöktes, där 10 råttor var i sen dräktighet, 12 råttor nyförlösta och 14 var ej dräktiga råttor i östrusfas. I narkos togs ett venöst blodprov från alla råttor. Efter avlivning fridissekerades hippocampus, cortex och striatum. Vävnadsbitarna homogeniserades och peptidinnehållet extraherades. Koncentrationer av galanin, NPY, CCK, substans P samt estradiol bestämdes med RIA-metod. Vi fann att koncentrationerna av de fyra neuropeptiderna samvarierade med serum estradiolnivåer i cortex och striatum. Koncentrationer av dessa neuropeptider i hippocampus påverkades ej av förändringar i serum estradiolnivå.

Konklusion

Depression efter förlossning är vanligt förekommande och kan påverka både moderns och barnets välbefinnande. Vi har visat att mödrahälsovården kan användas för att upptäcka depression under graviditet och efter förlossning. Det är därför lämpligt att utveckla rutiner inom mödrahälsovården i syfte att försöka förebygga, upptäcka och behandla depression i samband med barnafödande. Detta bör ske i nära samarbete med psykiatrisk kompetens och barnhälsovården.

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