Neuroendocrine and behavioral consequences of untreated and treated depression in pregnancy and lactation

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Abstract

Depression during pregnancy and in the *post partum* period is a significant health issue in modern society. The estimated prevalence of depression in pregnancy ranges from 13–20%. The major dilemma for gynecologists is to treat or not to treat depression during gestation and lactation. Consequences of untreated depression can be so serious that the benefit of antidepressant therapy may overweigh the possible risk for injury of fetal/neonatal development. Currently, selective serotonin re-uptake inhibitors (SSRIs) and serotonin and noradrenaline re-uptake inhibitors (SNRIs) are commonly used for treatment of maternal depression. The review article brings up-to-date knowledge on effects of maternal adversity (depression) and/or antidepressants on the development of the hypothalamus-pituitary-adrenal axis of the offspring in relation to postnatal behavior and reactivity to stressful stimuli. Treated as well as untreated maternal depression presents a risk for the developing fetus and neonate. The authors stress the need to evaluate the relative safety of SNRIs/SNRIs by means of relevant experimental models to assess if these drugs can be assigned to treat pregnant and lactating depressive women.

INTRODUCTION

Depression is a mental disorder characterized by long-term sadness, loss of interest and pleasure in current enjoyable activities, low self-esteem, feeling guilty, sleep disorder, low appetite, fatigue, attention and psychomotor deficit. From the biological point of view is the etiology of this disorder still not fully understood. Depression is associated with decreased levels of neurotransmitters, hormonal dysregulation and macroscopic changes in the brain. At present, treatment of depression has focused primarily on stabilizing the balance of neurotransmitter systems. Depression as a major psychiatric disorders affects about 350 million people worldwide. It affects both the younger and older generation. However, depression is more common in women as men since estrogens increase the susceptibility of women to depression (Van den Bergh *et al.* 2008; Brummelte & Galea 2010). In fact women represent a high risk group especially during pregnancy and in the postpartum period. According to statistical indicators 1–2 of 10 women suffer from depression during pregnancy or after childbirth (Brummelte & Galea 2010; Rayen *et al.* 2013; WHO 2012). While the

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incidence of depression may actually be higher due to the reluctance of many mothers to admit their depressive states. This makes depression one of the most common complications of pregnancy (Rayen *et al.* 2011; Pawluski *et al.* 2012a; Oberlander *et al.* 2008).

The etiology of antenatal depression (AD) and postpartum depression (PPD) is multifactorial. Significantly involved are enviromental factors such as maternal anxiety, excessive stress during pregnancy (death in the family, divorce, etc.), young maternal age, low social support, luck of family support, domestic, psychological or/and sexual violence, as well as the negative attitude towards pregnancy (Grote *et al.* 2010; Karmaliani *et al.* 2009; Mohammad *et al.* 2010; Oyebode *et al.* 2012). An increased risk of depression during pregnancy occurs in women who have previously suffered from some form of affective disorders. Epidemiological studies and meta-analyses suggest that similar psychological and psychosocial reasons underlie also PPD (Dennis 2005). It is known that women with PPD had experienced difficulties also during pregnancy (McDonald *et al.* 2012). However, in a woman's life postpartum period is considered as the most risky period for the development of depression. During this period, significant neuronal and hormonal changes take place which may play an important role in the progress of depressive manifestations (Drevets & Todd 2005).

STRESS AS A TRIGGER OF DEPRESSION

In up to 85% of the cases, stress is reported as a major factor in the development of depression (Parker *et al.* 2003; Brummelte & Galea 2010). Stress alters the levels of hormones which are released by the hypothalamic-pituitary-adrenal (HPA) axis, i.e the corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). CRH is produced and secreted by the hypothalamus and stimulates ACTH production and secretion by the pituitary. In turn, ACTH stimulates the production and secretion of cortisol/corticosterone by the adrenal cortex. Regulation of these hormones is achieved by a negative feedback mechanism.

Prenatal stress is associated with an increased level of cortisol of the mother (Parker *et al.* 2003; Oberlander *et al.* 2008; Pawluski *et al.* 2009b; Brummelte & Galea 2010). Along with high levels of basal cortisol levels, abnormal circadian rhythm of cortisol with lower levels in the morning and higher in the evening do also occur (Burke *et al.* 2005). However only about 20% of the maternal cortisol passes to the fetus (Gitau *et al.* 1998; Peña *et al.* 2012). This is achieved through the protective actions of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β–HSD2), which converts cortisol/corticosterone into the inactive metabolites cortisone/11β-dehydrocorticosterone, thus preventing the activation of glucocorticoid receptors (Benediktsson *et al.* 1997; Peña *et al.* 2012) and protecting the fetus from maternal glucocorticoid excess. However chronic maternal stress as well as decreased food intake of the mother reduces placental 11β-HSD2 levels and thus allows increased access of active glucocorticoids to the fetus (Mairesse *et al.* 2007). In the human placenta, 11β-HSD2 levels constantly increase throughout pregnancy. In addition glucocorticoid receptor expression stay constant in the placenta throughout the whole gestation, thus natural fluctuations in 11β-HSD2 levels may control glucocorticoid action in the placenta as well as in the foetus during the whole development (Harris & Seckl 2011). Since glucocorticoids promote correct brain development by initiating terminal maturation, remodeling of axons and dendrites, and by affecting cell survival (Meyer,1983). Disruption at this level can lead to permanent changes in the formation and development of the brain and HPA system and these may subsequently become the basis for behavioral disorders in childhood or in adulthood (Herlenius & Lagercrantz 2004; Van der Bergh *et al.* 2005; Van der Bergh *et al.* 2007; Talge *et al.* 2007; Pawluski *et al.* 2012).

Fetal exposure to stress, and thus to high levels of glucocorticoids, can also affect the expression of glucocorticoid receptors (GR). Inhibition and/or lack of 11β-HSD2 reduces the number of GR in the hippocampus, yet on the other hand, it increases the expression of GR in the amygdala (Welberg *et al.* 2000; Harris & Seckl 2011). In addition increased GR levels in amygdala could increase positive drive onto the HPA axis which increases stress responsivity (Welberg *et al.* 2000). As well as intensive postnatal maternal care may increase the expression of hippocampal GR mRNA and enhanced glucocorticoid feedback sensitivity, which would suggest that maternal care could also influence HPA responsevness to stress in the offspring (Liu *et al.* 1997).

In the 80s of the 20th century, Richard Katz presented with the chronic unpredictable stress paradigm as an animal model of human depression (Katz *et al.* 1981; 1982). Animal studies have shown that individuals with genetic predisposition to depression were more sensitive to effects of chronic stress (Murray *et al.* 2013). Epidemiological studies support the theory that stressful life experiences play an important role in the etiology of depression. Depression caused by chronic stress involves several systems including monoaminergic systems and inflammatory factors associated with the HPA axis which play a key role in the regulation of stress responses (Massart *et al.* 2012). Hypothalamic hormones regulate the activity of the HPA axis which triggers alterations in neurotransmitter systems, including catecholamines and inflammatory cytokines which in turn will lead to down-regulation of 11β-HSD2 level. As a consequences of these changes, higher HPA axis activity together with greater stress reactivity could be associated with the development of many depressive and anxiety-related disorders (Sarkar *et al.* 2001; Tsugita *et al.* 2008; Harris & Seckl 2011).

In animal models, gestational stress was associated with behavioral disorders and with altered regulation

of the stress response of the offspring (Talge *et al.* 2007; Harris & Seckl 2011; Rayen *et al.* 2011; Pawluski *et al.* 2012b). Prenatally stressed animals showed delayed motor development in adulthood, altered habituation, increased anxiety in new a stressful enviroment, depression like behavior, altered social and sexual behavior, etc. (Dubovický *et al.* 1999; Harris & Seckl 2011; Gerardin *et al.* 2011; Rayen *et al.* 2011; Pawluski *et al.* 2012b). Animal studies have also identified a reduced volume of the hippocampus by prenatal stress, which plays an important role in memory formation and in learning procesess, and may lead to impaired cognitive ability as well as to altered responsiveness of the HPA axis (Coe *et al.* 2003; Harris & Seckl 2011; Di-Chaves *et al.* 2013). In addition, prenatal stress in rodents can cause alteration of the number of glucocorticoid and mineralocorticoid receptors in the hippocampus, which could explain why the corticosterone response to a stressor is both increased and prolonged (Harris *et al.* 2013).

Similarly, in clinical trials, an association between antenatal depression and cognitive, behavioral and emotional disorders of children were described. Emotional disorders of children are up to 15% associated with prenatal maternal anxiety (Talge *et al.* 2007). Other outcomes associated with exposure to high levels of glucocorticoids during development include autism, attention deficit and hyperactivity disorder, language problems and depression (Van Den Bergh *et al.* 2005; Talge *et al.* 2007; Hadjikhani 2010; Gerardin *et al.* 2011; Glover *et al.* 2015). In addition, excessive stress was found to inhibit neurogenesis in the hippocampus which in adulthood is responsible for a decreased formation of new neurons and in turn a deficit in these areas might result in cognitive disorders (Snyder *et al.* 2011; Saaltink & Vreugdenhil 2014).

CONSEQUENCES OF UNTREATED DEPRESSION ON THE DEVELOPMENT OF THE HPA AXIS

In every day life organisms have to face many stressors of different severity, and subsequently to respond to these stressors with physiological adaptations to restore homeostasis. Moreover homeostasis of the fetus or newborn is extremely vulnerable. The HPA system is not fully mature at birth, which is manifested by developmental changes throughout childhood in basal HPA activity and cortisol reactivity (Gunnar & Donzella 2001; Tarullo & Gunnar 2006). During the critical pre- and perinatal period stress experiences play an important role in shaping the basal rhythms and reactivity of the HPA system (Tarullo & Gunnar 2006). Thus a higher level of cortisol via maternal stress can negatively influence fetal and child responses to stress and the function of the HPA axis which may induce epigenetic changes in programing of the HPA axis. This could possibly result in dysregulation potentially associated with altered emotional processing and heightened responsiveness to stress (Van der Bergh *et al.* 2008; Harris & Seckl 2011). The stress induced by depressed mothers may result in reduced birth weight, pre-term delivery, developmental delays as well as impaired language skills or low IQ scores (Deave *et al.* 2008; Paulson *et al.* 2009; Velasquez *et al.* 2013). The most common physiological manifestations of affected children are reduced vagal tone, higher levels of cortisol and norepinephrine as well as lower levels of dopamine and serotonin (Gentile 2011; Van der Bergh *et al.* 2008). Related is also an excessive cortisol response of the child, so called "Fetal programing hypotheses" (Barker 1993; de Bruijn *et al.* 2009), which has been tested in preclinical experimental studies (Maccari *et al.* 2003; Macri *et al.* 2007). The fetal programming hypothesis includes different adrenocortical and cardiovascular responses of the child to acute stress (Barker 2002; 2004). Furthermore, intrauterine fetal exposure to psychological stress such as antenatal depression can affect cognitive, behavioral and emotional status of the child (Talge, *et al.* 2007; Van der Bergh *et al.* 2008; Oberlander, *et al.* 2012). However untreated depression affects negatively not only the child´s health but also that of mother. Complications are mainly related to increased morbidity of pregnant women, including preeclampsia and eclampsia, suicidal thoughts of the mother, with PPD after childbirth and with a disturbed mother-child relationship.

CONSEQUENCES OF TREATED DEPRESSION ON THE DEVELOPMENT OF THE HPA AXIS

Treatment of depression during pregnancy raises questions about the safety of antidepressant therapy. In fact, if could affect the health of the pregnant mother, as well as the fetal and neonatal development of the child and the overall their health. From clinical practice it is well known that pregnant women who are undergoing treatment with antidepressants are more likely to have spontaneous abortions and an increased number of stillbirths (Grote *et al.* 2010; Oyebode *et al.* 2012). Infants who were exposed to antidepressant therapy during the prenatal period show excessive crying, convulsions, agitation, tremor, feeding problems, reflux and sleep disturbances (Sanz *et al.* 2005; Thormählen 2006; Galbally *et al.* 2009; Oberlander *et al.* 2008). There were no major malformations in children affected by antidepressants during pregnancy, however persistent pulmonary hypertension and congenital developmental defects of the heart may be associated with antidepressant therapy in late pregnancy (Källén *et al.* 2008; Reis *et al.* 2010; Oyebode *et al.* 2012). Treatment in the third trimester is closely associated also with an increased incidence of Poor Neonatal Adaptation (PNA), which is characterized by a decreasing Apgar score, hypoglycemia, poor muscle tone, breathing difficulties and overall restlessness (Oyebode *et al.* 2012).

The most commonly used antidepressants in pregnancy are selective serotonin re-uptake inhibitors (SSRIs) and serotonin and noarderenaline re-uptake inhibitors (SNRIs). The mechanism of the action of these drugs is associated with inhibiting the re-uptake of monoamines from the synaptic cleft and with increasing the extraneuronal concentration of monoamines in the brain (Pawluski *et al.* 2012a; Oyebode, *et al.* 2012; Da-Silva *et al.* 1998). Most of the work is done with fluoxetine, which is widely used for a variety of medical conditions. Venlafaxine (VENF), as a representative of SNRIs is also used to treat a spectrum of mood disorders. However the limited number of prenatal and perinatal studies raises the question about VENF therapy safeness during gestation and lactation. Since these antidepressants cross the placental and blood-brain barrier and are excreted in breast milk, they increase the level of monoamines also in the fetus and can negatively interfere with the functional brain development. However there is lack of knowledge which would clearly summarize the risk of functional damage of the developing brain of the offspring.

From clinical practice it is known that SSRI-exposed neonates have lower cord blood levels of S100β protein, a biomarker which reflects altered early brain maturation and central serotonergic function (Pawluski *et al.* 2009a). These newborns are at increased risk for neurobehavioral disturbances which include altered motor activity, tremors, as well as decreased response to acute pain conditions (Oberlander *et al.* 2002; Oberlander *et al.* 2005; Knaepen *et al.* 2014). Oberlander *et al.* (2012) also found that antenatal exposure to SSRIs was associated with an increased risk of internalizing behavior of the children as assessed at 3 years of age. SSRI treatment also could alter HPA function in infants by reducing umbilical cord blood cortisol levels (Davidson *et al.* 2009), the early evening cortisol levels as established at 3 months of age (Oberlander *et al.* 2008), and the basal cortisol levels in saliva studied at 6 months of age (Brennan *et al.* 2008).

The effect of SSRI therapy was also well studied on the model of maternal adversity in rats. The consequences of the treatment were associated mainly with reduced locomotor activity in the open-field test (Lee *et al.* 2007; Karpova *et al.* 2009), reduced tactile sensitivity (Lee 2009), altered social (Olivier *et al.* 2011) and sexual behavior (Maciag *et al.* 2006; Rayen *et al.* 2013) as well as an increased anxiety-like behavior (Rigter-Smit *et al.* 2012; Olivier *et al.* 2011). Prenatal maternal stress in combination with developmental fluoxetine exposure in rats increased the corticosterone-binding globulin (CBG) level, and in turn it altered the free corticosterone index in male rats (Pawluski *et al.* 2012a,b). This could reflect possible long-term effects of SSRI exposure on the development of the HPA system. Rayen *et al.* (2011) showed that fluoxetine prevented the reduced depressive-like behavior in forced swim test. Moreover, fluoxetine reversed the decrease of hippocampal cell proliferation and neurogenesis in maternally stressed adolescent offspring. In addition, fluoxetine alone significantly reduced hippocampal cell proliferation even in non-stressed animals.

Further experimental studies suggest that the use of SSRIs and SNRIs during pregnancy may be related to an altered neural plasticity of the individual, which is expressed in altered levels of the brain-derived neurotrophic factor (BDNF) (Thoenen *et al.* 1995; Basterzi *et al.* 2008). *In vitro* studies reported that chronic use of antidepressants induced "up-regulation" of serum levels of BDNF in the rat brain (Duman 1999; Popoli *et al.* 2002). Increased levels of BDNF as well as improved neurogenesis and synaptic plasticity as a result of treatment for depression found at rats could provide some clarification of antidepressant activity with delayed action (Harmer *et al.* 2013).

CONCLUSION

Depression as a major psychiatric disorder is more common in women than men. According to statistical analysis, 1–2 of 10 women suffer from depression during pregnancy or after childbirth. The etiology of antenatal depression and postpartum depression is multifactorial. Significantly involved are environmental factors, such as maternal anxiety, excessive stress during pregnancy, young maternal age, low social support, luck of family support, domestic, psychological or/and sexual violence. In up to 85% of the cases, stress is reported as a major factor in the development of depression. Stress alters the levels of hormones, which are released by the hypothalamic-pituitary-adrenal (HPA) axis. As homeostasis of the fetus and newborn is extremely vulnerable, any imbalances in stress hormones in mother and fetus/newborn can have deleterious effects on the development of the HPA axis. Consequences of untreated depression in pregnancy involve altered neuroendocrine responses to stressful stimuli in adulthood as well as behavioral and cognitive disorders of various intensity. Clinical and experimental studies have shown that SSRIs/SNRIs may prevent /reverse adverse effects of maternal adversity. However, serious experimental studies need to be conducted to reveal possible unfavorable effects of these drugs and their interactions with prenatal stress/depression on the developing neuroendocrine system and on postnatal behavior.

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