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Antenatal depression and antidepressants during pregnancy: Unraveling the complex interactions for the offspring

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ABSTRACT

During pregnancy the risk for a woman to develop a depressive episode is as high as 20%. Antenatal depression is not harmless for the developing child as several changes, including neurodevelopmental alterations, have been reported. Sometimes it is unavoidable to treat a pregnant mother with antidepressants, especially when she is suicidal. Currently, selective serotonin reuptake inhibitors (SSRIs) are the pharmacological choice of antidepressant treatment. SSRIs do not cause gross teratogenic alterations and are generally considered safe for use in pregnancy. However, although SSRIs may relieve the maternal symptoms, they definitively cross the placenta partially influencing the neurodevelopment of the fetus. In this review an overview is given of the effects on the offspring of maternal antenatal depression and the putative neurodevelopmental effects of SSRI treatment during pregnancy. Although we primarily focus on human data, some animal data are discussed to describe possible mechanisms on how SSRIs are affecting underlying biological mechanisms associated with depression. In summary, maternal depression may have long-lasting effects on the offspring, whereas prenatal SSRI exposure also increases the risk for long-lasting effects. It remains to be determined whether the effects found after SSRI treatment in pregnant women are only due to the SSRI exposure or if the underlying depression is also contributing to these effects. The possibility of epigenetic alterations as one of the underlying mechanisms that is altered by SSRI exposure is discussed. However much more research in this area is needed to explain the exact role of epigenetic mechanisms in SSRI exposure during pregnancy.

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1. Introduction

Major depressive disorder (MDD) has devastating consequences for men and women of all ages. According to the WHO report in 2004 concerning the top causes of disability expected for the year 2030, major depressive disorder is ranking first (WHO, 2004). From a reproductive perspective it is important to note that depression affects women twice as much than men (Alonso and Lepine, 2007; Kessler et al., 1994), and that the risk of developing a depressive episode is highest during the childbearing years (Kessler et al., 2005). During pregnancy as many as one out of five women report symptoms of depression (Marcus, 2009; Patkar et al., 2004; Ryan et al., 2005), and 4–7% of pregnant women develop major depression (Andersson et al., 2003; Gorman et al., 2004; Melville et al., 2010). Pharmacological treatment for a maternal mood disorder is sometimes unavoidable, and the use of antidepressants during pregnancy has dramatically increased during the last decade. Selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed antidepressants because of good efficacy, a few side-effects, and therapeutic safety (Barbey and Roose, 1998). Currently, around 2–3% of the women in Europe (Kieler et al., 2012; El Marroun et al., 2012) and up to 13% of the women in the U.S. (Cooper et al., 2007; Hayes et al., 2012) are using antidepressants during pregnancy. It is well known that depressive disorders are part of a developmental process where susceptible genes in combination with environmental influences (and/or experiences) contribute to the development of the disease (Uher, 2014). In antenatal depression, i.e. a depressive episode during pregnancy, the genetic setup of the mother, hormonal/reproductive history, current stressors, and life experiences are well known risk factors (Miller and LaRusso, 2011). Although it is difficult to study the effects of antenatal depression without taking the postnatal environmental influences into account, some studies have tried to correct for the postnatal effects. For instance Davis et al. (2004) showed that antenatal anxiety and depression were associated with infant negative behavioral reactivity to novelty at the age of 4 months, and this association remained after

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controlling for the postpartum maternal psychological state. Several studies have shown that maternal mood symptoms during pregnancy increase the risk for neuropsychiatric disorders in the child later in life (see Section 2.4); however, psychotropic exposure in utero also interferes with the neurobehavioral development, thereby increasing the risks for the future child (see Section 3.1). At this point, it still needs to be investigated whether the use of antidepressants during pregnancy has better or worse outcome in the offspring than untreated antenatal depression. In this review we are summarizing the literature on the effects of antenatal depression and the effects of psychotropic medication during pregnancy on the offspring. Recently we (Olivier et al., 2013) and others (Bourke et al., 2014) have reviewed the effects of prenatal SSRI exposure. We will therefore only focus on the neurodevelopmental effects of SSRI exposure. Moreover, we focus on human data although some animal data are included for the discussion of possible mechanisms underlying depression/SSRI exposure during pregnancy.

2. The effects of antenatal depression on the offspring

2.1. Biochemical findings

Maternal adversities during pregnancy such as anxiety, depression and high levels of stress have been associated with increased baseline levels of stress hormones (Field and Diego, 2008; Mancuso et al., 2004; Wadhwa et al., 1996; Weinstock, 2005), while stress responsivity in depressed pregnant women appears unaltered (Hellgren et al., 2013). During pregnancy stress hormones levels are increasing as the pregnancy advances due to the growth and development of the placenta. The increase in these hormone levels is of great importance for the organization of the fetal nervous system (Sandman et al., 1999). Under normal circumstances the fetus is protected from excess levels of stress hormones by placental enzyme hyodroxysteroid dehydrogenase type 2 (11β-HSD2) that converts cortisol to the inactive cortisone (Stewart et al., 1995). Moreover, cortisol binding globulin (CBG) binds to free cortisol in the circulation preventing cortisol from being active (Lewis et al., 2005). At the end of pregnancy the activity of 11β-HSD2 and CBG robustly drops so that fetal lungs, the central nervous system and other organ systems can mature (Ma et al., 2003; McLean et al., 1995; Murphy and Clifton, 2003). These endocrine changes are adaptive and important for fetal maturation. However, when stress hormone levels are high, for instance in response to stress/antenatal depression, detrimental neurological consequences for the fetus may occur. Several studies have shown that infants of depressed mothers have higher cortisol levels in urine and saliva compared to infants of mothers with a normal pregnancy (Field et al., 2004b; Kaplan et al., 2008; Lundy et al., 1999). These increased cortisol levels could be due to the increased cortisol levels found in depressed mothers (Field et al., 2004a; Lundy et al., 1999) as 40% of the cortisol levels cross the placenta (Gitau et al., 1998). Irrespective of the origin, increased cortisol levels in infants of depressed mothers may contribute to altered neurodevelopment. For instance, fetal exposure to increased levels of maternal stress hormones during the second and third trimester was associated with decreased physical and neuromuscular maturation in the newborn, reflecting reduced neurological development (Ellman et al., 2008). Moreover, elevated levels of stress hormones early in gestation were associated with slower neonatal behavioral recovery from a painful heel-stick stressor, while exposure during the second half of gestation was associated with a larger and more prolonged neonatal cortisol response to the stressor (Davis et al., 2011). In addition, prenatal increases in stress, anxiety and depression have been associated with increased infant fearful temperament (Davis et al., 2004, 2007) and delayed infant cognitive and neuromotor development (Davis et al., 2007; Huizink et al., 2003), which may persist into adolescence (Mennes et al., 2006). Besides the increased stress hormone levels found in infants of depressed mothers, Field et al. (2004b) also reported a decrease in urine dopamine levels. Although these lower levels might contribute to a lower motor-tone and activity found in newborns of depressed mothers (Abrams et al., 1995), a study in 2 year old children showed improved motor development (normal tone, fine and gross motor proficiency during tasks, and appropriate motor speed (IBR-Motor Quality; DiPietro et al., 2006)). Moreover, fetuses were more active during midgestation (Emory and Dieter, 2006) and 4-year old children had better motor behavior in response to several novel stimuli (Harvard Infant Behavioral Reactivity Protocol) following exposure to antenatal depression (Davis et al., 2004). Thus, exposure to antenatal depression may have an inhibiting effect on motor activity immediately after birth, probably due to the mother's biochemistry, but does not affect (Werner et al., 2007), or increase motor activity (Davis et al., 2004) at the age of four months and beyond. The last two studies also suggested that prenatal depression is a predictor of greater infant crying reactivity in response to a standard series of novel stimuli. Greater crying and fussing, higher activity, and more disturbed sleep were found in newborn infants who had been exposed to antenatal depression (Diego et al., 2004; Field et al., 2007; Zuckerman et al., 1990). Moreover, O'Connor et al. (2007) showed that higher levels of maternal anxiety and depression predicted more sleeping problems in children at the age 18 and 30 months.

2.2. Fetal growth findings

Fetal growth was also shown to be affected by antenatal depression as an association between antenatal depression and decreased infant growth was found in India and Pakistan (reviewed by Stewart (2007)). Although antenatal depression was also associated with reduced fetal growth in well developed countries (El Marroun et al., 2012; Henrichs et al., 2010) the influence was most profound in low-income countries and countries with great health inequalities (Grote et al., 2010).

2.3. Physiological findings

On a physiological level, Monk et al. (2004) showed that when depressed mothers performed a psychological challenge (stroop color–word matching test), their fetuses (gestational week 36–38) responded with larger heart rate increases compared to those of healthy mothers. This effect was also found in fetuses of mothers that had co-morbid depression and anxiety (Monk et al., 2011). In addition, Allister et al. (2001) showed that the baseline heart rate was higher in gestational week 32–36 old fetuses of depressed mothers compared to those of healthy mothers.

Midterm and 32–36 week old fetuses from depressed mothers reacted with lower accelerations in heart rate after a vibroacoustic stimuli, and also showed reduced movement with fewer changes in heart rate and heart rate variability after vibratory stimulation (Allister et al., 2001; Emory and Dieter, 2006). This data suggest that the responses to the environment are lower and delayed but the effects are long-lasting.

2.4. Behavioral findings

On a behavioral level, Austin et al. (2005) showed that maternal antenatal anxiety and postnatal depression, but not antenatal depression were associated with difficult child temperament at the age of 4–6 months. In line with this, O'Connor et al. (2002)

showed that antenatal maternal anxiety and postnatal depression, but not antenatal depression, were associated with increased behavioral and emotional problems in 4-year old children. This suggests that antenatal anxiety has a larger effect on offspring behavioral outcomes compared to antenatal depression. It is possible that maternal antenatal depression increases the vulnerability for maladaptive stress responses in the offspring. This idea is supported by the study of Pawlby et al. (2011) where children were at almost 12 times increased risk to develop a psychopathology when exposed to both maternal depression and childhood maltreatment than those not exposed at all. However, although several studies imply that prenatal anxiety has more impact than prenatal depression, there are also studies suggesting a more pronounced effect of maternal antenatal depression. Barker et al. (2011) found that both antenatal and postnatal depression had a more general effect on child functioning compared to that of maternal anxiety. Antenatal depression was associated with small increases in child externalizing behaviors and small decreases in IQ, whereas antenatal anxiety was more associated with small increases in child internalizing difficulties. This is in line with findings from Hay et al. (2010) who showed that depression during pregnancy was associated with violent behavior during adolescence, even when corrected for postnatal depression. Furthermore it was shown that both antenatal depression and anxiety increased the child attention problems at the age of 3 and 4 (Van Batenburg-Eddes et al., 2012). In addition, Misri et al. (2006) showed that with increased reporting of depressive (and anxiety) symptoms, more internalizing behaviors were found in 4-year old children. Antenatal depression was also found to increase the risk of becoming depressed during adolescence (Pawlby et al., 2009) and during adulthood (Pearson et al., 2013) by 4–7 fold. Hay et al. (2008) also noted a similar increase in the risk to become depressed later in life, although they only found the effect in adolescent girls, not in boys. Recently an association was found with antenatal depression and an increased risk for autism in children, although these associations were largely limited to children of mothers who reported antidepressant use during pregnancy (Rai et al., 2013). Antenatal depression was also shown to cause a delayed development in 18 month-old infants (measured with a modified Denver Developmental Screening test) (Deave et al., 2008). Thus both maternal antenatal depression and anxiety have an effect on the developing child. Although some studies show that the offspring is more sensitive to effects of antenatal anxiety, other studies show that the offspring is more sensitive to the effects of antenatal depression. It is often difficult to disentangle maternal depression from maternal anxiety as co-morbidity between these disorders is common (Glover, 2014). Moreover the effects seen in postnatal depression may have been caused by the antenatal depression as well, or at least in part, since similar results are found for antenatal as for postnatal depression. In conclusion, prenatal mood has an impact on the developing child as shown at stress hormone, biochemical, physiological and behavioral levels. The question remains, however, whether it is better or worse to treat the depressed pregnant women with antidepressants. We will therefore describe the impact of antidepressants in the following section.

3. Treatment of depression during pregnancy

3.1. Behavioral findings

All psychotropics studied so far in vivo do cross the placenta and are found in amniotic fluid (Hostetter et al., 2000; Loughhead et al., 2006). Antidepressants may relieve the symptoms of the mother, but limited information is available on the effects on the offspring. Of all antidepressants, SSRIs are the most frequently used ones during pregnancy (Andrade et al., 2008). So far most data have been generated from SSRIs, but given the increasing use of antidepressants there is a great need for well-designed, and long-term studies on the developmental consequences for the offspring. However, several effects have been reported as a result of SSRI exposure during pregnancy. In utero SSRI exposure accelerated speech perceptual development, shown with a decline in heart rate to both vowels and consonants at 36 weeks gestation, while non-exposed fetuses only showed a decrease in heart rate when exposed to vowels (Weikum et al., 2012). Moreover, neonates and 2 month old infants who had been prenatally exposed to SSRIs showed an attenuated response to acute noxious events (heel lance) (Oberlander et al., 2002; Oberlander et al., 2005). Greater amounts of uninterrupted rapid eye movement (REM) sleep were found in infants exposed to prenatal SSRIs (Zeskind and Stephens, 2004). In line with this, Mulder et al. (2011) found increased fetal movements in the third trimester upon SSRI treatment, indicating disrupted REM sleep as well. Interestingly, mothers using SSRIs during pregnancy interrupted their infants more often during mother–infant interactions (Weikum et al., 2013b). Moreover, at the age of three months, infants who had been exposed to SSRIs and antenatal depression displayed a greater willingness to interact with the mother, suggesting that social–emotional development is affected (Weikum et al., 2013b). In the longer term 4 year old child externalizing behaviors tended to be higher in children who were prenatally exposed to SSRIs compared to those of non-exposed children (Oberlander et al., 2007). Internalizing behaviors were also found to be increased in 3–4 year old children in utero exposed to SSRIs (Oberlander et al., 2010), although data are conflicting (Misri et al., 2006). No effects were found on language development, IQ and temperament in 16–86 month old children (Nulman et al., 1997; Nulman et al., 2002; Simon et al., 2002). However, a mild effect on motor development and control and lower Psychomotor Developmental Index scores was found in 6–40 month old SSRI-exposed children (Casper et al., 2003). In general, antidepressant exposure during pregnancy increased the risk for abnormal psychomotor development, such as hearing, sight and motor attention (Mortensen et al., 2003). Moreover, it was recently shown that in utero exposure to SSRIs, but also other antidepressants, increased the risk for autism spectrum disorders (Croen et al., 2011; Rai et al., 2013).

3.2. Biochemical findings

On the stress level, it was shown that in utero exposure to SSRIs attenuated basal salivary cortisol levels (Brennan et al., 2008; Oberlander et al., 2008). Moreover, in response to an acute painful stressor, infants displayed attenuated facial action and heart rate responses (Oberlander et al., 2002, 2005). Increased levels of CBG were found in newborns who were exposed to SSRIs during pregnancy and this increased level was negatively associated with diurnal changes in salivary cortisol at 3 months of age (Pawluski et al., 2012). Furthermore, lower evening basal cortisol levels together with differential cortisol responses to a stress challenge were found in infants that were in utero exposed to SSRIs (Oberlander et al., 2008). Hanley and Oberlander (2012) showed that the maternal caring environment is of great importance since they found that non-SSRI exposed and non-breastfed infants had lower post-stress cortisol levels compared with SSRI-exposed and non-SSRI exposed infants who were breastfed at 3 months of age.

3.3. The serotonin transporter and prenatal SSRI exposure

Weikum et al. (2013a) studied the interaction among prenatal SSRI exposure, genetic variations in the serotonin transporter (5-HTT) and maternal mood on executive functions in 6-year old children. Genetic variations in the promoter of the 5-HTT include a

short (S) and a long (L) allele. Children with at least one S allele who were exposed to prenatal SSRI had stable executive functions, regardless of the mother's mood state. In contrast, children with two L alleles were more sensitive to the maternal mood. When mothers had low levels of depressive symptoms, LL-children outperformed all other genotype groups in executive functions. However, when mothers were more depressed, LL-children underperformed in executive functions compared to all other groups. In fact the executive functions were best in children with at least one S-allele, who also had been exposed to depressed mood and SSRI treatment, highlighting the importance of the environmental influence that together with a certain gene susceptibility increases (S-allele) or decreases (L-allele) the executive functions in the offspring.

3.4. Epigenetic findings

Current antidepressants are far from 100% effective, and are actually used to combat the symptoms of the depression. However, the degree to which SSRIs will affect the underlying causes or biological mechanisms associated with depression is not known. Furthermore, it is very difficult to disentangle the effects of antidepressants from the maternal depression effects. In animal studies, on the other hand, the effects of SSRIs may be separated from the effect of depression. One potential mechanism through which the environment (maternal depression or SSRI exposure) may work is the epigenetic system. The vulnerability of epigenetic markers to environmental alterations and their implications on the etiology of various diseases such as cancer, pediatric syndromes, autoimmune diseases and genetic disorders have been repeatedly demonstrated (Gomes and Pelosi, 2013). It is believed that alterations in the intrauterine environment are directly passed into the embryo-fetal epigenetic programming, and can therefore be involved in the development of various diseases. In a rat study it was shown that offspring of mothers that received low levels of maternal care displayed increased levels of anxiety-like behavior and stress reactivity compared to those who received high levels of maternal care (Weaver et al., 2004). Moreover in animals that received low maternal care, decreased hippocampal glucocorticoid receptor mRNA expression together with decreased H3K9 acetylation and increased DNA methylation around the glucocorticoid gene promoter was found (Weaver et al., 2004). The alterations found in and around the glucocorticoid receptor expression help to determine the maternal care delivered by these animals, thereby transmitting patterns of maternal care behavior into the next generation (Nestler, 2014). Such epigenetic findings are of great importance as epigenetic mechanisms in depression models may reveal new insights in the working mechanism behind antidepressants. Studies on epigenetic alterations induced by antidepressant treatment during pregnancy are very limited. So far only one study investigated the epigenetic effects of prenatal fluoxetine exposure during pregnancy in rats (Toffoli et al., 2014). They showed that DNA methylation patterns of global DNA methylation were abnormal in particular in the hippocampus and cortex of 22 days old rats. Although it is not known whether the altered DNA methylation pattern will persist across the lifespan, the authors suggest that DNA methylation may be a candidate molecular mechanism underlying the physiological alterations caused by prenatal fluoxetine exposure. Nevertheless more studies are needed to find out whether the expression of specific genes is altered or not.

4. Concluding remarks

The studies described in this review have important clinical implications. Maternal depression, as well as other maternal adversities such as anxiety or high stress may have long-lasting effects on the offspring. Here we have reviewed the effects of maternal depression during pregnancy on a physiological, biochemical, and behavioral level. Although antidepressants may relieve the symptoms from the mother it is not yet clear whether the child benefits from the treatment as well. Several studies have shown an increased risk for the offspring after SSRI exposure, but it is not always clear whether these risks are only due to the SSRI exposure or if the underlying depression is also contributing to these effects. For instance increased internalizing and externalizing problems have been reported in children exposed to antenatal depression (with or without co-morbid anxiety levels), but these increased risks have also been shown after SSRI exposure. Therefore these effects could be due to the effects of SSRIs, but it is also possible that the SSRIs are only partly effective (as with many antidepressants) thereby not taking away all adverse effects of the depression. For future studies it would be interesting to study 1) children from mothers taking SSRIs during pregnancy and fully recovered from their depression, 2) children from mothers taking SSRIs who still have depressive symptoms and compare them to 3) children from normal pregnancies. To answer the question whether prenatal SSRI exposure is beneficial for the offspring, more studies are needed to get more insight in the effects of maternal adversity on the offspring. Not much is known about the underlying mechanisms causing the effects in children that are exposed to antenatal depression or SSRIs during pregnancy. We have reviewed a possible mechanism for an embryo-fetal epigenetic programming as alterations in the pattern of global DNA methylation have been found after exposure to prenatal SSRIs. Much research in this area is needed to find out whether specific gene expression is altered as well. Moreover, more epigenetic studies are necessary to unravel the epigenetic mechanisms underlying prenatal SSRI exposure in the long run as the study by Toffoli et al. (2014) only described animals on weaning age.

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