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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.

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)