Chapter

Influences of Maternal Vulnerability and Antidepressant Treatment during Pregnancy on the Developing Offspring

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Abstract

Maternal vulnerability to adversity has long-term impact on the developing child. About 20% of the pregnant women suffer from affective disorders. Fetal exposure to maternal adversity may lead to detrimental consequences later in life. Maternal affective disorders are increasingly treated with antidepressants, especially selective serotonin reuptake inhibitors (SSRIs). However, the long-term consequences for the offspring after exposure to this medication are unclear. The interplay between maternal adversity and SSRI treatment has been under investigation and here we discuss how maternal adversity and SSRIs are able to shape offspring development. Specifically, we will discuss animal models addressing behavioral outcomes to understand how the prenatal environment influences the health of the developing child across the life span.

Keywords: maternal vulnerability, maternal depression, selective serotonin reuptake inhibitors, antidepressants, pregnancy, neurodevelopment

1. Introduction

Although pregnancy is often portrayed as a time of great joy, that is not the reality for all women. Depressive symptoms during pregnancy are not uncommon; in fact, 20% of women experience some depressive symptoms during any time of their pregnancy [1]. The number of women who suffer from major depression during pregnancy is estimated to be 4–8% [2, 3]. According to the DSM-5, this disorder is characterized by a depressed mood or loss of interest or pleasure in daily activities for more than 2 weeks. Depression is accompanied by impaired social, occupational, and educational functioning. Untreated antenatal depression, that is to say a depressive episode during pregnancy, may have a tremendous effect on the developing child [4].

Maternal vulnerabilities during pregnancy, such as depression, anxiety, or high stress levels due to other reasons, are associated with increased and continued activation of the hypothalamic-pituitary-adrenal (HPA) axis. The continued activation of the HPA axis in depressed patients causes an elevated stress response and increased cortisol levels [5]. About 40% of the cortisol passes through the placenta [6]. Consequently, increased cortisol levels are found in the urine and saliva of the infants of depressed mothers [7].

Fetal exposure to increased maternal stress levels impacts the developing child. For example, high levels of maternal cortisol are associated with reduced neurological development [8] and altered cortisol responses of the unborn child to a stressor [9]. Furthermore, maternal vulnerabilities such as anxiety, depression, and elevated stress levels are associated with the increased fearful temperament and negative behavioral reactivity to novelty in infants [9, 10], and delayed cognitive and neuromotor development [11, 12] that persists into adolescence [13]. In addition, antenatal depression has also been linked with disturbed sleep patterns in infants [14] and in 18 and 30 months old children [15]. Furthermore, antenatal depression has been linked to reduced fetal growth [16, 17] and altered cardiovascular responses to stress [18].

Several studies have looked into the effects of maternal vulnerability on the behavioral development of the child. For example, maternal anxiety, but not antenatal depression is linked to a difficult child temperament at the age of 4–6 months [19], an increase in behavioral and emotional problems at the age of 4 [20] and more internalizing behavior at the age of 8 [21]. Moreover, antenatal depression is associated with delayed development in 18-month-olds [22], increased externalizing behaviors and a slight decrease in IQ in 8-year-old children [21], and violent behavior during adolescence [23]. On the long-term prenatal exposure to maternal depression is associated with a higher chance of developing depression during adolescence [24, 25] and adulthood [26], or risk of developing other psychopathologies [27]. Maternal anxiety as well as maternal depression during pregnancy is correlated with child attention problems at the age of 3 and 4 [28]. Moreover, an increase in reporting symptoms of antenatal depression and anxiety positively correlated with an increase in internalizing behaviors in 4-year-olds [29]. So anxiety and depression appear to have similar but, at the same time, different effects on offspring development; however, it is difficult to discern between maternal anxiety and depression, due to common comorbidity between these mental health conditions [30].

Overall, maternal vulnerability, such as depression and anxiety, during pregnancy can negatively influence the unborn child on both physiological and behavioral levels. However, it remains difficult to discern the direct effects of antenatal depression (an aversive postnatal environment due to a depressed mother), and genetic predisposition to vulnerability on fetal and infant development. In addition, an increasing percentage of women suffering from depression and/or anxiety are treated with antidepressants, which on itself might have tremendous effects on the developing child.

2. Maternal SSRI treatment and offspring development

Pharmacological treatment of antenatal depression and/or anxiety is sometimes unavoidable. The treatment with antidepressants may relieve the symptoms of the depression of the mother and could help in reducing the impact on the unborn child. Nowadays, a considerable number of women are treated with antidepressants during pregnancy. In Europe, this concerns 2–3% of the pregnant women [16, 31], while in the U.S., the occurrence is as high as up to 13% [32, 33]. The most prescribed antidepressants are selective serotonin reuptake inhibitors (SSRIs), because of their good efficacy, few side effects, and therapeutic safety [34]. These drugs work by blocking the serotonin transporter and hereby preventing the reabsorption of the neurotransmitter serotonin into the presynaptic nerve cell. Subsequently, extracellular serotonin levels in the synaptic cleft are increased and more serotonin is available to bind the postsynaptic receptors. Although, SSRIs are considered safe for antenatal use [35], it has been reported that the use of SSRIs during pregnancy may negatively influence the development of the unborn child. SSRIs can cross the

placenta and are found in the amniotic fluid [36, 37], affecting therefore not only the mother but also the developing child. This is of extra concern as serotonin plays a key role in embryonal development. During the development of the fetal brain, serotonin acts as a neurotrophic factor, regulating cell division, differentiation, migration, growth cone elongation, dendritic pruning, myelination, and synaptogenesis [38]. In fact, serotonin receptors and serotonergic metabolic enzymes are expressed before serotonin-producing neurons are present in the brain [39]. Thus, changes in the serotonin levels during neurodevelopment, for instance, by the administration of SSRIs during pregnancy, potentially affect a number of processes in the offspring.

Indeed, literature shows a number of side effects in the offspring due to prenatal SSRI exposure. First of all, SSRI exposure during pregnancy has been associated with attenuated basal cortisol levels in neonates [40, 41], and differential cortisol levels in 3-month-old infants in response to a stressor [42]. Also, the neonatal heart rate response to an acute noxious event is attenuated [43]. Furthermore, several behavioral changes have been reported, such as increased internalizing behaviors, such as depression, anxiety, and social withdrawal during childhood [44, 45], increased externalizing behaviors in 4-year-old children [46], and disrupted sleep patterns in newborn [47]. In addition, SSRIs reduce utero-placental blood flow, a mechanism thought to be involved with hypertension in preeclampsia and gestational diabetes [48, 49].

Recently, there has been much interest in the link between antenatal SSRI treatment and the development of autism spectrum disorders (ASDs) in the child. ASD is a neurodevelopmental condition characterized by difficulties in social communication and unusually restricted, repetitive behavior and interests. The available literature shows an association between the prenatal use of SSRIs and the increased risk of ASDs in the child [50–54]. It is theorized that this is facilitated by an increase in serotonergic activity during brain development [55]. Several studies found abnormal placental histology to be associated with autism diagnosis [56, 57]. Moreover, autistic patients have elevated blood platelet serotonin levels [58, 59]. Taken together, these results imply the serotonergic influences on maternal-fetal interaction, although the exact mechanisms remain elusive.

A possible route for passing adverse intra-uterine effects to the fetus is via epigenetic regulation. For example, increased maternal depressive mood during pregnancy is associated with reduced methylation of the promotor of the gene coding the serotonin transporter (SERT) in both mothers and newborns [60]. These results suggest increased SERT mRNA levels and subsequently modified serotonin levels, contributing to increased vulnerability later in life [61]. St-Pierre and colleagues therefore conclude that all parameters that can alter serotonin homeostasis during early development could lead to structural and functional changes in fetal development and brain circuits [62], which could subsequently result in a predisposition to psychopathology in adulthood.

Thus, several studies have shown an increased risk for developing the child both during antenatal depression and after prenatal SSRI exposure. However, it is difficult to discern between the effects of the SSRIs and the effects of the depression itself, as healthy mothers do not administer antidepressants. For example, meta-analyses show that the risk found for ASD in the offspring after prenatal SSRI exposure is decreased after correcting for maternal mental illness [63]. Thus, the effects of SSRIs mentioned could be solely due to the administration of the SSRIs, or alternatively, the SSRIs are only partially effective and therefore do not eliminate all the adverse effects of the depression, thereby adding up to the adverse effects of antenatal depression [4].

3. Preclinical studies: perinatal SSRI exposure

In humans, it is difficult, if not impossible, to discern the effects of the SSRI and the depression itself on fetal development. It is not ethical to study the effects of SSRIs in healthy pregnant women. In addition, it is impossible to study gene expression and epigenetic changes in the fetal brain as a result of prenatal SSRI exposure. Due to these limitations of human research, researchers often use animal models, specifically rodents, to get a more profound insight into the mechanisms underlying the observations seen in human studies.

It should be noted that the timing of brain development is different in humans compared to rodents. A rodent brain at postnatal day 7–10 is considered to be the rough equivalent of a newborn human infant [64]. Thus, to mimic SSRI exposure during the entire pregnancy in humans, rodents should be exposed both pre- and postnatally. In addition, it is known that SSRIs are also found in breast milk [65], again underlining the need to research both the effects of pre- and postnatal SSRI exposure. For exposure to SSRIs around these time points, we will use the term perinatal SSRI exposure; when timing of the SSRI exposure is of particular importance, we will distinguish between pre- and postnatal exposure to SSRIs.

3.1 Social behavior

As serotonin is a key regulator of social responses and prenatal SSRI exposure is being linked to ASDs, which are characterized by impaired social behavior [54], this behavioral parameter is often addressed in researching the effects of prenatal SSRI exposure in animals.

Social play at juvenile age is an essential behavior in rodents for the development of the necessary social, cognitive, emotional, and physical skills [66]. SSRIs are well described in literature as reducing social play behavior in young rats when prenatally [67] or postnatally [68–71] administered. These effects of SSRIs seem sex-mediated, as males are more affected than females [70], or females are not even affected at all [71]. This is interesting because this is analogous to the situation, where men are 3–4 times more likely to get diagnosed with ASDs compared to women [72]. In spite of that, not all studies found similar results. In a recent study [73], social play behavior was unaltered after prenatal SSRI exposure. However, in the latter study, social play was assessed with a familiar play partner (littermate), while other studies use a novel conspecific.

Findings on the effects of prenatal SSRI exposure on social behavior at adult age are more conflicting. Olivier and colleagues [67] found reduced social exploration in adult male rats after prenatal SSRI exposure. While another study found that 4 days of postnatal treatment with SSRIs led to increased sniffing, contact with, and total social interaction with a novel conspecific in males [74]. On top of that, other studies found no effect of prenatal SSRI exposure on social exploration in both males and females [75, 76]. In general, studies on the exposure of SSRIs during early development on adult social interaction are unconvincing. Studies on social motivation on the other hand, measured as the preference of a rodent to spend time with a novel conspecific over interaction with an object, appear to be more in line. Decreased social motivation is found in both males and females, when postnatally exposed to SSRIs [69–71, 77]. On the other hand, prenatal exposure to SSRIs led to an increase in motivation to interact with a conspecific in mice [75]. Thus, while literature on the effects of perinatal SSRI exposure on social behavior during adult is still limited, both timing of the exposure and sex are important factors in the subsequent social development.

Another form of social interaction under the influence of the neurotransmitter serotonin is aggression [78]. Indeed, during both childhood and adulthood, SSRIs are successfully used to reduce aggressive and violent behavior in certain mental disorders

[79, 80]. Perinatal exposure to SSRIs, on the other hand, leads to increased externalizing behavior, such as aggression, in children [46]. In rodents, the effects of perinatal SSRI exposure on aggressive behavior are conflicting. Several studies show an increase in male, but not female aggressive behavior [73, 75, 76, 81], while other studies show reduced aggressive behavior in male rodents perinatally exposed to SSRIs [82, 83].

Serotonin is known to be involved in the regulation of maternal care [84]. Thus, perinatal SSRI exposure can be expected to alter maternal caregiving behavior of both the SSRI-treated mother and her female offspring, when they are mothers later in life. Typical maternal behaviors include nest building, gathering the young into the nest, maternal licking, and nursing the pups. Studies on the effect of direct SSRI exposure found an increase in these behaviors [85, 86], or no effect at all [87]. So far, only one study has been performed on the effects of prenatal exposure on maternal care later in life, and interestingly here, they found a reduction in maternal caregiving behaviors [75]. This suggests that direct changes in serotonin levels, such as an increase in extracellular serotonin levels during SSRI treatment and changes in serotonin levels during development differentially alter the quality of maternal care.

Another role for serotonin is its signaling in sexual development, on both the brain and at a behavioral level [88]. In addition, chronic SSRI treatment may result in sexual dysfunction [89]. Not much is known on the effect of perinatal SSRI exposure on the sexual behavior of these children later in life; however, several studies have been performed in rodents. The effect of perinatal SSRI exposure depends on the timing of treatment. When postnatally administered, male sexual behavior later in life is reduced [70, 90–93]. In contrast when the SSRI is prenatally, or both prenatally and postnatally, administered, there is no effect on sexual behavior of male rodents [94, 95]. Interestingly, there appears to be an opposite effect in female offspring, where postnatal SSRI exposure leads to an increase in sexual behaviors [75, 96]. Thus, apart from the effect of timing, sex of the offspring also differentially alters the effect of perinatal SSRI exposure on reproductive behavior.

3.2 Affective behavior

It has long been established that serotonin is involved in affective disorders [97]. Affective disorders, also called mood disorders, include psychiatric disorders such as major depressive disorder and anxiety disorders.

A large body of preclinical research has shown the relationship between perinatal SSRI exposure and anxiety. Although there are some studies finding no effects, several studies did find an increase in anxiety-like behavior and/or less explorative behavior in an open field test, when rodents are perinatally exposed to SSRIs [67, 83, 98–104]. An increase in anxiety-like behavior in the elevated plus maze and the novelty-suppressed feeding test are also found [67, 98, 99, 105]. Nevertheless, there are also studies that did not find effects at all [87, 91, 106–111], and two studies even found a decrease in behaviors related to anxiety [92, 112]. Even though results differ among studies, these differences are not clearly linked to sex of the offspring or timing of the SSRI exposure. So even though there appears to be a clear link between perinatal SSRI exposure and anxiety later in life, to get a more profound insight into the mechanisms behind this and the role of timing and sex, more researches have to be done.

It is difficult to determine if a rodent is depressed, moreover, to determine if it is even possible for rodents to experience depression. However, rodents can show behavior characteristics of the behaviors, and humans show during episodes of major depression. Such behaviors encompass despair and anhedonia [113]. To measure behavioral despair in rodents, the forced swim test is usually performed [114]. In this test, the animal is placed in an unescapable container filled with water, forcing the rodent to swim. After making efforts to escape the animal may

eventually stop his efforts and become immobile. The amount of time spent immobile is used as a measure of helplessness and behavioral despair. As reviewed [115], many, but not all, studies performing the forced swim test after perinatal SSRI exposure found an increase in immobility [83, 99, 100, 105, 106, 109, 110, 116–121]. Three studies did not find an effect [67, 87, 111], and three studies even found a decrease in immobility [103, 112, 122]. The reviewers propose that these differences may be due to strain effects, some strains could be more susceptible to early life SSRI exposure, while others are resistant. In addition, they point out that the effect of perinatal SSRI exposure is greater, when the animals are exposed during early postnatal period rather than the prenatal period.

Anhedonia is another behavior often assessed as a measure for depression. Anhedonia is the inability or lack of motivation to experience pleasure from rewarding activities and is measured in rodents with the sucrose preference test [123]. In this test, two drinking bottles are placed in the rodent's home cage. One is filled with water and the other with a sucrose solution. Preference for the sucrose solution is considered as the typical hedonic behavior, and lack of bias toward the sucrose water is characterized as a sign of anhedonia. It appears that only postnatal SSRI exposure increases anhedonia later in life [124], as opposed to prenatal exposure [67, 125]. This once more emphasizes that the moment of exposure is an important factor in assessing the effects of perinatal SSRI exposure.

Thus, not only sex of the offspring, but also the timing of the SSRI exposure appears to play an important role in behavioral development. However, all aforementioned studies are performed in offspring from healthy mothers. In practice, pregnant women are usually treated with SSRIs when they are suffering from anxiety and/or depression. It is likely that both maternal factors and the treatment with SSRIs affect serotonin functioning in the embryo and infant. The interplay of these two factors might shape the development of the fetus in a different way than antenatal depression or prenatal SSRI exposure on its own. Thus, to make a more valid translational step to the human situation, animal models of maternal vulnerability have to be used.

4. Preclinical studies: maternal vulnerability and perinatal SSRI exposure

To induce maternal vulnerability in healthy rodents, researchers often use the early life stress model (ELS). Maternal separation is one of the manipulations often used to create ELS; in this procedure, the offspring is taken away from the mother for few hours during the day, and this happens daily during a period of few early postnatal weeks. This procedure leads to a long-term and intergenerational increase in anxiety and depressive-like behaviors [126–131]. Female offspring exposed to ELS and showing an increase in anxiety and depressive-live behaviors can be used as a model of maternal vulnerability later in life. Little is known about the interaction of such maternal vulnerability and treatment with SSRIs during pregnancy.

4.1 Social behavior

So far, only two studies have been looking into the combined effects of maternal vulnerability and perinatal SSRI exposure on social play behavior and social interaction of the offspring later in life. In 2017, Gemmel and colleagues [73] showed that the reduction in social play behavior in juveniles due to maternal vulnerability is prevented by perinatal SSRI treatment regardless of the sex of the offspring. This suggests a rescuing effect of SSRIs on social behavior in offspring of stressed mothers. However, social aggressive play was increased in adolescent offspring exposed

to perinatal fluoxetine and maternal vulnerability in both sexes. In addition, time grooming a novel conspecific was decreased in males only. In a later study, Gemmel and colleagues [132] did not find such an interaction effect on social behavior in adult offspring. Even though, maternal vulnerability itself decreased social investigation in adult males while perinatal SSRI exposure increased social investigation in adult females and increased social play in adult males. Thus, normalization, by SSRIs, of altered social play and social interaction, due to maternal vulnerability might only be short-lived as it does not persist into adulthood. With regard to aggression, however, long-term protective effects of SSRIs are found [81]. In this study, aggressive behavior was decreased as a result of maternal vulnerability, which was normalized when perinatal SSRI exposure was included in the treatment.

One study has looked into the combined effect of SSRI exposure and maternal vulnerability on offspring sexual development [133]. Perinatal SSRI exposure reduced sexual behavior in male offspring, while interestingly maternal vulnerability alone or the combination of maternal vulnerability and perinatal SSRI exposure did not have any effect on the development of sexual behavior.

So, even though SSRI treatment of vulnerable mothers appears to have protective effects on offspring social development, these findings are not consistent over all types of behavior and differ with the moment of assessment of the offspring.

4.2 Affective behavior

Affective behaviors of the offspring such as anxiety and depression-like behaviors have also been studied after the offspring was exposed to a combination of maternal vulnerability and perinatal SSRI exposure. One study [134] shows that the increase in anxiety due to maternal vulnerability can be reversed by the postnatal administration of SSRIs. When prenatally administered, such a rescuing effect is not found [87]; however, the effect of maternal vulnerability was limited and was only found in males in this study. Two studies assessed depressive-like behavior after perinatal exposure to both maternal vulnerability and SSRIs. Both studies found that SSRIs normalize the increase in immobility in the forced swim test due to maternal vulnerability [87, 135]. Thus so far, the effect maternal vulnerability has on anxiety and depressive-like symptoms in the offspring later in life appear to be reversed by SSRIs.

5. Conclusion

Thus, children from mothers who suffer from anxiety or major depression during their pregnancy are at risk of developing several psychopathologies later in life. Moreover, treatment with SSRIs during pregnancy can also lead to long-term consequences for the children. However, it is difficult to determine if these effects are due to the SSRI treatment, maternal vulnerability, or a combination of both. Preclinical research in rodents shows that perinatal SSRI exposure on itself leads to alterations in social behavior later in life. Specifically, social play in juveniles, sexual behavior, maternal care in females, and aggression in males are influenced. Affective behaviors are also influenced, and both anxiety and depressive-like behaviors are increased due to perinatal SSRI exposure. Both the moments of SSRI exposure, pre- or postnatal, and sex of the offspring appear to be important factors in the development of social and affective behaviors after perinatal SSRI treatment.

Recently, researchers have started to look into the combined effects of maternal vulnerability and perinatal SSRI exposure in preclinical studies to make a more valid translational step to the human situation. Even though only a few studies have been done so far, it seems that, at least some, developmental alterations on offspring

behavior due to maternal vulnerability can be normalized by perinatal SSRI exposure. These are interesting and promising results and further investigation into the risks and benefits of SSRI use during pregnancy in appropriate animal models are necessary to help depressed women in their decision to use SSRIs during pregnancy.

Conflict of interest

The authors declare that there is no conflict of interest.

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