

SELECTIVE SEROTONINE REUPTAKE INHIBITORS (SSRI) USAGE DURING PREGNANCY

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SUMMARY

Depressive disorders in pregnancy are common and generate concerns regarding their treatment. The effects of untreated maternal depressive symptoms on preterm birth, low birthweight, fetal growth restriction and postnatal complications are well known. When left untreated, depressive disorders continue postpartum and have a big impact on the patients' functioning. Selective serotonin reuptake inhibitors (SSRIs) are the first choice of treatment of depressive disorders. However, there are some concerns which should be addressed. The aim of this systematic review is to explore the SSRI usage in pregnancy. We studied the latest literature in the PubMed databases and recommendations from the guidelines. Decision to treat depression in pregnancy should be taken with careful consideration of many factors. Clinicians should weigh the use of SSRIs during pregnancy against the risk of untreated depressive disorder.

Key words: perinatal depression - serotonin - SSRI - pregnancy - breastfeeding

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INTRODUCTION

Serotonin is a neurotransmitter derived from the amino acid tryptophan and distributed widely throughout the brain. It influences mood, emotions, impulsivity, learning, memory, attention, sleep, aggression and neurovegetative control (Pawluski et al. 2019). It has several important roles during embryonic and fetal brain development including neuronal maturation, migration, synaptogenesis and differentiation of neural crest cells which are involved in facial and cardiac development (Berger et al. 2009, Oberlander 2012). It is also an important factor in several epigenetic processes such as stress responsivity via the hypothalamic-pituitary-adrenal axis (Oberlander 2012, Monti 2011). Serotonin has the capacity to modulate many socially motivated behaviors and plays an important role in the transition to motherhood and the regulation of care giving (Pawluski et al. 2019). Pregnancy and the postpartum period produce changes in central serotonin neurochemistry, receptor expression and neuroplastic changes at a cellular level in the maternal dorsal raphe nucleus (Pawluski et al. 2019).

Selective serotonin reuptake inhibitors (SSRIs) block the reuptake of serotonin and present an effective treatment of depression and anxiety. The use of SSRIs during pregnancy is steadily increasing, reaching 2–6% of all pregnancies in recent years (Ornoy & Koren 2014). Indeed, 63% to 85% of pregnant women with exposure to antidepressants are treated with SSRIs (Jimenez-Solem 2014, Taouk et al. 2018). Furthermore, women in their reproductive ages are three times as likely to use antidepressants compared to men (Pratt et al. 2011).

The aim of the present review is to explore the usage of SSRIs during pregnancy with its positive effects and possible risks. First, we will discuss the influence of

perinatal depression and anxiety on pregnancy and fetal development. Then we will review current treatment guidelines. Furthermore, we will discuss influence of SSRI treatment on pregnancy complications, congenital malformations, cardiac anomalies, neonatal effects, possible long-term neurodevelopmental effects and epigenetic changes. At the end we will describe pharmacokinetic and pharmacodynamic changes during pregnancy and strive to reach conclusions based on the available extensive published literature.

PERINATAL DEPRESSION AND ANXIETY

Perinatal depression occurs in the period from conception to the end of the first postnatal year and affects up to 15% of women (Woody et al. 2017, Bödecs et al. 2013). A recent meta-analysis showed a pooled prevalence of 11.9% of all pregnancies, without significant differences between prevalence estimates for the prenatal and postnatal periods (Woody et al. 2017). Perinatal depression can have negative effects on the child and the mother. It carries an increased risk for premature delivery, low birth weight, gestational hypertension (Grigoriadis et al. 2013, Grote et al. 2010) and perinatal death (Howard et al. 2007). Infants whose mothers have perinatal depression are more likely to stop with breastfeeding early (Wouk et al. 2017). Furthermore, perinatal depression is linked to behavioural, emotional, cognitive and motor problems in the early childhood (Field 2011, Talge et al. 2007). Maternal depression can influence the mother-infant relationship, which is important for healthy infant development (Goodman et al. 2011, Tronick & Reck 2009). Positive mother-child attachment and quality parenting strategies promote child development and

secure attachment in children (Curry et al. 2019). Women with untreated perinatal depression may exhibit significantly lower levels of positive maternal behaviors, such as praising and playing with their child (Lovejoy et al. 2000). Furthermore, there may be higher levels of negative maternal behaviors and disengagement from their infants in comparison with women without perinatal depression (Lovejoy et al. 2000). Acts of harming oneself, the fetus or the newborn are very rare, however, perinatal depression increases the risk of suicidal ideation and suicide (Lovejoy et al. 2000). Twenty to sixty percent of depressed mothers experience comorbid anxiety (Miller et al. 2015). Maternal anxiety during pregnancy is also positively related to an increased risk of preterm birth and low birth weight (Ding et al. 2014).

CURRENT TREATMENT GUIDELINES FOR PERINATAL DEPRESSION AND ANXIETY

Early symptom identification and intervention are essential in ensuring optimal maternal-child well-being. Screening for perinatal depression as a part of routine examination helps to find early depressive symptoms in pregnant women. The management of perinatal depression is based on the principle of avoiding the exposure of the developing foetus to both the maternal illness and the potential harmful effects of medication. Guidelines recommend to discuss all treatment options and their potential benefits and harms with the patient. This way, patients can make a well-informed decision on preferred treatment (Molenaar et al. 2018). Most guidelines agree that psychotherapy, especially cognitive behavioural therapy (CBT), should be considered as initial treatment for mild to moderate depression, both during pregnancy and in the postpartum period (Molenaar et al. 2018). Psychotherapy, such as CBT or interpersonal therapy, has a robust treatment effect for depressive disorder during pregnancy (van Ravesteyn et al. 2017). Antidepressants are the preferred treatment options in moderate to severe depression (van Ravesteyn et al. 2017). On the contrary, the American College of Obstetricians and Gynaecologists (ACOG; USA) guideline recommends antidepressants as the preferred initial therapy, independent of symptom severity. For suitable decision-making, the following should be taken into consideration: psychiatric history and indication for antidepressant medication, current psychiatric symptoms, previous attempts of tapering medication, availability of alternative treatment options such as preventive psychotherapy and the presence of a social support network (Molenaar et al. 2018). Detached mindfulness and stress management training can be effective as adjuvant treatments (Ahmadpanah et al. 2018). Some treatments are still in research phase, such as the bright light therapy (Bais et al. 2016).

Many maternal and child-related factors govern full recovery of depression and anxiety in the postpartum period. Early awareness of these predictors could lead to timely interventions, ensuring long-term maternal-child well-being (Shankar et al. 2017). Factors that predict full recovery from depression are the absence of maternal health concerns, low total parental stress, and few child behavioural issues, whereas low levels of spousal stress were a significant factor in achieving full recovery from anxiety (Shankar et al. 2017).

SSRI DURING PREGNANCY

The antidepressives are prescribed when the potential benefit of treatment outweighs the risk. In moderate or severe depression, advantages in treating with SSRIs seem to exceed potential drug side effects. The target dose should be the lowest effective. SSRIs, preferably sertraline, may be the medication of choice during pregnancy (Källén 2004). Paroxetine is better avoided because of a possible increased risk for congenital heart malformations. Most guidelines agree on encouraging breastfeeding. The Nordic Federation of Societies of Obstetrics and Gynaecology (NFOG; Norway) advises switching medication when breastfeeding with unfavourable medication. Sertraline and paroxetine are favourable antidepressants during breastfeeding due to their low level in breast milk and infants serum (Molenaar et al. 2018, Pinheiro et al. 2015, Uguz 2019, Orsolini & Bellantuono 2015).

Congenital malformations and cardiac anomalies

Although antidepressants are generally considered safe during pregnancy, this remains controversial (Simioncelli et al. 2010). Antidepressant use has been associated with an increased risk for cardiovascular malformations (Grigoriadis et al. 2013), preterm delivery, lower birth weight (Ross et al. 2013), poor neonatal adaptation (Grigoriadis et al. 2013) and neonatal persistent pulmonary hypertension (Kieler et al. 2012).

In 2005, the FDA cautioned that exposure to paroxetine during the first trimester of pregnancy may increase the risk of cardiac malformations. Since then, the association between maternal use of SSRIs during pregnancy and congenital malformations in infants has been the subject of much discussion and controversy (Gao et al. 2018). Some studies reported that the SSRI use during first trimester of pregnancy is associated with an increased risk of cardiovascular-related malformations of infants including septal defects (Zhang et al. 2017). However, a meta-analysis of cohort studies including more than nine million births suggests a generally small risk of congenital malformations and argues against a substantial teratogenic effect of SSRIs (Gao et al. 2018). Indeed, the association with congenital malformations was markedly attenuated after controlling for psychiatric diagnosis (Gao et al. 2018).

Pregnancy complications

Research showed that women who received SSRI during pregnancy were not at an increased risk of having a miscarriage (Ornoy & Koren 2019), gestational diabetes or higher blood glucose (Wartko et al. 2019), however there was an increased risk of gestational hypertension and preeclampsia (Guan et al. 2018). Studies also suggest that SSRIs are safe regarding postpartum bleeding (Perrotta et al. 2019).

Neonatal effects

The fetus is exposed to significant concentrations of SSRI during the latter half of pregnancy. Transient neonatal symptoms are common after SSRI use in late pregnancy (Ornoy & Koren 2019) and may be caused by withdrawal. Breastfeeding seems to reduce the risk of developing withdrawal symptoms (Kieviet et al. 2017). Most symptoms do not develop until eight hours after birth and proceed even though medication exposure has ceased. Adverse neonatal effects affecting the respiratory, gastrointestinal and neurological systems are predominantly mild and self-limiting (Soufia et al. 2010). Symptoms may include feeding difficulties, irritability and tremors. When antidepressive treatment is taken during pregnancy, observation of the neonate is generally recommended, ranging from 12-hours to 3-days post partum (Kieviet et al. 2013). The dosage of antidepressants does not seem to be related to the risk of poor neonatal adaptation (Kieviet et al. 2013). Most cases of poor neonatal adaptation are mild, of short duration and self-limiting without need for treatment (Kieviet et al. 2013). The risk of persistent pulmonary hypertension of the newborn is also important to address. The risk for persistent pulmonary hypertension (Huybrechts et al. 2015) and birth defects (Furu et al. 2015, Huybrechts et al. 2014) may be more modest than previously indicated (Chambers et al. 2006, Alwan et al. 2007). The risk of pulmonary hypertension is probably less than 1% (t Jong et al. 2012). According to research, sertraline ranked as most likely to have the lowest risk of persistent pulmonary hypertension of the newborn compared to other SSRIs, suggesting it may have the best safety profile for use in pregnancy in this regard (Masarwa et al. 2019).

Neurodevelopmental effects

Prenatal exposure to SSRIs may induce some transient motor delay, however, there seems to be no evidence for long-term adverse developmental effects (Ornoy & Koren 2019). Recent study did not find evidence of an association between intellectual disability and maternal antidepressant medication use during pregnancy (Viktorin et al. 2017). In addition to clinical data on social behaviors, animal models are pointing to a long-term effect of perinatal SSRIs on social interactions, play behavior and reproductive behavior (Ober-

lander et al. 2007). These SSRI effects cannot be completely separated from the effect of maternal mood and maternal care-giving behaviors. Importantly, human studies are frequently challenged by a failure to isolate the effects of the drug exposure from the effects of maternal mental health (Gemmel et al. 2018). A recent large study suggests no substantial increased risk for externalizing, emotional, or social problems in pre-school-aged children following prenatal SSRI exposure (Lupattelli et al. 2018). Some recent clinical findings link prenatal SSRI exposure to abnormal development of social behaviors with increased risk for Autism Spectrum Disorder (ASD) (Kobayashi et al. 2016) and increased externalizing behaviors in children prenatally exposed to SSRIs (Oberlander et al. 2007). On the contrary, some studies do not show association between SSRI in pregnancy and increased risk of ASD in the offspring (Viktorin et al. 2017). Instead, the results suggest that the association is explained by factors related to the underlying susceptibility to psychiatric disorders (Viktorin et al. 2017). One of the possible explanations for the differences in the results of the studies may lie in genetic and epigenetic differences among the populations. SSRI may have epigenetic effects, and epigenetic changes are known to be associated with ASD (Ergaz et al. 2016).

Epigenetic changes

Serotonin is involved in the function of the hypothalamic–pituitary–adrenal axis, directly and indirectly, via modulation of glucocorticosteroids. SSRIs may induce epigenetic changes in the hypothalamic–pituitary–adrenal axis, as demonstrated in several human studies (Ornoy & Koren 2019). These systems in utero as well as postnatally play an important role in stress response and may also be involved in the pathogenesis of depression and other psychiatric illnesses (Ornoy & Koren 2019).

Pharmacokinetic and pharmacodynamic changes

The SSRIs are metabolized in the liver by CYP450 enzymes. CYP2D6 metabolizes paroxetine and fluoxetine, while CYP2C19 metabolizes citalopram and escitalopram. Polymorphisms in these enzymes change the metabolic clearance and serum levels of these drugs. Higher metabolism of most SSRIs in late pregnancy results in lower maternal levels, which could result in decreased efficacy (Koren & Ornoy 2018). In this case there is a necessity for higher SSRI doses, especially during the third trimester of pregnancy and readjustment after delivery (Ornoy & Koren 2019). Presently, there are no clear clinical implications of SSRI pharmacogenetic status in pregnancy and lactation. In late pregnancy, women may exhibit lower steady state concentrations of SSRIs, necessitating increased doses but these are presently guided clinically and not through genotyping.

Much more work is needed to define whether SSRI genotype has clinical implications and predictive value for either mother or offspring (Koren & Ornoy 2018).

Future research

Serotonin has an important role during embryonic and fetal brain development. The numerous studies demonstrate distinct neurobehavioral, epigenetic and other effects of SSRI in rodents (Ornoy & Koren 2019). There is, therefore, a need for additional and appropriate human studies to shed a light on this issue (Ornoy & Koren 2019). Research shows importance of observation of the movement and behaviour of the fetus prenatally (Kurjak et al. 2019).

We hope that in the near future personalized medicine would offer better individualised treatment options (Jakovljevic & Borovecki 2018). Indeed, epigenetic profiling before treatment could be used in the near future to increase the likelihood of good treatment response by selecting the appropriate medication (Jakovljevic & Borovecki 2018). Treatment outcome may be seen as a result of complex epigenetic interplay involved in treatment, resilience and comorbidity (Jakovljevic & Borovecki 2018).

CONCLUSION

Healthcare providers should give a close attention to depression and anxiety in pregnant women and provide appropriate mental health support in order to improve outcomes for both mothers and infants (Ding et al. 2014). Early intervention and treatment of perinatal depression can prevent the appearance of postpartum depression. In everyday clinical practice instruments should be introduced for the early identification of pregnant women with a higher risk for depression development (Mikšić et al. 2018). Depression negatively affects maternal functioning and has detrimental, long-lasting effects on the child's behaviour and physical health (Green et al. 2015, Daglar & Nur 2018). Indeed, one of the strongest predictors of mental illness and behavioral disorders in adult life is early-life stress (Eiland & Romeo 2013, Mikšić et al. 2018). Maternal mental health is important and needs cooperation of many health and social professionals. It is essential to address depression in this period individually and decide whether the patient needs antidepressant medication. SSRIs are effective treatment of depression and anxiety in pregnancy, however it is also important to acknowledge their possible side effects.

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