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MINIREVIEW

Risks of using SSRI / SNRI antidepressants during pregnancy and lactation

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ABSTRACT

At present, affective disorders are among the most commonly diagnosed mental diseases. In pregnancy, they can occur as pre-delivery depression, recurrent depressive disorder or postnatal depression. The estimated prevalence of depressive disorders in pregnancy is approximately 9–16%, with some statistics reporting up to 20%. Approximately 2–3% of pregnant women take antidepressants during pregnancy, and the number of mothers treated increases by birth to 5–7%. Treatment of depression during pregnancy and breastfeeding is a controversial issue, as antidepressants can negatively affect the developing fetus. According to epidemiological studies, the effects of treated depression in pregnancy are related to premature birth, decreased body weight of the child, intrauterine growth retardation, neonatal adaptive syndrome, and persistent pulmonary hypertension. However, untreated depression can adversely affect maternal health and increase the risk of preeclampsia and eclampsia, as well as of subsequent postnatal depression, which can lead to disruption of the mother-child relationship. Based on the above mentioned facts, the basic question arises as to whether or not to treat depression during pregnancy and lactation.

KEY WORDS: depression; antidepressants; pregnancy; lactation; fetus; brain; behavioral disorders

Introduction

The most commonly used antidepressants during pregnancy are serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), such as venlafaxine. The mechanism of action of these drugs is mainly associated with the inhibition of reuptake of monoamines and an increase of their extraneural concentration in the brain (da-Silva *et al.*, 1999; Oyebode *et al.*, 2012). Catecholamines and serotonin play an important role in adult brain processes such as learning, memory, mood control, anxiety, fear, social and reproductive behavior, as well as in higher mental functions. However, before these monoamines act as traditional neurotransmitters, they play a significant organizational role in the prenatal and perinatal period. They manage and regulate processes of neuronal proliferation, migration, differentiation and synaptogenesis, cerebral cortex maturation and development of the neuroendocrine system (Herlenius & Lagercrantz, 2004). As the antidepressants cross the placental and blood-brain barrier and pass into breast milk, they may increase the level of mediators in the developing fetus and can adversely affect the functional development of the brain. They thus represent a risk for neurobehavioral, emotional, cognitive and mental disorders, which can be manifested in the further development of the child. Despite the risk of functional brain damage, experimental studies are not available to address the potential adverse effects of SSRIs and SNRIs in the prenatal and early postnatal period.

Depression is one of the most common complications during pregnancy. Psychiatric disorders in pregnancy are mainly associated with pre-delivery depression, recurrent depressive states, as well as postpartum depression. The prevalence of antenatal depression (AD) and postpartum depression (PPD) is around 20% (Leung & Kaplan, 2009; Rayen *et al.*, 2013). The incidence of depression may be higher due to the reluctance of many mothers to admit their depressive states.

The etiology of AD and PPD is multifactorial. However, environmental factors are significant. The most important factors that are associated with AD include maternal anxiety, excessive stress during pregnancy (family death, divorce, etc.), the mother's young age, low social support, lack of family support, low family income, domestic, psychological and sexual violence, and a negative attitude

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towards pregnancy (Gausia *et al.*, 2009; Karmaliani *et al.*, 2009; Hartley *et al.*, 2011; Mohammad, Gamble, & Creedy, 2011). An increased risk of depression during pregnancy occurs in women who have suffered some form of affective disorder in the past. Epidemiological studies and meta-analyses show that similar psychological and psychosocial reasons also stand in the background of PPD (Dennis, 2005). It is known that women suffering from PPD experience difficulties during pregnancy (McDonald *et al.*, 2012). However, in the life of a woman, the postpartum period is considered the riskiest period for the development of depression. Significant hormonal changes are taking place during this period, which can play an important role in the development of depressive symptoms (Drevets & Todd, 2005).

Untreated depression

The question of treating depression during pregnancy has been a long-term relevant topic. Both the public and doctors have been skeptical of antidepressant therapy during pregnancy. Since the drugs pass through the placental barrier, the blood-brain barrier and they also pass into the breast milk, they thus increase the level of monoamines in the developing fetus and can affect the functional maturation of the brain. Since there has not been a sufficient number of well-controlled studies to assess the safety of antidepressants, the scientific community is mostly inclined not to treat depression during pregnancy by drugs.

However, the current experience of doctors as well as experts shows that untreated depression can adversely affect the health of both mother and child. Complications are mainly associated with increased morbidity in pregnant women, including preeclampsia and eclampsia, suicidal tendencies of mothers, later PPD depressions and mother-child relation disabilities. In children, particularly reduced birth weight, increased risk of preterm labor, and increased irritability of the newborn have been observed. The most frequent physiological manifestations of affected children are reduced vaginal tonus, increased levels of cortisol and noradrenaline and lower levels of dopamine and serotonin (Talge *et al.*, 2007; Hollins, 2007; Gentile, 2011; Gerardin *et al.*, 2011; Witt *et al.*, 2014). This syndrome is related, for example, to an excessive cortisol response of the child, the so-called *„fetal programming hypothesis"* (de Bruijn *et al.*, 2009) that affects the adrenocortical and cardiovascular response of a child to acute stress (Gump *et al.*, 2009). In addition, intrauterine fetal exposure to emotional stress, such as pre-delivery depression, may affect the child's cognitive, emotional and behavioral status (Talge *et al.*, 2007; Kinsella & Monk, 2009; Oberlander, 2012). The consequences of untreated depression can be so serious that they overweigh the potential risk caused by the use of antidepressants during pregnancy (Oyebode *et al.*, 2012).

There are currently several screening methods (e.g. Edinburgh Depression Scale (EDS)) that are used to identify the extent of depression during pregnancy. Patients thus diagnosed should be monitored for at least one year after birth. In patients with mild to moderate disease, psychotherapy is recommended, whereas antidepressant therapy is recommended in patients who suffer from severe depression.

Treated depression during pregnancy

Treatment of depression during pregnancy raises a number of questions concerning the safety of psychiatric drugs. These can ultimately affect the health of the pregnant mother, pregnancy, fetal and neonatal development, as well as the overall health of the individual. The effects of treated depression are known from the available literature. These are mainly associated with spontaneous abortions, preterm births, decreased child's body weight and intrauterine growth retardation,as well as increased birth deaths (Grote *et al.*, 2010; Oyebode *et al.*, 2012). For newborns who have been exposed to antidepressants during the prenatal period, excessive crying, restlessness, tremor, feeding problems, reflux and sleep disorders have been reported to be characteristic (Sanz *et al.*, 2005; Thormahlen, 2006; Oberlander *et al.*, 2008; Galbally *et al.*, 2009). Persistent lung hypertension in the neonatal period may be a potentially unfavorable effect of fetal exposure to antidepressants in the third trimester (Källén & Olausson, 2008; Reis & Källén, 2010). The risk of serious malformations in children affected by antidepressants during pregnancy, including the third trimester, was not elevated (Addis & Koren, 2000; Gentile, 2005; Einarson *et al.*, 2009). However, an association between the treatment with paroxetine during pregnancy and congenital heart disorders was reported (Oyebode *et al.*, 2012).

The most recent meta-analyses and reviews suggest that the risks of antidepressant intake during pregnancy for fetal/congenital malformations are small or non-existent, and the risk for poor maternal and fetal outcomes are small to medium. Importantly, untreated maternal depression carries its own risks for both mothers and unborn babies, often showing very similar detrimental outcome profiles. For both conditions, some effects on the offspring can last into childhood and adolescence (Muzik & Hamilton, 2016).

Clinical studies of adverse effects of antidepressants during pregnancy and lactation

It is known from clinical practice that pregnant mothers exposed to antidepressants have more spontaneous abortions and an increased number of stillbirths. Treatment in the third trimester of pregnancy is closely linked to an increased incidence of Poor Neonatal Adaptation (PNA). PNA is characterized by a decrease in the Apgar score (normal range 7–10, relatively low 4–6 and critically low is less than 3), hypoglycemia, weak muscle tone, respiratory

difficulties, and total restlessness (Oyebode *et al.*, 2012). Other clinical signs and symptoms include cyanosis, apnea, spasms, temperature instability, feeding difficulties, vomiting, hypertonia/hypotonia, hyperreflexia, tremor, nervousness, irritability and crying (Sanz *et al.*, 2005; Thormahlen, 2006; Galbally *et al.*, 2009). Thus, newborns exposed to SNRIs or SSRIs at the end of the third trimester require longer hospitalization, tube feeding and breathing support. The signs and symptoms may indicate either a direct toxic effect of SSRIs and SNRIs, or may be classified as withdrawal symptoms. It should be noted that in some cases the clinical picture is consistent with the serotonin syndrome.

Children exposed to prenatal venlafaxine in the postnatal period had a slightly reduced IQ compared to children whose mothers did not suffer depression during pregnancy. In children of affected mothers, higher incidence of problematic behavior was also observed (Nulman *et al.*, 2002). Similarly, children who were perinatally exposed to SSRIs (especially fluoxetine) had decreased birth weight, neurobehavioral disorders and decreased heart rate (Rayen *et al.*, 2011). The complexity of these issues is highlighted, as depression itself can adversely affect the development of the child. It is therefore difficult to divide the effect of depression itself and subsequent treatment. For example, newborns whose mothers suffered from depression during pregnancy are characterized by increased irritability, reduced activity and attention, as well as lacking mimic expressions compared to neonates of healthy mothers. Some studies also noted elevated cortisol levels in depressed mothers as well as decreased peripheral serotonin and dopamine levels, decreased vagal tonus, and electroencephalogram changes (Yonkers *et al.*, 2009).

Experimental studies

Experimental work on rats and rabbits did not detect malformations or morphological changes in pups after administration of SSRIs and SNRIs to pregnant females. In contrast, *in vitro* developmental toxicity studies with fluoxetine and sertraline, as well as other serotonin reuptake inhibitors showed disruption in craniofacial morphogenesis of mouse embryos (Shuey, Sadler, & Lauder, 1992). Findings from in *vivo* studies did not confirm these conclusions. These works did not evaluate possible functional or behavioral disorders of pups.

Rayen *et al.* (2013) found that prenatally administered fluoxetine reduced the anogenital distance of juvenile male rats and reduced the amount of copulation. There is a longer latency to the first copulation and a longer latency in ejaculation in adult subjects. It is believed that elevated serotonin levels due to perinatal administration of SSRIs (fluoxetine) could affect male sexual behavior. Serotonin is a key neurotransmitter responsible for the correct development of sexual centers in the brain. Other studies found that females who were perinatally affected by fluoxetine had facilitated sexual behavior, compared with adult females who underwent antidepressant treatment during adulthood exhibiting reduced sexual behavior. According to the authors, this could point to the activation and organizational effects of fluoxetine. The authors assume the involvement of certain compensatory mechanisms in developmental processes, which may be permanent and are directed to decreasing serotonin levels during adulthood (Rayen *et al.*, 2013).

The most recent preclinical studies show that the use of SSRIs and SNRIs during pregnancy could also be related to altered neural plasticity of individuals exhibited by altered BDNF levels (Basterzi *et al.*, 2008). *In vitro* studies have shown that chronic use of antidepressants induces up-regulation of serum BDNF levels in the rat brain (Popoli, Gennarelli, & Racagni, 2002; Pittenger & Duman, 2008). Elevated BDNF levels were also observed in *post-mortem* hippocampi of patients treated with antidepressants(Chen *et al.*, 2001). Larsen *et al.* (2008) found that venlafaxine and imipramine, but not fluoxetine, produced neuroplastic changes in the hippocampus by stimulating mRNA expression for BDNF. The above-mentioned works indicate that besides BDNF levels, up-regulation of the cAMP-CREB cascade could occur. Control of the cAMP-CREB cascade involves increased expression of cAMP-dependent protein kinase and CREB (Pittenger & Duman, 2008). Thorne *et al.* (2000) reported that antidepressant therapy enhanced the phosphorylation of CREB and CRE-mediated gene expression in limbic regions of the brain. Increased expression of BDNF and CREB raises the question of whether antidepressant therapy could prevent cell death through increased production of Bcl-2 (Duman *et al.*, 2000). Increased BDNF levels as well as improved neurogenesis and synaptic plasticity due to antidepressant treatment could provide some explanation for delayed antidepressant activity (Harmer & Cowen, 2013).

Likewise, the S100β protein is a potential biomarker of altered neural maturation and plasticity due to the administration of SSRIs and SNRIs (Pawluski *et al.*, 2009). S100β is a calcium-binding peptide that is released by astroglial cells in response to 5-HT1A receptor activation, thereby mediating neuronal growth and survival (Whitaker-Azmitia, 1991). *In vivo* and *in vitro* experiments confirmed the role of S100β in nerve cell energetic metabolism, cell cytoskeletal regulation, and regulation of proliferation and differentiation of neurons and glial cells (Rothermundt *et al.*, 2003). S100β may act trophically or toxically depending on its concentration. At nanomolar concentrations, S100β stimulates neuronal growth and increases survival during prenatal development of the individual (Pawluski *et al.*, 2009). In micromolar concentrations it stimulates expression of proinflammatory cytokines and induces cell apoptosis. Many studies have shown that S100β regulates the stability of the cytoskeleton through interactions with primary microtubule components such as tubulin (Hesketh & Baudier, 1986) or inhibition of protein kinase phosphorylation of target cytoskeleton proteins such as tau and GAP-43 (Sheu *et al.*, 1994). High levels of S100β in immature brain tissue led to a faster development of dendrites, which resulted in increased concentration of

MAP-2 protein on day 35 of PP in mice. However, by aging the high concentration led to a decrease in MAP-2 levels resulting in a subsequent collapse of the cytoskeletal system and cell death. S100β levels in cerebrospinal fluid, urine and serum are indicative of brain damage and in perinatal medicine can serve as biomarkers to determine brain maturity and the risk for prenatal drug exposure. Elevated S100β levels were found in preterm infants and children with Down syndrome (Gazzolo *et al.*, 2000). Reduced levels of S100β were described in animal models after prenatal exposure to glucocorticoids (Bruschettini *et al.*, 2005), cocaine (Clarke *et al.*, 1996) or prenatal stress (Van den Bergh *et al.*, 2005). Prenatal exposure to glucocorticoids and related S100β deficiency are associated with altered central serotonin levels, which supports the view that increased extracellular serotonin levels in the developing brain may delay/slow down the growth of serotonin neurons by self-regulation. Delay in serotonergic neuronal growth may delay maturation of astroglial cells, leading to slowing neuronal maturation that may be associated with functional learning and memory deficits (Pawluski *et al.*, 2009).

In the case of venlafaxine (VENL), no morphological changes were observed in pups or changes in selected biochemical markers (Dubovický *et al.*, 2012). Prenatally administered VENL did not result in significant changes in the length of pregnancy of rats, in litter size, in the number of stillborn pups, or duration of lactation between the affected and control groups (da-Silva *et al.*, 1999). VENL, however, at high doses (70 mg/kg), caused mild maternal intoxication, which was manifested by the reduced body weight of pregnant females (de Oliveira *et al.*, 2004; Dubovický *et al.*, 2012). It is also known from the literature that administration of VENL caused increased locomotor activity in rats. Increased behavior (climbing, swimming) may in this case reflect increased serotonin and dopamine levels. Increased levels of dopamine due to VENL administration were described also in the striatal region of the brain (de Oliveira *et al.*, 2004).

Although SSRIs and SNRIs have been clinically used for decades, the molecular and cellular bases of their action are not fully elucidated. Current studies focus on BDNF assessment, which is an indicator of nerve plasticity and neurogenesis. Animal models of depression are associated with decreases in BDNF levels as well as reduced neurogenesis. In the case of chronic treatment with SSRIs, these effects have been reversed. However, latent changes that occurred in adulthood or in old age have not been studied.

Conclusion

Epidemiological and experimental studies point to the risks of both untreated and treated depression. Untreated depression presents a risk for the mother, the developing fetus and the newborn. Untreated depression increases the risk of intrauterine growth retardation, low birth weight, and maternal-child relation disturbances. Treating depression during pregnancy and breastfeeding also represents a risk for the developing fetus and neonate. SSRI/SNRI antidepressants cross the placenta, the blood-brain barrier and pass into the milk and they increase the levels of monoamines in the brain. These can then affect the functional development of the brain and the behavior of the child. The potential of antidepressant drugs to cause functional neuroteratogenicity and the development of neurobehavioral dysfunctions has not been adequately investigated. With the increasing incidence of mental illness in human populations, experts should address this issue at different levels, including experiments on appropriate animal models.

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