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SSRI use in pregnancy: Evaluating the risks and benefits

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Selective serotonin reuptake inhibitor (SSRI) antidepressants are considered the primary pharmacological treatment for moderate to severe depression during pregnancy. Data regarding the safety of their use during pregnancy remain controversial and conflicting. Decisions regarding the prescription of antidepressant treatment are often fraught with concern around potential harmful medication effects on the pregnancy, fetus and infant. Information on potential risks remains extremely varied and inconsistent across sources. This lack of clarity regarding drug safety brings significant uncertainty not only for treating physicians, but also for women seeking information about depression during pregnancy. This review aims to summarise and evaluate the current evidence base and to aid clinicians in performing a risk/benefit analysis for SSRI use during pregnancy and lactation.

S Afr J Psychiatr 2015;22(2):48-53. DOI:10.7196/SAJP.587

Perinatal depression is common, with a prevalence of 10 - 15% in economically developed countries. These prevalence rates are even higher in low- and middle-income countries.[1] In South Africa (SA), the prevalence of perinatal depression has been estimated to be as high as 39% in peri-urban areas[2] and 49% in rural areas.[3] It is not surprising that the World Health Organization has identified maternal mental health as an integral component of its global maternal health improvement plan.[4]

Maternal mental health within the perinatal context presents unique challenges for the detection and management of depressive disorders, especially in resource-poor countries. Diagnosis is often obscured by the fact that the core symptoms of depression such as fatigue, poor sleep, weight change and concentration difficulties are also effects of pregnancy and often go unnoticed. Cognitive behavioural therapy and interpersonal therapy are both well-established treatment modalities for mild to moderate perinatal depression.[5] In developing countries, barriers to psychotherapeutic interventions as optimal treatment choice include the limited availability of trained therapists, time constraints, child care issues, costs and the sensitivity of the therapist to cultural and sociodemographic factors.[6]

Selective serotonin reuptake inhibitor (SSRI) antidepressants are considered the primary treatment for moderate to severe depression during pregnancy. Although providing antidepressant treatment would seem to be an obvious clinical option, extant data regarding the safety of its use during pregnancy remains controversial and conflicting. Decisions regarding the prescription of antidepressant treatment are often fraught with concern about potential harmful medication effects on the pregnancy, fetus and infant. Potential exposure risks associated with antidepressant drugs during pregnancy include the risk of teratogenicity, neonatal toxicity and the risk of long-term neurobehavioural sequelae. A possible reason for the dissonance between the evidence supporting and the practice of prescribing SSRI antidepressants may relate to these concerns.

Information on potential risks remains extremely varied and inconsistent across sources.[7-10] This lack of clarity regarding drug safety creates significant uncertainty not only for treating physicians, but also for women seeking information about depression during pregnancy. It can be challenging to encourage adherence in the best of circumstances, even more so when suggesting medication to a pregnant woman who has been labelled a 'dangerous' patient.

When pharmacological treatment with SSRIs is indicated during pregnancy, the possible negative effects of untreated psychiatric symptoms on mother, child and family need to be carefully weighed against the possible adverse effects of medication use.

This review aims to summarise and evaluate the current evidence base and to aid clinicians in performing a risk/benefit analysis for SSRI use during pregnancy and lactation.

The impact of perinatal depression

Undetected and untreated depression can lead to detrimental effects for both mother and baby. These risks may be conceptualised as maternal, gestational, neurodevelopmental and behavioural effects.

Maternal health

Common negative effects of maternal depression include decreased support from the family and social support network, poor antenatal care attendance, decreased ability for self-care and poor nutrition and weight

gain.[8] Studies have shown that the interruption of antidepressant treatment during pregnancy results in relapse of symptoms in as many as 60 - 70% of women.[11] Depression during pregnancy is one of the strongest predictors of postpartum depression, which, in turn, has deleterious and long-lasting effects on infant and child wellbeing, as well as on the mother's mental health.[12] The prevention of postpartum depression is important, as these women are more likely to have recurrent depressive episodes which can become chronic, leading to substantial impairments in the mother's ability to care for her child.

Suicidal tendencies associated with depression are a leading contributor to maternal mortality globally. Suicidal thoughts and actual self-harm occur in up to 20% of mothers in low- and middle-income countries, in comparison with 5 - 14% of mothers in high-income countries.[4] Several contributing factors to suicide, such as young maternal age, intimate partner violence and high prevalence of perinatal depression, are constant reminders of why this is a serious challenge in the developing world. Although successful suicide following childbirth is rare (estimated at a rate of 0.3 per 1 000 for women referred to psychiatric services following childbirth), it is nonetheless a devastating event for the child and family involved and highlights the importance of effective treatment of intrapartum depressive episodes.[13]

In SA, 60% of all first pregnancies are unplanned.[14] The first challenge is thus the early identification of pregnant women with psychiatric illness, as they are less likely to seek prenatal care than healthy pregnant women.[15] They are also more likely to engage in high-risk behaviour such as substance abuse that can be harmful to themselves and their unborn babies, e.g. pregnant women who abuse substances have higher rates of infectious diseases such as HIV.[16]

Gestational effects

Research has suggested that maternal depression and/or anxiety during pregnancy is an independent risk factor for operative delivery,[17] preterm birth, and low birth weight.[18] Preterm delivery and low birth weight are the leading causes of infant mortality in both developed and developing countries.[19] Associations have also been described with serious gestational complications such as antepartum bleeding, pregnancy-induced hypertension, pre-eclampsia and decreased uterine artery blood flow.[20]

Indirect exposures associated with maternal depression, such as poor nutrition, poor compliance with pre- and postnatal care, increased use of over-the-counter remedies and substance abuse, increase the risk of poor obstetrical and fetal outcomes.[21] *In utero* exposure to alcohol has serious consequences for the developing fetus, leading to a range of conditions collectively known as fetal alcohol spectrum disorders (FASD).[22] Alcohol exposure affects the development of the brain during critical periods of differentiation and growth, leading to long-term cognitive and behavioural deficits. SA has the highest documented rate of FASD and fetal alcohol syndrome. A recent population-based study estimated the prevalence of FASD in a high-risk area of the Western Cape at between 135.1 and 207.5/1 000.[23]

Neurodevelopmental and behavioural effects

Increasingly psychopathologies are conceptualised as the late-stage culmination of aberrant developmental processes shaped by a complex interplay of genes and experience, including *in utero* experiences. Pregnant women with depression and/or anxiety experience greater life stress, and illness-related alterations in their neurobiology, with a potential to impact fetal neurobehavioural development via associated changes in the intrauterine environment.[24-26] Infants of depressed mothers display a number of negative behaviours such as more irritability, less crying, less attentiveness and fewer facial expressions than infants of healthy mothers.[26]

Children of mothers with depression are at an increased risk of disruptive and oppositional behaviour.[27] Long-term follow-up studies have also shown that offspring of depressed mothers are at a higher risk for neuropsychiatric disorders, social impairment and increased risk of mortality from medical causes.[28] The STAR*D Child study was able to demonstrate that a remission of maternal depressive symptomatology, irrespective of its timing, was related to decreased problematic symptoms and behaviour in their offspring.[29]

In summary, evidence suggests that untreated perinatal depression is not only associated with significant adverse risks for the mother, but also exerts a transgenerational effect on the unborn baby. The healthcare provider is thus advised to view maternal depression as a priority. Clinicians should familiarise themselves with the different treatment modalities available to treat depression in pregnant women in a safe and appropriate manner.

Selective SSRIs: navigating the evidence base

SSRIs are one of the best-studied classes of medication used in pregnancy in terms of their potential risk to the newborn. Prior to 2005, the majority of studies supported the view that SSRIs were relatively safe for use in pregnancy, with no increase in the prevalence of major congenital malformations found.[30-32] Evidence that has since linked SSRI use during pregnancy with adverse birth and neonatal outcomes had largely been derived from retrospective cohort epidemiological studies and case reports.[33-35] However, correlation does not equate with causation. The study methodology is often flawed, failing to take into account a number of intrinsic confounding variables such as the dose, timing of exposure, and use of other medications or the severity of depression. SSRIs are prescribed for a number of disorders, making the exposed population heterogeneous and thus more difficult to standardise for study. Ultimately, pregnancy does not preclude illness or disease, and due consideration needs be given to differentiating between other contributing events, independent of drug effects, such as concurrent substance abuse, domestic violence, quality of antenatal care, nutrition, and comorbid medical disease.

Impact of SSRI use during pregnancy

Several poor outcomes have been associated with maternal use of antidepressant treatment during pregnancy, including: gestational adversities, congenital anomalies, neonatal adaptation syndrome and neonatal persistent pulmonary hypertension. In recent years, concern has also arisen regarding the potential long-term effect of SSRI exposure *in utero* on neurodevelopmental outcomes.

Obstetrical complications

Some, but not all, studies suggest that the use of SSRIs during pregnancy increases the risk of poor obstetrical outcomes such as: preterm delivery, intrauterine growth restriction and the risk of spontaneous miscarriages.[35] In a recent meta-analysis by Huang et

al.[7] antidepressant use in pregnancy was significantly associated with low birth weight (relative risk (RR): 1.44, 95% confidence interval (CI): 1.21 - 1.70) and preterm delivery (RR: 1.69, 95% CI: 1.52 - 1.88). The studies included varied widely in design, populations, control groups and methodology, with a high level of heterogeneity as measured by I2 statistics for both outcomes examined. In a Danish population-based study, antidepressant exposure was associated with an adjusted risk ratio (aRR) of 1.14 (95% CI: 1.10 - 1.18) for spontaneous abortion compared with no exposure to antidepressants. Among women with a diagnosis of depression, the aRR for spontaneous abortion after any antidepressant exposure was 1.00 (95% CI: 0.80 - 1.24). Thus antidepressant use in general, as well as individual SSRI agent exposure, was not associated with spontaneous abortions.[36]

There have also been negative studies in this regard. Oberlander *et al.*[37] found that both the duration of gestation and the risk of preterm delivery did not differ significantly between depressed women who had used SSRIs during pregnancy and those who had not.

While some studies have shown an association between the use of SSRIs during pregnancy and risk of preterm delivery, and spontaneous miscarriage, the reviewed studies are scarce and methodologically inadequate to draw definitive conclusions about the hypothesised risk associated with exposure during early pregnancy.

Congenital anomalies

Congenital malformations may occur in the general population independent of any drug exposure. The majority of early studies were in consensus that SSRIs are unlikely to increase the 1 - 3% congenital abnormalities found in the general population,[38] despite the suggestion that SSRIs could putatively increase the incidence of congenital malformations as serotonin is important in aspects of early embryonic development that impact neural tube, brachial arch and heart development.[39] Although most studies have not shown an increase in the overall risk of major malformations,[40] some studies have suggested that specific SSRIs (fluoxetine (odds ratio (OR) 1.14, 95% CI: 1.01 - 1.30) and paroxetine (OR 1.29, 95% CI: 1.11 - 1.49) are associated with an increased risk of major malformations.[41] Overall these associations have been conflicting or not replicated in other studies[42] and are contrary to the expectation that a teratogen would cause similar types of malformation across all studies.[39]

Paroxetine's use during pregnancy has elicited the most concern. During 2005, a report by the drug manufacturer of paroxetine noted a 1.5-fold risk of cardiac defects (primarily atrial and ventricular septal defects) in children exposed *in utero* to paroxetine v. a control group. This prompted the US Food and Drug Administration (FDA) to change the pregnancy category of paroxetine from C to D and issue an advisory for clinicians to consider discontinuation of this medication, or to reduce the dose to decrease incidence. The data contained in this report had not however been published in a peer-reviewed journal; instead they had been derived from a Swedish registry and a US insurance-claims database, both sources with inherent bias and methodological limitation.[43] Since then, only 1 of 5 meta-analyses investigating the risk for malformations associated with antidepressant use has found an increased risk of congenital malformation in infants exposed to paroxetine.[9] A recent, large Danish population-based study has provided evidence that may resolve this debate. Unlike previous studies, the authors were able to identify and include a group of depressed women who had avoided taking their SSRIs during pregnancy in their analysis. From 848 786 pregnancies identified, 4 183 women were exposed to an SSRI during their pregnancy, and 806 ceased treatment. The risks of congenital malformations were similar for the SSRI-exposed group (adjusted OR: 2.01; 95% CI: 1.60 - 2.53), as well as for the pregnancies where SSRI treatment was interrupted (adjusted OR 1.85; 95% CI: 1.07 - 3.20) (p=0.94). Additionally the risks were similar for the individual SSRIs, and no dose-response association was observed.[44] The authors concluded that previously ascribed associations between maternal SSRI use and cardiac malformations are likely to be due to ascertainment bias. Depressed women (treated or untreated) are more likely to have special investigations such as ultrasound and echocardiograms performed; therefore there is a higher likelihood of detection of cardiac malformations.[39]

At present it is not possible to draw definite conclusions regarding the teratogenicity of the different SSRIs as the available studies contain several methodological limitations. Evidence that SSRI exposure increases the risk of congenital anomalies is conflicting, but reassuring overall. Observed risks have been of very low magnitude and clinical significance remains unknown.[39,45] If there is indeed an increased risk, the question of biological plausibility remains.

Perinatal neonatal adaptation syndrome

A cluster of symptoms termed the perinatal neonatal adaptation syndrome (PNAS) has been found in up to 30% of neonates exposed to SSRIs late in pregnancy.[46] Other terms that have been used to describe this presentation include: neonatal behavioural syndrome, postnatal adaptative syndrome and neonatal abstinence syndrome.[47] This syndrome generally presents with fairly nonspecific symptoms such as crying, irritability, jitteriness, tremor, feeding problems, respiratory disturbances, muscular tone changes, impaired thermoregulation and, rarely, seizures. The symptoms are usually mild, transient and self-limiting, without a need for specific treatment.

The impact of timing, as well as dose and duration of SSRI exposure is still uncertain. Initially it was suggested that late (third trimester) exposure to SSRIs carried a higher risk for the development of PNAS because SSRI withdrawal or intoxication were thought to be the possible underlying mechanism of PNAS. To reduce the risk of PNAS, or to possibly ameliorate neonatal symptoms, some researchers have suggested ceasing SSRI use near term. This can have deleterious consequences, including relapse, exacerbation of symptoms, suicidal ideation, especially in the vulnerable postpartum period.[48] PNAS has most often been reported after exposure to paroxetine, fluoxetine and venlafaxine.[49-51] Using population-based data linking maternal mental health and medication and neonatal health outcome, greater length of gestational exposure rather than timing of exposure was associated with significantly increased risk of adverse outcomes after controlling for maternal characterisitics.[51]

Ultimately, the mechanisms underlying this syndrome have not yet been fully elucidated. The pathogenesis is likely to be multifactorial, which would account for the variability of symptoms. Evidence suggests that genetic factors, such as maternal and infant hepatic cytochrome P450 isoenzyme genotypes are potentially involved.[47] Other potential contributing factors include the severity of maternal mental illness, prematurity, type of feeding and exposure to other

medication or illicit substance use.[47] General supportive measures, such as the provision of a quiet environment, frequent small feedings on demand, swaddling and increased skin-to-skin contact with the mother, are considered sufficient management.[49] Discontinuation, lowering the dose or switching to another type of antidepressant is not currently recommended.

Persistent pulmonary hypertension

Persistent pulmonary hypertension of the newborn (PPHN) is a rare disorder occurring in approximately 1 - 2 per 1 000 births.[52] PPHN is a failure of the pulmonary vascular structures to reduce resistance at birth. This can lead to poor oxygenation, central cyanosis and ultimately respiratory failure. There are several established perinatal risk factors for the development of PPHN including maternal overweight, smoking, diabetes, or use of non-steroidal anti-inflammatory drugs during pregnancy.[52] More recently, the mode of delivery, specifically caesarean delivery, was added to the list of risk factors.[53]

Studies on the association between SSRIs and PPHN have yielded largely differing and conflicting results. While some studies have suggested an increased risk with later gestational exposure,[37,54] others have not.[52] As mentioned, several factors are associated with the development of PPHN. In a large Nordic population cohort study of 1 618 255 infants, the authors suggest that maternal use of SSRIs in late pregnancy increased the risk of persistent pulmonary hypotension (PPH) more than two-fold (OR 2.1; 95% CI: 1.5 - 3).[55] However, several other causative explanations such as the severity of depression, smoking, mode of delivery and maternal weight had not been addressed adequately. Additionally, solely using drug registry data carries the risk of exposure misclassification, given that it is not clear whether women who were issued prescriptions later in pregnancy took them as prescribed. Overall the observed associations with SSRI use have been of very low magnitude (absolute risk of PPHN <1%) and the clinical significance of study results remains unknown.[39] No study to date has described a neonatal death from PPHN associated with SSRI exposure.

Despite this uncertainty of association between SSRIs and PPHN, both the obstetrician and the paediatrician need to be informed of maternal use of SSRIs to assure adequate monitoring of the newborn.

Neurodevelopmental and behavioural outcomes

There have been few neurodevelopmental studies to date. Although the majority of studies have not demonstrated neurodevelopmental sequelae in children prenatally exposed to SSRIs, there are some studies that showed slight developmental delay, mainly in their motor function.[33,56] Small studies have shown that SSRI exposure in the third trimester may have subtle effects on motor development and motor control.[57] Nonetheless, it remains unclear whether findings that have been detected represent transient observations or are indicative of subsequent neurobehavioural problems that may be detected at a later age.

Beyond childhood, animal studies have shown that neonatal SSRI exposure during a developmentally sensitive stage of central nervous system development can suppress adult serotonergic signalling and elicits depressive- and anxiety-like behaviours in adulthood.[58] Human studies have also suggested that the use of SSRIs by pregnant women is associated with an elevated risk of developing autism spectrum disorder in their children.[59-61] In a recent large Danish birth registry analysis, Hviid *et al.*[61] did not demonstrate a significant association between maternal use of SSRIs during pregnancy and autism spectrum disorder in the offspring, as compared with other children (aRR 1.20, 95% CI: 0.90 - 1.61). However, in subsequent analysis, a significant association was observed between maternal SSRI use prior to conception and autism spectrum disorder. (aRR 1.46, 95% CI: 1.17 - 1.81). The authors concluded that the effects of the maternal disorder or other unmeasured factors related to the maternal disorder (e.g. other medication use, smoking, parity) increased the risk of autism spectrum disorders, rather than the use of SSRIs themselves.[61]

A prospective cohort study by Nulman *et al.*[62] found that factors such as the severity of maternal depression during pregnancy, rather than antidepressant exposure, were better predictors of the child's intellect and behaviour. Using measures such as the Conner's Parent Rating Scale and Child Behaviour Checklist, it was shown that children born of depressed mothers exhibited clinically more problematic behaviours and higher temperament scores than the children of non-depressed women. This confirms similar findings from earlier studies that the degree of maternal illness rather than drug exposure may predict a child's internalising and externalising behaviours.[63]

Existing data on the long-term neurodevelopmental and behavioural outcomes for children exposed prenatally to SSRI are sparse. A major challenge remains disentangling the effects of maternal depression from maternal use of SSRIs on later neurodevelopment in offspring. Available evidence does not suggest that these drugs adversely affect neurodevelopment. Further long-term studies in this area are however needed.

Lactation

The benefits of breastfeeding are well established. Breastmilk is the ideal source of nutrients for a baby, and studies show that breastfed infants have less risk of mortality and morbidity (i.e. gastrointestinal and respiratory infections, urinary infections, sepsis, meningitis, necrotising enterocolitis).[64]

Breastfeeding also provides health benefits for the mother, such as reduced risk of breast and ovarian cancer.[65,66] Furthermore, the intimate bodily contact between the mother-infant dyad during breastfeeding fosters bonding in early infancy.[67] These early life experiences, specifically in terms of mother-child interactions, have a profound impact on adult mental and physical health.[68]

Concerns about potential harm to the nursing infant are often cited as a reason to cease lactation. Alternatively the question arises of whether an effective antidepressant treatment given during pregnancy should be continued when the mother wants to breastfeed. Though no generalisations can be made regarding antidepressant drug use during lactation, there is a growing body of research that supports most agents as safe for use.

SSRIs are the antidepressant group for which the most data exist for use in lactation and their use appears to be quite safe. A number of factors determine the amount of SSRI present in breastmilk such as half-life, time of peak serum concentration, dissociation constant, volume of distribution, molecular size, degree of ionisation, pH of

plasma and milk and the solubility of the drug in water and lipids.[69] The SSRIs reach breastmilk in different concentrations with sertraline showing the lowest concentration, followed by paroxetine, fluvoxamine and then citalopram and fluoxetine. All SSRIs have relatively long half-lives and there is a risk of drug accumulation, especially in the neonatal period when drug clearance values are significantly reduced. If an SSRI is considered essential and the prescriber is selecting a drug for use in the postnatal period for a breastfeeding mother, fluoxetine is best avoided. Based on current available evidence, the long elimination half-life can cause the drug to accumulate in the newborn and increase the risk of side-effects.[49]

Postpartum use of SSRIs is not contraindicated during breast-feeding, and women who choose to breastfeed should be supported. The discontinuation of essential antidepressant treatment during the postpartum period should be avoided, as well as switching to another antidepressant. A practical recommendation is for the mother to consume medication immediately following breastfeeding as this will not only minimise the amount present in the breastmilk but also maximise the clearance prior to the next feed.[70]

Recommendations

An integrated, collaborative approach during the perinatal period presupposes thoughtful consideration of both the risks and benefits of treatment v. untreated disease. No medication is 100% safe during pregnancy and all pregnancies have risks. Unfortunately, there is no 'one-size-fits-all strategy'; the attainment of optimal mother-fetal wellbeing is more likely through individualised treatment planning.

Given the inconclusive evidence regarding the overall safety of SSRI use, it is pertinent that clinicians consider both the risk of exposure to untreated illness, as well as antidepressant use. The different treatment options should be carefully evaluated and, if possible, non-pharmacological treatment should be offered. Psychotherapy should be considered a first-line treatment for mild or moderate depression.

By screening and treating perinatal depression the treating clinician is also uniquely poised to detect additional factors which may put the mother and child at risk, such as intimate partner violence.[71] Non-pharmacological aspects of treatment should also include nutrition, weight management, prenatal care, childbirth education, and treatment for substance abuse.

Non-pharmacological interventions might not relieve moderate to severe depression or be available to all women. When SSRI-prescription is contemplated, several factors influence the choice of antidepressant, including prior response, gestation, intention to breastfeed and the safety profile based on the available evidence and experience. There is no single best SSRI for all pregnant women. Current recommendations include using the lowest effective dose, monotherapy to avoid compounding the risk of harm, and avoiding changes in treatment regimens. Clinicians may be tempted to underdose medications in the belief that this will lessen the exposure risk. This however exposes the fetus to not only the negative effects of undertreated maternal MDD but also continued exposure to the medication. Rational, collaborative treatment decisions, informed consent, and good documentation are important when treating these women if SSRIs are used throughout the pregnancy. Furthermore, the newborn may require additional observation for the first few days following delivery to monitor for potential withdrawal syndromes or pulmonary hypertension. Liaison with the paediatrician/neonatologist is strongly advised.

Conclusion

Antidepressant drugs have been the most studied drugs during pregnancy. Although many reviews have been published on pregnancy outcome after maternal use of antidepressants, interpretation of the various results is often difficult. Whether the risks identified relate to SSRI treatment or perinatal depression and its correlates remains inconclusive. Adequate treatment of depression in pregnant women is however important for maternal, fetal and neonatal wellbeing. Moderate to more severe depression often requires treatment with an antidepressant, typically an SSRI. There is a definite and urgent need for larger, well-designed epidemiological studies, especially comprehensive meta-analyses that are sufficiently powerful to detect differences in outcomes for infants exposed to SSRIs *in utero*. Management of maternal depression or anxiety is best evaluated and adjusted prior to conception to ensure proper treatment during pregnancy. Clinicians should familiarise themselves with the concerns regarding potential adverse outcomes, critically appraise published results and use any medications with the necessary caution.

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