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REVIEW ARTICLE

Gestational Exposure to Serotonin Reuptake Inhibitors and Pregnancy Outcome; Exploring the Role of Bias and Confounders

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Abstract: There is no other example in human teratology where, after more than 40 epidemiological studies, repeated meta-analyses and thousands of pregnancies, the fetal safety or risk of an agent has not been verified and settled.

The objectives of the present review were to identify and discuss sources of bias that may lead clinicians and scientists to believe that SRIs cause malformation or other adverse outcomes, where, in fact, they may not.

The present study highlights sources of bias that may explain why children exposed in utero to SRI exhibit higher rates of congenital malformations, mostly cardiovascular and other complications. It appears that pregnant women treated for depression and anxiety are distinctively different from healthy women in numerous covariates, which may confound pregnancy outcomes. Acknowledging and adjusting for these sources of bias are critical before one selects to withhold therapy for moderate or severe cases of depression and anxiety in pregnancy.

Keywords: Bias, congenital malformations, IUGR, serotonin reuptake inhibitors, pregnancy, prematurity.

1. INTRODUCTION

Serotonin (5 hydroxy tryptamine: 5-HT) is a monoamine neurotransmitter produced from tryptophan. Among the functions of serotonin are: regulation of mood and emotion, regulation of motor activity, memory processing and cognition as well as regulation of sleep and appetite. Serotonin has several roles in fetal neuronal maturation, migration, synaptogenesis and in the differentiation of neural crest cells in facial and cardiac development [1-4]. It also plays a role in epigenetic processes such as stress responsivity [3, 4].

Numerous published sources have declared that it is logical that medications affecting serotonin metabolism and pharmacodynamics such as selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (collectively dubbed here as SRI) may affect embryonic and fetal brain development and induce various neurobehavioral insults. By crossing the placenta and fetal blood-brain barrier, they may modify serotonin signaling, potentially altering morphological and behavioural development [3].

The use of SRI during pregnancy has steadily increased, reaching in recent years 2%-6% of all pregnancies [5-7]. These medications are prescribed for the treatment of depression, anxiety, obsessive-compulsive disorder (OCD), panic disorder and phobias. Yet many symptomatic women are not treated pharmacologically, probably due to fears of adverse fetal effects. The lack of clarity regarding fetal risks in humans is clearly a major concern for the woman, her family and health professionals. These fears are fueled by a large number of animal experiments showing adverse effects on pregnancy outcome when SRIs are used, inducing anatomical and neurobehavioral deficits [3, 8]. In spite of the fact that SRIs appear to be the most studied drugs during pregnancy, there are still conflicting views on their risks for the fetus and newborn infant [5, 9, 10].

SRIs inhibit the serotonin transporter which mediates the reuptake of serotonin into the presynaptic terminals, thus increasing synaptic serotonin concentrations. These medications readily cross the human placenta [11, 12] and are excreted in relatively small amounts in human milk.

There is no other example in human teratology where, after more than 40 cohort studies, repeated meta-analyses and thousands of pregnancies, the fetal safety or risk of an agent has not been verified and settled. Specifically, the most common and hotly debated inconsistency is whether SRIs are associated with increased risk of cardiovascular malformations, which are apparently the most prevalent group of congenital malformation inflicting 0.8% of all pregnancies. Moreover, as stated above, serotonin has an important role in cardiovascular development. Over the last 20 years, increasing evidence has been accumulated, suggesting that these inconsistencies stem from unrecognized and uncontrolled sources of bias, such that it may not be the SRIs but rather factors associated with maternal morbidity that result in a signal of more malformations.

Inconsistencies among studies exist in the definition of cardiac anomalies, some including small atrial and ventricular septal defects that tend to close spontaneously, while

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others excluding these anomalies. Other inconsistencies among studies are differences in the study design, control of maternal lifestyle (*i.e.* smoking, alcohol drinking), co-administered medications, or underlying maternal diseases (*i.e.*, different psychiatric disorders, diabetes and obesity). It has been suggested that the contradictory results may stem from genetic differences among different populations studied rather than from different methodologies and confounding factors [13].

2. SRI AND THE RISK OF CARDIAC MALFORMATIONS

The earliest description of an increased rate of cardiac malformations was related to paroxetine, with mainly ventricular septal defect (VSD) [5, 14] and atrial septal defects [15]. These anomalies were claimed to be related to first-trimester paroxetine exposure and were described as dose-dependent [16]. In a prospective cohort study published with several European Teratogen Information Services [15], the increased rate of cardiac malformations was described following treatment with both paroxetine (aOR 2.66, 95% CI 0.80,8.90) and fluoxetine (aOR 4.47, 95% CI 1.31, 15.27). However, when adjusting for confounding factors such as maternal smoking, only exposure to fluoxetine remained significant [17]. A study [18] examined echocardiograms on any newborn infant with a persistent cardiac murmur and found an increased rate of cardiac malformations following prenatal exposure to different SRI.

A study based on the Danish National Prescription Registry [19] found a similar rate of ASD and VSD in the exposed and control children, but the rate of "severe" cardiac anomalies was 4 times higher than among the non-exposed. A study evaluating the EUROCAT congenital anomalies reported an increased prevalence of "severe" cardiac anomalies [20].

In another study [21] of 12 EUROCAT congenital anomaly registries, a higher rate of cardiac malformations was found among the offspring of mothers using different SRIs. There was also an increase in severe cardiac malformations such as Tetralogy of Fallot and Ebstein's anomaly.

These studies clearly suggested an increased rate of cardiac anomalies. However, one should remember the limitations of registries and data based on prescriptions without accurate knowledge, as women may not have taken the drugs [22]. There might be a substantial disagreement between prescriptions and self-reported use of SRIs. In addition, there is a lack of data on the possible effects of maternal disease, confounding by indication.

In contrast to the above studies, there are also large prospective cohort studies where no increase in cardiac or other congenital malformations were observed [23-29].

Moreover, a large number of meta-analyses have been published perpetuating the confusion seen in single studies, showing both positive or negative associations [30-35].

A detailed review of the effects of SRIs in pregnancy on congenital malformations was published by us previously [9, 10].

The objectives of the present review are to identify and discuss sources of bias that may lead clinicians and scientists to believe that SRIs cause malformation where, in fact, they may not.

3. THE EFFECT OF ASCERTAINMENT BIAS

If women taking SRIs are more likely than other women to undergo diagnostic tests that detect cardiac malformations, then the apparently higher rates of such birth defects may constitute an ascertainment bias. There are several possible reasons why women taking antidepressants may have such tests more often than healthy women:

1) Women with clinical depression tend to have more fears and anxiety related to birth defects. There is ample evidence that women with depression or anxiety utilize significantly more health care services for their infants than healthy women. This could lead to higher detection rates of such malformations.

In 2007, we documented that pregnant women using antidepressants utilized significantly more ultrasound, amniocentesis or echocardiograms than women not receiving antidepressants. Moreover, they had a twofold increased likelihood of having echocardiograms on their babies than women not receiving SRIs [36]. Studies have shown that women with depression or anxiety utilize significantly more health care services for their infants than healthy women [37, 38]. Clinically speaking, women who have twice as many echocardiograms have a significantly higher chance of detecting a child with a cardiac malformation that was clinically undetected. To further strengthen the effect of this bias- the most common cardiac malformation is a ventricular septal defect (VSD). The most prevalent muscular type of this birth defect tends to be resolved spontaneously in infancy; hence it would not be found as commonly in children of healthy women who have been tested later. This means that in the control group, many more cases will "disappear" and would not be detected by a later echocardiogram.

2. With the wide publicity of the presumably increased risk of cardiac malformations caused by SRIs, it becomes more likely that women with depression or anxiety treated with these medications will seek diagnostic tests for their babies than healthy women, further strengthening this source of bias.

The proof of the effect of this bias came powerfully from Danemark, where a large national cohort has shown that the risk of VSD is higher among women who took SRIs in pregnancy than among controls, but it was identical among women with depression who decided not to use SRI in pregnancy. In this study, Jimenes-Solem *et al*. [23], performed a large national population based study in Denmark on 848,786 pregnancies and analysed the relation between the SRI use during pregnancy and major congenital malformations, with a focus on cardiac defects, and compared their rate to that of children born to a group of 806 women with depression who avoided taking their SRI in pregnancy. They found that the risk of cardiac malformations was similar in

Table 1. Covariates considered by Huybrechts *et al* [39] that may affect the relative risk of cardiac malformations in women receiving SRI.

Sociodemographic Covariates	Known or Suspected Risk Factors	Proxies for Depression Severity
Year of delivery	Multiple gestation	Number of depression diagnoses as inpatient/outpatient
State of residence	Chronic maternal illness	Other indications for antidepressants
Age	Use of other psychotropic medications	-
Race	Use of antidiabetic and antihypertensive medications	-
Parity	Number of distinct prescription drugs used	-

the offspring of women who took SRIs to that in mothers who stopped SRIs treatment before pregnancy. Thus, the increase in cardiac anomalies was probably related to maternal disease, by increasing the likelihood of monitoring fetal and neonatal heart than among healthy control women [23].

4. CONTROLLING FOR DIFFERENT SOURCES OF BIAS

In 2014, Huybrechts and colleagues analyzed 64,389 women using antidepressants out of a cohort of 949, 504 Medicaid participants (6.8%) [39]. In the original unadjusted analysis, the rate of cardiac malformations was higher among those exposed to SRIs (90.1 per 10,000 infants vs 72.3 per 10,000) [unadjusted RR 1.25(95% confidence interval 1.13-1.38)]. In an analysis restricted only to women diagnosed with depression, the risk was substantially less significant [RR1.12, 95% CI 1.00-1.26). Critically, in the fully adjusted model, adding also an adjustment for a large group of potential confounders shown in Table (**1**), the RR was non-significant [RR 1.06 (95% CI 0.93-1.22)] [39].

In a large Norwegian study, Nordeng and colleagues included 63,395 women, 699 of whom reported using antidepressants during pregnancy, mostly SRIs [40]. The researchers adjusted for maternal depression, age, parity, pregnancy BMI and use of psychotropic medications during pregnancy. The authors did not detect an association between first-trimester exposure to SRIs and risk of malformations in general [OR 1.22 (95% CI 0.81-1.84)] or cardiovascular malformations [1.51 (95% CI 0.67-3.43)]. Women using antidepressants in pregnancy were less likely to have tertiary education, or normal BMI, and were more likely to smoke cigarettes, to be hospitalized, or to have asthma. These women used significantly more other psychotropic drugs and analgesics. The authors cautioned that without adjustment for the level of maternal depression and various sociodemographic and lifestyle factors, the use of antidepressants in pregnancy could wrongly be labeled as the cause of more malformations [40].

5. POTENTIAL SOURCES OF BIAS FOR OTHER PERINATAL EFFECTS OF SRI

SRIs have been associated in some studies with an increased rate of miscarriage. Ban *et al*. [41], reported a relative risk (RR) for spontaneous abortion at 1.5 and 1.6 for perinatal death.

Johansen *et al*. [42], reported a small increase in miscarriages among women prescribed SRIs for psychiatric causes (hazard ratio (HR) of 1.08), but a higher HR,(1.26) if treatment was discontinued before pregnancy. The authors were aware of a possible bias related to gestational age at the time of the first antenatal visit. They found a large difference in the rate of spontaneous abortions among pregnant women contacting early in gestation (10.7% of miscarriages) compared to those arriving late (only 4%). This immortal time bias is well recognized in studies on miscarriage. Those who are followed up early will be captured, whereas those reporting later- the miscarriages have occurred already and would not be known to the researchers.

In contrast, Andersen *et al*. [43], found no difference in the rate of miscarriages in the SSRIs exposed (12.6%) compared to non-exposed (11.1%).

In conclusion, there is no convincing data showing that SRIs indeed increase the rate of spontaneous abortions. Many of the studies that demonstrated an increased rate of spontaneous abortions associated with the use of SRIs did not control for the pregnancy stage at the initial contact and/or with the underlying disease as both might increase the rate of spontaneous abortions not related to the drugs.

Several studies have demonstrated an increased risk of low birth weight and preterm delivery in infants prenatally exposed to SRIs. Oberlander *et al*. [44], reported decreased birth weight and gestational age at delivery in mothers with depression treated with SRIs compared to untreated depressed mothers. Similar findings were reported by Calderon *et al*. [45], among 138 pregnancies exposed to SRIs or SNRIs. However, the difference was significant only if treatment continued after the first trimester of pregnancy.

Malm *et al*. [46], found that SRI treatment even lowers the risk of preterm birth compared to untreated women with psychiatric disease, highlighting the importance of control for the underlying disease. When this confounder was adjusted for, there was no increase in preterm deliveries or IUGR.

Poor neonatal adaptation syndrome (PNAS) has been confirmed following third-trimester exposure to SRIs in up to 30% of pregnancies. PNAS is characterized by irritability, abnormal crying, tremor, jitteriness, lethargy, respiratory distress, poor muscle tone and rarely, seizures. These generally mild and transient effects are different from those caused by

Table 2. A selection of Product Monograph warning regarding SRI in pregnancy

Medication	Product Monograph Warning
Fluoxetine	Some evidence of a possible increase in the risk ofcardiac malformations. The use of Prozac in pregnancy should be considered only if the potential benefits justify the potential risk to the fetus.
Paroxetine	Epidemiological studies of pregnancy outcomes following maternal exposure to antidepressants in the first trimester have reported an increased risk of congenital malformations, particularly cardiovascular. If a patient becomes pregnant while on Paxil, consideration should be given to switching to other treatment options
Venlafaxine	Venlafaxine should only used during pregnancy if clearly needed,

opioid analgesics in their expression of severe respiratory illness [47].

The association between maternal use of SRIs in late pregnancy and persistent pulmonary hypertension of the newborn(PPHN) is well established with an absolute risk of PPHN is typically less than 1% and it is not severe, unlike other causes of PPHN, where mortality is up to 15% [48].

In conclusion, it seems that most of the studies showing an association between SRI and IUGR and/or prematurity are potentially confounded by the underlying psychiatric disorder.

Most of the covariates highlighted by Huybrechts as factors distinguishing women with clinical depression and anxiety Table (**2**) would also be affecting the rates of prematurity and intrauterine growth restriction.

6. THE DETRIMENTAL EFFECTS OF THE SRI BIAS

Depression in pregnancy can affect women's health and quality of life in major ways. A large systematic review and meta-analysis has documented that the prevalence rates of depression in pregnancy were 7.4%, 12.8% and 12.0% in the first, second and third trimesters, respectively [41]. Yet, large population-based studies have documented that the rates of use of antidepressants are merely 2.1%, 1.7% and 1.3% in the first, second and third trimesters [49]. The low prevalence of SRI use, coupled with the high proportion of women who discontinue their treatment raises questions about the inadequate treatment of depression in many pregnant women [50].

This reflects a serious inadequacy and a devastating gap in public health, because lack of treatment or insufficient therapy of depressed pregnant women is associated with increased risk of morbidity and mortality among these women. Moreover, the strongest predictor of the life-threatening postpartum depression is untreated depression in late pregnancy.

Because of the litigious environment around the use of drugs in pregnancy, none of the manufacturers of SRI has an approved indication for their use in pregnancy. Table (**2**) presents some of the disclaimers used by major manufacturers who naturally try to avoid litigations.

CONCLUSION

The present study highlights sources of bias that may explain why children exposed in utero to SRIs exhibit higher rates of congenital malformations, mostly cardiovascular or other complications of pregnancy such as IUGR and prematurity. It appears that pregnant women treated for depression and anxiety are distinctively different from healthy women in numerous covariates highlighted herein, which may confound pregnancy outcomes. These sources of bias are critical and are not merely theoretical. Because of the high risks of morbidity among suboptimally- treated depressed women, discontinuing their SRIs for the wrong reasons may be detrimental.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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