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REVIEW ARTICLE

Safety of Selective Serotonin Reuptake Inhibitors in Pregnancy: A Review of Current Evidence

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Abstract Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressant medications worldwide. However, over the past decade, their use during pregnancy, a period of extreme vulnerability to the onset of depression, has become highly concerning to patients and their healthcare providers in terms of safety to the developing fetus. Exposure to SSRIs in pregnancy has been associated with miscarriage, premature delivery, neonatal complications, birth defects—specifically cardiac defects—and, more recently, neurodevelopmental disorders in childhood, specifically autism spectrum disorders. Studies addressing the effect of individual SSRIs indicate a small but higher risk for birth defects with maternal fluoxetine and paroxetine use. Though the excess in absolute risk is small, it may still be of concern to some patients. Meanwhile, antenatal depression itself is associated with adverse perinatal outcomes, and discontinuing antidepressant treatment during pregnancy is associated with a high risk of relapse of depression. Whether the observed adverse fetal effects are related to the mother's medication use or her underlying maternal illness remains difficult to determine. It is important that every pregnant woman being treated with an SSRI (or considering such treatment) carefully weighs the risks of treatment against the risk of untreated depression for both herself and her child. The importance of recognizing a higher risk for the development of adverse outcomes lies in the potential for surveillance and possibly a timely intervention. Therefore, we recommend that pregnant women exposed to any SSRI in early pregnancy be offered options for prenatal diagnosis through ultrasound examinations and fetal echocardiography to detect the presence of birth defects. Tapering off or switching to other therapy in early pregnancy, if appropriate for the individual, may also be considered on a case-by-case basis.

Key Points

Maternal selective serotonin reuptake inhibitor (SSRI) treatment in early pregnancy may slightly increase the risk of major malformations overall, and cardiac malformations in particular, over the background population risk.

Maternal SSRI treatment in late pregnancy has been associated with premature delivery and other neonatal complications, as well as neurodevelopmental disorders in childhood, specifically autism spectrum disorders.

While limited data are available to separate the effect of SSRIs from the disease being treated in pregnancy, it is important to focus more on assessing the individual needs for each pregnant woman with a psychiatric illness by providing comprehensive counseling and support, with all treatment options discussed on a case-by-case basis.

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1 Introduction

Maternal use of selective serotonin reuptake inhibitors (SSRIs) in pregnancy has gained considerable clinical attention over the past decade because of their increasingly common use [1, 2] and their effectiveness in the treatment of depression and other psychiatric and non-psychiatric conditions [3]. Many studies of the effects of such maternal treatment on development of the fetus and child have been reported, but the results have been inconsistent; consequently, what pregnant women should be counseled regarding the risks of SSRI treatment remains controversial.

The SSRI medications currently available on the market are citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. SSRIs share a similar mechanism of action in blocking the reuptake of serotonin (5-HT) via the serotonin transporter, thereby increasing extracellular serotonin levels. However, each individual medication is different with regard to its chemical structure and pharmacological properties. Therefore, each product may potentially affect the developing fetus differently. In early studies, and in most meta-analyses performed to assess the risk of maternal SSRI use for the fetus, exposure data have been grouped for the entire class of SSRIs. This has been done because of limited sample sizes and in an attempt to simplify the overall estimation of risk for adverse outcomes from a clinical perspective. However, it is better to evaluate the risk of each SSRI individually to understand the unique potential of each drug for reproductive toxicity and to provide more accurate information for decision making by healthcare providers and patients who may require treatment during pregnancy.

Despite the current scrutiny over their potential risk for adverse reproductive outcomes, SSRIs are commonly prescribed during pregnancy [1, 4, 5]. The exception is paroxetine, the use of which in pregnancy has declined substantially [4] following warnings issued by the US FDA in 2005 regarding the potential risk for cardiac defects in the fetus. The product label was revised to indicate evidence of an elevated teratogenic risk to the fetus with first-trimester maternal paroxetine use [6, 7].

Data from animal studies indicate the importance of serotonin in the regulation of cellular proliferation, migration, and differentiation, and in neural crest cell morphogenesis in embryonic development [8, 9]. A specific role of serotonin in cardiac and craniofacial morphogenesis [10–12] and in processing sensory stimuli [13] has been established in mouse and rat models. The potential for SSRIs taken in gestation to alter morphogenesis and neurocognitive development of the infant has been suggested by various animal studies [12, 14–16].

Earlier analyses of SSRIs in pregnancy have focused primarily on the potential risk of birth defects when taken in the first trimester of pregnancy or on adverse neonatal outcomes appearing shortly after delivery when mothers were treated later in pregnancy. More recently, with more data available on prenatally exposed children, studies addressing long-term behavioral and cognitive development are becoming increasingly feasible and these outcomes are of high interest.

2 How is the Teratogenic Risk of Selective Serotonin Reuptake Inhibitors (SSRIs) Assessed in Human Studies?

Several types of epidemiological studies have assessed the magnitude of risk of maternal SSRI exposure for adverse fetal outcomes in humans. The first reported analytical studies were exposure cohort studies based on data collected from teratogen information services (TIS) [17–19]. In this type of study, women were identified when they called a TIS for counselling about the teratogenic potential of an SSRI during their pregnancy and were then prospectively followed through maternal interviews to determine the frequency of an adverse outcome as compared with the outcomes of an unexposed group of pregnant women. In some TIS studies, the outcome in both exposed and unexposed participants was determined through a meticulous blinded physical examination of the child performed by a dysmorphologist rather than relying on a verbal report of the mother or medical records. This approach permits the recognition of the recurrent patterns of minor anomalies that characterize most known human teratogenic effects. However, the sample sizes in these studies are relatively small, and they can therefore only detect very strong teratogenic effects. Furthermore, women who enrolled in these studies consisted of volunteers who are known not to be representative of the population of all women who take SSRIs in pregnancy. Therefore selection bias presents a potential limitation in these studies.

Population-based prospective cohort studies differ from TIS studies in that exposure information is obtained for an entire population in a comprehensive and ongoing manner. The largest existing study of this type on assessing safety of SSRI exposure in pregnancy used data from the Swedish Medical Birth Register [6, 20, 21]. This register contains information, collected through maternal interviews including exposures in early and late antenatal periods and postpartum, on nearly all births in Sweden. Information on the outcomes is based on standardized medical records and physical examinations by qualified pediatricians. Because the register is cumulative over time, the number of exposed pregnancies increases the longer a medication has been

available, which improves power to test associations with rare outcomes. The Norwegian Mother and Child Cohort Study adopted a similar design as the Swedish registry, although it is only a research-based cohort, and has published one study so far assessing antidepressants, including SSRIs, used in pregnancy in relation to pregnancy outcome [22].

It is worth noting that the majority of other published cohort studies that have assessed the teratogenic potential of maternal SSRI use in pregnancy were based on linked records collected in a defined geographical region or country [7, 23–30]. In such studies, data were typically initially collected for administrative purposes, such as insurance claims. Prescription records and pregnancy diagnoses were then electronically linked to birth outcome from hospital discharge summaries or other databases using personal identifiers for each case. The data were not specifically collected for the purpose of reproductive outcome studies, and this can lead to some limitations. For example, the dispensing of an SSRI might not necessarily represent the specific timing of exposure or whether the woman actually took the medication at all, and some record-linked studies may lack data on many potentially important confounders.

Retrospective case–control studies that measure the frequency of exposure as derived from maternal interviews, between cases (mothers of children with birth defects) and controls (mothers of children without birth defects), have also been used to assess the effect of SSRIs on pregnancy outcome [31–35]. Large case–control studies of maternal SSRI exposure have been able to look at rare and specific birth defects rather than lumping all birth defects or categories of birth defects together, which is often done in cohort studies because of lack of statistical power. On one hand, this increases the likelihood of finding a true association because a teratogenic exposure is expected to produce specific defects depending on its mechanism of action, rather than increasing the frequency of all birth defects. On the other hand, case–control studies are often limited by multiple comparisons, so some associations reported are likely to have occurred by chance and do not indicate a causal relationship. Because exposure information in case–control studies is usually collected retrospectively through standardized validated interviews administered to the mothers several months after the baby was born, recall bias does present another common limitation in these studies. However, this is thought to be less of a concern for prescription medications that are used for chronic conditions such as SSRIs for the treatment of depression. Furthermore, non-participation bias may also limit these studies when a high non-response rate exists. Large case–control studies that had the power to assess the risk of SSRI exposures in pregnancy included the National Birth Defects Prevention Study (NBDPS) [31] and the Slone Epidemiology Center Birth Defects Study [32, 35], both based in the USA, as well as another from the Netherlands [34].

Recently, a new epidemiological approach to studying the potential teratogenicity of maternal exposures, called the case–population design, has gained popularity [36]. These studies are based on a case–control design and compare exposure in pregnancy to the risk factor of interest in infants with birth defects (cases) with exposure to the same risk factor in pregnancy in the whole population cohort. In one such study that used this approach to assess safety of SSRIs in pregnancy, information on exposure was retrieved from prescription databases [37].

In this narrative review, we present available human data from controlled epidemiological studies, excluding articles such as case reports, looking at each SSRI separately with regard to first-trimester exposure and risk of miscarriages, congenital malformations, and—specifically—cardiac malformations, as the most common and complex category of birth defects We also review later gestational exposure and risk of other reported adverse outcomes, including persistent pulmonary hypertension of the newborn and other neonatal abnormalities. Finally, we review the recent literature on maternal SSRI use in pregnancy and later-onset cognitive and neurodevelopmental conditions, specifically autism spectrum disorder (ASD) in children. We searched the PubMed computerized database using the key words ‘selective serotonin reuptake inhibitors’, ‘SSRI’, ‘antidepressants’, ‘pregnancy’, ‘birth defects’, ‘malformations’, ‘teratology’, ‘newborn’, ‘persistent pulmonary hypertension of the newborn’, ‘Autism Spectrum Disorders’, ‘behavioural’, ‘cognitive’, and ‘pharmacokinetics’. References cited in studies obtained through the PubMed search that related to the subject of this review were also obtained.

3 Early Maternal Exposure to SSRIs and Birth Outcome

3.1 Citalopram/Escitalopram

For the purpose of this review, data on the potential risks in human pregnancy of citalopram and escitalopram, the pharmacologically active s-enantiomer of racemic citalopram, are combined. Although ideally each product should be studied separately, in this review the data are summarized together as these two drugs are not pharmacologically different from one another.

3.1.1 Congenital Anomalies

To date, the risk of having a baby with a congenital malformation following maternal citalopram use during

Table 1 Cohort studies of maternal specific SSRI use in early pregnancy and risk of congenital and cardiac malformations

Study (year)	Design (country)	Number of exposed				Reported positive associations	
		Citalopram	Fluoxetine	Paroxetine	Sertraline	Congenital anomalies	Cardiac malformations
Chambers et al. (1996) [17]	Prospective cohort (TIS) (USA)	–	228	–	–		
Kulin et al. (1998) [18]	Prospective cohort (TIS) (USA, Canada)	All SSRIs studied as a group: 267					
Cole et al. (2007) [7]	Retrospective cohort (USA)	–	–	815	–	Paroxetine with any congenital malformation (OR 1.89; 95 % CI 1.20–2.98)	
Davis et al. (2007) [23]	Record linkage (USA)	–	–	182	–		
Diav-Citrin et al. (2008) [19]	Prospective cohort (TIS) (Israel)	–	314	410	–		Fluoxetine with any cardiac malformation (OR 4.47; 95 % CI 1.31–15.27)
Oberlander et al. (2008) [24]	Record linkage (Canada)	101	638	993	608		Citalopram with any cardiac malformation (OR 6.4; 95 % CI 1.6–20.9)
Einarson et al. (2009) [38]	Prospective cohort (TIS) (Canada)	184	61	148	61		
Merlob et al. (2009) [47]	Prospective cohort (Israel)	All SSRIs assessed as a group: 235					Any SSRI with cardiac malformations (RR 2.17; 95 % CI 1.07–4.39)
Pedersen et al. (2009) [25]	Record linkage (Denmark)	460	348	299	259		Citalopram with septal heart defects (OR 2.52; 95 % CI 1.04–6.10). Sertraline with septal heart defects (OR 3.25; 95 % CI 1.21–8.75)
Colvin et al. (2011) [26]	Record linkage (Australia)	775	291	572	908	Citalopram with any congenital malformation (OR 1.36; 95 % CI 1.02–1.81), vesicoureteric reflux (OR 3.11; 95 % CI 1.28–7.58), and lower limb anomalies (OR 9.8; 95 % CI 1.1–7.2). Fluoxetine with GI tract malformations (OR 3.09; 95 % CI 1.27–7.48) and congenital anomalies of the ear, face, or neck (OR 4.39; 95 % CI 1.40–13.79). Sertraline with respiratory system defects (OR 3.73; 95 % CI 1.18–11.82)	Citalopram with patent ductus arteriosus (OR 4.9; 95 % CI 2.0–12.1)
Malm et al. (2011) [27]	Record linkage (Finland)	2799	1818	968	869	Citalopram with neural tube defects (OR 2.46; 95 % CI 1.20–5.07). Fluoxetine with "other malformations" (OR 3.1; 95 % CI 1.1–8.2)	Fluoxetine with any cardiac malformation (OR 1.40; 95 % CI 1.01–1.95) and isolated ventricular septal defects (OR 2.03; 95 % CI 1.28–3.21). Paroxetine with right ventricular outflow tract defects (OR 4.68; 95 % CI 1.48–14.74)

Table 1 continued

Study (year)	Design (country)	Number of exposed				Reported positive associations	
		Citalopram	Fluoxetine	Paroxetine	Sertraline	Congenital anomalies	Cardiac malformations
Jimenez-Solem et al. (2012) [28]	Record linkage (Denmark)	1606	928	568	817	Citalopram with any congenital malformation (OR 1.51; 95 % CI 1.21–1.87), congenital anomalies of the urinary system (OR 2.02; 95 % CI 1.05–3.89), digestive system malformations (OR 2.50; 95 % CI 1.19–5.27) and eye malformations (OR 2.62; 95 % CI 1.09–6.34). Paroxetine with malformations of the external genital organs (OR 3.83; 95 % CI 1.71–8.57). Sertraline with any congenital malformation (OR 1.41; 95 % CI 1.03–1.92)	Citalopram with any cardiac malformation (OR 1.91; 95 % CI 1.31–2.77) and septal heart defects (OR 1.86; 95 % CI 1.15–3.00). Fluoxetine with any cardiac malformation (OR 2.05; 95 % CI 1.27–3.31) and atrial septal defects (OR 2.53; 95 % CI 1.2–5.32). Paroxetine with atrial septal defects (OR 3.51; 95 % CI 1.57–7.87). Sertraline with any cardiac malformation (OR 2.73; 95 % CI 1.75–4.26), septal defects and specifically with atrial septal defects (OR 3.09; 95 % CI 1.82–5.25), and ventricular septal defects (OR 2.85; 95 % CI 1.35–5.99)
Klieger-Grossman et al. (2012) [39]	Prospective cohort (TIS) (Canada)	Escitalopram 212	–	–	–		
Nordeng et al. (2012) [22]	Prospective cohort (population based) (Norway)	243	51	76	99		
Kallen et al. (2013) [21]	Prospective cohort (population based) (Sweden)	6996	2879	1687	6691		Paroxetine with any cardiac anomaly (OR 1.63; 95 % CI 1.17–2.27) and specifically septum defects (OR 1.67; 95 % CI 1.12–2.50)
Ban et al. (2014) [29]	Record linkage (UK)	1946	3189	1200	757	Citalopram with congenital malformations of the urinary system (OR 2.07; 95 % CI 1.10–3.92) and digestive system malformations (OR 2.60; 95 % CI 1.07–6.32). Sertraline with congenital anomalies of the respiratory system (OR 4.04; 95 % CI 1.00–16.27)	Paroxetine with any cardiac anomaly (OR 1.78; 95 % CI 1.09–2.88)
Huybrechts et al. (2014) [48]	Record linkage (USA)	–	11,048	11,126	14,040	–	No associations after adjusting for depression
Berard et al. (2015) [30]	Record linkage (Canada)	–	–	–	366	Sertraline with craniosynostosis (OR 2.0; 95 % CI 1.1–3.7)	Sertraline with cardiac septal defects (OR 1.3; 95 % CI 1.0–1.8)

CI confidence interval, *GI* gastrointestinal, *OR* odds ratio, *RR* relative risk, *SSRI* selective serotonin reuptake inhibitor, *TIS* Teratogen Information Service, – not analysed

Table 2 Case–control studies of maternal-specific selective serotonin reuptake inhibitor use in early pregnancy and risk of congenital and cardiac malformations

Study (year)	Country	Number of cases	Reported positive associations	
			Congenital anomalies	Cardiac malformations
Alwan et al. (2007) [31]	USA	Infants with major birth defects (9622) subdivided in 18 categories, assessed for exposure with citalopram, fluoxetine, paroxetine, and sertraline	Craniosynostosis, omphalocele, and anencephaly (as a pooled birth defect category) with citalopram (OR 4.0; 95 % CI 1.3–11.9), fluoxetine (OR 1.9; 95 % CI 1.0–4.0), paroxetine (OR 4.2; 95 % CI 2.1–8.5), and sertraline (OR 2.0; 95 % CI 1.0–3.9)	
Berard et al. (2007) [33]	Nested case–control (of linked health record data) (Canada)	Major congenital malformations: 101. Major cardiac anomalies: 24	Major congenital anomalies with >25 mg/day paroxetine exposure (OR 2.2; 95 % CI 1.2–4.2)	Major cardiac malformations with >25 mg/day paroxetine exposure (OR 3.1; 95 % CI 1.0–9.4)
Louik et al. (2007) [32]	USA	Infants with birth defects (9849) subdivided in 14 categories, assessed for exposure with citalopram, fluoxetine, paroxetine, and sertraline	Neural tube defects with paroxetine (OR 3.3; 95 % CI 1.1–10.4). Club foot with paroxetine (OR 5.8; 95 % CI 2.6–12.8). Omphalocele and sertraline (OR 5.7; 95 % CI 1.6–20.7). Limb reduction defects and sertraline (OR 3.9; 95 % CI 1.1–13.5). Anal atresia and sertraline (OR 4.4; 95 % CI 1.2–16.4)	Septal heart defects and sertraline (OR 2.0; 95 % CI 1.2–4.0). Right ventricular outflow tract obstructive defects and paroxetine (OR 3.3; 95 % CI 1.3–8.8)
Bakker et al. (2010) [34]	Netherlands	Isolated heart defects: 678	–	Isolated atrial septal defects with paroxetine (OR 5.7; 95 % CI 1.4–2.4, $n = 56$)
Yazdy et al. (2014) [35]	USA	Infants with clubfoot: 646	Citalopram with club foot (OR 2.9; 95 % CI 1.1–7.2)	–

CI confidence interval, *OR* odds ratio, *RR* relative risk, – not analysed

pregnancy has been assessed in ten population cohort studies [21, 22, 24–29, 38, 39] and three case–control studies conducted in the USA [31, 32, 35] (Tables 1, 2). Maternal citalopram use in early pregnancy was associated with an increased risk for any malformation in two record-linkage cohort studies [26, 28]. However, in one study, the association was suggested to be related to maternal depression rather than to treatment because of the similar risk in infants of mothers who filled an SSRI prescription before and after pregnancy but not throughout gestation [28]. In three of the five studies specifically assessing anomalies of the urinary system, an association was found with early citalopram use in pregnancy [26, 28, 29]. Maternal citalopram treatment early in pregnancy was also associated with congenital anomalies of the digestive system in two record-linkage studies [28, 29] and with neural tube defects in a large Finnish record-linkage study [40]. In contrast, the risk of neural tube defects following maternal citalopram use was not confirmed in several other large retrospective cohort studies [26, 28, 29]. In the NBDPS case–control study, an increased frequency of citalopram use in early pregnancy was associated with a pooled group of three birth defect categories, including anencephaly, craniosynostosis, and omphalocele [31]. Other associations in single epidemiological studies that have not been replicated so far include eye malformations [28], lower limb abnormalities (not including club foot) [26], club foot [35], and musculoskeletal abnormalities [37].

3.1.2 Cardiac Malformations

Maternal citalopram treatment in early pregnancy has been associated with congenital heart defects as a group [24, 28], and specifically with septal heart defects [25, 28]. In a Canadian record linkage study, the association with heart defects did not remain significant when the exposures were restricted to the period of organogenesis [24]. An increased frequency of patent ductus arteriosus (PDAs) among

infants of mothers exposed to citalopram in early pregnancy was observed in an Australian record-linkage study [26]. However, it is hard to compare the prevalence of PDAs across other studies, as they may not be regarded as a birth defect, depending on the gestational age of the newborn, and are often excluded as birth defects by the NBDPS and other birth defect surveillance systems.

3.1.3 Miscarriage

An increased frequency of miscarriage occurred among women who redeemed a prescription for citalopram or escitalopram any time from 30 days before conception or throughout pregnancy in a Danish record-linkage study (odds ratio [OR] 1.43; 95 % confidence interval [CI] 1.34–1.53) [41]. However, this association did not remain statistically significant when the analysis was restricted to women with a hospital-based diagnosis of depression, suggesting that confounding by indication may have played a role. Based on the same linked data, a more recent analysis also showed increased risks for miscarriage associated with redeeming a prescription for citalopram (OR 1.29; 95 % CI 1.21–1.37) or escitalopram (OR 1.25; 95 % CI 1.09–1.42) within the first 35 days of pregnancy. However, redeeming prescriptions for either drug 3–12 months before pregnancy and not during pregnancy was also associated with increased risk for miscarriage [42]. These results also indicated that maternal depression could underlie the observed increased risks. Other studies specifically looking at maternal citalopram treatment in early pregnancy did not find associations with spontaneous abortion [39, 43].

3.2 Fluoxetine

Fluoxetine was the first SSRI to be marketed for the treatment of depression, in 1988. It gained much popularity under its trademark name Prozac, becoming the world's most frequently prescribed antidepressant [44], and it is now also used to treat obsessive–compulsive disorder, panic attacks, post-traumatic stress syndrome, pre-menstrual syndrome, neuropathic and other chronic pain, migraine headaches, and alcoholism.

3.2.1 Congenital Anomalies

In total, 12 cohort studies have specifically looked at the risk of birth defects following maternal fluoxetine treatment early in pregnancy (Table 1). In smaller TIS studies, no statistically significant associations were found with major congenital malformations combined following fluoxetine treatment in early pregnancy [17, 19, 38]. However, these studies were limited in their statistical power to identify increases in infrequent outcomes such as specific birth defects. In a Canadian cohort record-linkage study, an increased risk of major malformations was reported among 81 infants whose mothers received prescriptions for fluoxetine along with a benzodiazepine, but not among the 638 infants whose mothers were prescribed fluoxetine alone in early pregnancy, which could indicate a possible relationship with severity of the underlying disease [24]. An association with an undefined group of "other malformations" was reported in the Finnish record-linkage study [27].

With regard to specific birth defects, other than cardiac anomalies, increased frequencies for gastrointestinal tract malformations or congenital anomalies of the ear, face, or neck in infants born to mothers receiving prescriptions for fluoxetine in early pregnancy were reported in an Australian record-linkage study [26]. However, this finding failed to be replicated in other large cohort studies or case–control studies that assessed fluoxetine use and these specific malformations. In the NBDPS case–control study, mothers of infants with craniosynostosis were more likely to have received fluoxetine in early pregnancy than mothers of control infants [31]. In this study, exposure to fluoxetine was also significantly associated with a pooled group of anencephaly, craniosynostosis, and omphalocele. Bayesian analyses of an updated subset of the NBDPS data combined with other published studies also confirmed fluoxetine's association with craniosynostosis (OR 1.9; 95 % CI 1.1–3.0) [45].

3.2.2 Cardiac Malformations

Maternal fluoxetine exposure in early pregnancy was associated with any cardiac malformation in a prospective cohort study involving data from three TIS centers [46] and two large Scandinavian record-linkage studies [27, 28]. In the latter two studies, the reported associations were specifically attributed to isolated ventricular septal defects in the Finnish study [27] or to atrial septal defects in the Danish study [28]. A twofold increased risk of non-syndromic cardiac anomalies was reported in infants whose mothers used any SSRI, including fluoxetine, in early pregnancy in a small TIS prospective cohort study in Israel [47]. No associations between heart defects and maternal fluoxetine exposure were reported in other record-linkage studies [24, 26, 29, 48], population-based prospective cohort studies (that reported larger numbers of exposures to fluoxetine in pregnancy compared with other studies) [21, 22], or case–control studies [31, 32]. However, in the Bayesian analysis combining data from the NBDPS case–control and other published analyses, associations with right ventricular outflow tract heart defects following maternal fluoxetine use were confirmed (OR 2.0; 95 % CI 1.4–3.1) [45].

3.2.3 Miscarriage

A record-linkage study from Denmark showed a significant association between maternal fluoxetine treatment during the first 35 days of pregnancy and having a miscarriage (OR 1.10; 95 % CI 1.01–1.21) [42]. However, a similar association was also shown in the same study for mothers discontinuing fluoxetine use 3–12 months prior to pregnancy, suggesting that another risk factor, such as maternal underlying depressive illness, may be related to the observed increased risks. No associations with miscarriage among mothers using fluoxetine in early pregnancy were reported in other TIS studies, which are limited in number of exposures [17, 18, 49], or in a meta-analysis [50].

3.3 Fluvoxamine

Limited information is available on maternal fluvoxamine treatment and effects on the fetus. No significantly increased risks of major malformations, including cardiac malformations, were shown in 66 or 43 infants born to women exposed to fluvoxamine in early pregnancy in a Finnish record linkage study [27] or the Swedish population registry study [20], respectively. Similarly, in a TIS study of 12 European centers with 66 fluvoxamine exposures in pregnancy [51], and in a Canadian TIS study with 52 mothers exposed to fluvoxamine [38], no significant associations were noted with any malformations.

3.4 Paroxetine

Two preliminary studies (unpublished at the time) reported increased risks of cardiac defects [6] or congenital malformations overall [7] among the children of women prenatally exposed to paroxetine compared with unexposed mothers. This prompted the US FDA in 2005 to issue a warning regarding paroxetine use in early pregnancy. The use of paroxetine as a percentage of all maternal antidepressants used in pregnancy subsequently substantially declined from 19 % in 2002–2006 to <0.1 % in 2007–2010 [4].

3.4.1 Congenital Anomalies

Early studies reported increased risks for any malformation after maternal paroxetine use in early pregnancy [7, 33]. In one study based on a large American healthcare database, this finding resulted from comparisons between the infants of mothers who had received prescriptions for paroxetine and the infants of mothers who had received prescriptions for other SSRIs or other antidepressant medications during the first trimester of pregnancy [7]. In a Quebec nested case–control study, a significant association with any congenital malformation was limited to those taking higher doses (above 25 mg per day) of paroxetine in early pregnancy [33]. Maternal treatment with paroxetine was associated with anencephaly (OR 5.1; 95 % CI 1.7–15.3) and omphalocele (OR 8.1; 95 % CI 3.1–20.8) as well as a pooled group of the three birth defects (anencephaly, craniosynostosis, and omphalocele) in the large NBDPS case–control study [31]. In the Slone Epidemiology Center Birth Defects Study, which assessed 14 individual types of birth defects, no association of paroxetine use in the mother was found with 115 cases of craniosynostosis or 127 cases of omphalocele. However, increased risks of neural tube defects or club foot in the infant were associated with maternal paroxetine use [32]. In a Bayesian analysis combining updated data from the NBDPS with those from other published studies, significant associations with anencephaly (OR 3.2; 95 % CI 1.6–6.2), gastroschisis (OR 2.5; 95 % CI 1.2–4.8), and omphalocele (OR 3.5; 95 % CI 1.3–8.0) were reported with paroxetine exposure [45]. Among 568 mothers prescribed paroxetine early in pregnancy, an increased risk of malformations of the external genital organs was observed in a Danish record-linkage study [28], but it is unclear whether those included mainly hypospadias or other abnormalities, such as undescended testes, which may be related to preterm birth.

3.4.2 Cardiac Malformations

The risk for cardiac malformations overall was increased among the infants of mothers receiving paroxetine treatment in early pregnancy in three different studies conducted in three different populations [21, 29, 33]. Specifically, an increased risk of right ventricular outflow tract defects (RVOTD) was found in two studies [27, 32]. In the NBDPS study, a borderline association with RVOTD was also noted (OR 2.5; 95 % CI 1.0–6.0) [31] Atrial septal heart defects, or septal defects overall, were also more frequently reported among women exposed to paroxetine in early pregnancy in more than one study [21, 28, 34, 45]. Non-syndromic cardiac malformations were found to occur more frequently than usual among women taking any SSRI in early pregnancy in an Israeli TIS prospective cohort study [47], where paroxetine exposures constituted over one-third of SSRI prescriptions. In several other studies that have specifically assessed cardiac defects with maternal paroxetine use, no associations were found [7, 23, 24, 26, 48, 52]. However, the lack of associations could have been attributed to limitations in these studies in terms of power of numbers and pooling groups of birth defects, obscuring effects that may pertain to a subgroup, such as heart defects.

3.4.3 Miscarriage

Maternal paroxetine use during the first 35 days of pregnancy was associated with an increased risk of miscarriage (OR 1.27; 95 % CI 1.14–1.42) in a large Danish record-linkage study [42]. However, the same increase in risk was evident in mothers who discontinued their treatment 3–12 months before pregnancy, indicating that the increased risk of miscarriage could be due to the underlying illness or other lifestyle factors. Adjusted analyses of a systematic review confirmed an association between maternal paroxetine use in early pregnancy and the risk of spontaneous abortions (OR 1.7; 95 % CI 1.3–2.3) [50].

3.5 Sertraline

Sertraline is currently the most commonly used SSRI during pregnancy in the USA, with prescriptions increasing from 16 % of all antidepressants prescribed in the period 2002–2006 to 35 % in 2007–2010 [4, 53].

3.5.1 Congenital Anomalies

Most studies assessing the teratogenic potential of maternal sertraline treatment in early pregnancy have not detected an increase in the risk of congenital malformations overall, except for one Danish record-linkage study that included 817 mothers who had redeemed prescriptions for sertraline during the first trimester of pregnancy [28]. Two retrospective cohort studies based on different populations both reported associations of prenatal sertraline use in early pregnancy and respiratory system defects [26, 29]. Mothers exposed to sertraline in early pregnancy were more likely to have a child with limb reduction defects or anal atresia in the Slone Epidemiology Birth Defects Study [32]. Frequency of sertraline treatment in pregnancy was also higher among mothers who delivered infants with anencephaly [31] or craniosynostosis [30]. Exposure to sertraline was also significantly higher among mothers who delivered infants who had one of a pooled group of birth defects (anencephaly, craniosynostosis, and omphalocele) compared with mothers of non-malformed infants in the NBDPS study [31].

3.5.2 Cardiac Malformations

One Danish record-linkage study found an increased risk of maternal sertraline treatment in early pregnancy for congenital heart defects overall [28]. The same study, along with several other population-based studies, reported a specific association between prenatal sertraline exposure and septal heart defects [25, 28, 30, 32]. However, in other well-powered studies, including the NBDPS case–control study [31, 45], and several cohort studies [21, 24, 26, 27, 29, 48], no association was noted with septal defects following maternal sertraline treatment in early pregnancy. It is important to note that, unlike in other studies, the diagnoses in the Danish study [28] were taken from hospital discharge registers, which may have led to differential increased ascertainment if SSRI-exposed infants were more often transferred to neonatal intensive care units and therefore could have been evaluated more intensely.

3.5.3 Miscarriage

Although maternal sertraline use during the first 35 days of pregnancy was associated with an increased risk of miscarriage in the Danish record-linkage study (OR 1.45; 95 % CI 1.33–1.58), a similar association was found in the infants of pregnant women who discontinued sertraline treatment 3–12 months before pregnancy, suggesting that the increase in risk could be related to the underlying indication for sertraline use or other lifestyle factors [42]. No associations with miscarriage among mothers using sertraline were found in a meta-analysis reviewing data from studies on maternal sertraline or other SSRI use in pregnancy and risk of spontaneous abortion [50].

3.6 Summary of Potential Teratogenic Risk of SSRI Therapy in Early Pregnancy

Overall, the available literature discussed above, along with recent reviews and meta-analyses [21, 54], suggest that the frequency of major malformations and cardiac malformations may be increased by a very small amount over the background population risk following maternal treatment with citalopram/escitalopram, fluoxetine, paroxetine, or sertraline in early pregnancy. Citalopram/escitalopram, fluoxetine, paroxetine, and sertraline have each been shown in more than one study to be associated with an increased risk of a major congenital malformation or a cardiac malformation based on the current literature, albeit not necessarily with the same type or category of malformation. Although we do not present a systematic review or meta-analysis to quantify or weigh the risk of birth defects from maternal use of each SSRI, it appears reasonable to conclude from the current literature that maternal treatment with paroxetine in early pregnancy probably bears a slightly higher risk for any birth defect, but specifically for heart defects, than treatment with other SSRIs. This cannot be attributed to the fact that paroxetine has been more extensively studied than other SSRIs (Tables 1, 2). Data available to date on fluvoxamine are too limited to provide any consensus on its risk in pregnancy.

It appears that women taking SSRIs in early pregnancy are at a slightly increased risk of having a miscarriage than those

who do not, and this may be related to the underlying maternal illness or other factors associated with it. However, studies on miscarriage risk should be interpreted with caution for many reasons, including the difficulty of obtaining complete ascertainment of miscarriage events in clinically recognized pregnancies. In addition, in many studies, exposures are compared between pregnancies that end in miscarriage and those that end in a live birth delivery, while the competing risk for induced abortions is not typically taken into account. This may introduce bias in the estimate of the risk if induced abortions occur more often in depressed women or those taking antidepressants than in the unexposed group. Furthermore, it is likely that part of the discrepancy among studies on some severe malformations, such as neural tube defects or severe heart defects, could be attributed to differences in their diagnoses prenatally and subsequent terminations, which would potentially bias the results towards the null. From a clinical perspective, it is important to highlight that no strong teratogenic risk has been detected with the use of any SSRI. However, if alternatives are appropriate, it is probably wise to suggest that neither fluoxetine nor paroxetine should be offered as first-line therapy options in treating depression or other mood disorders for women in early pregnancy or anticipating becoming pregnant. However, because of the increased risk of relapse in women discontinuing antidepressant medications during pregnancy than in those continuing to receive medication and the associated adverse neonatal complications that can result [55], stopping or switching of paroxetine to another antidepressant in an ongoing pregnancy may not be advisable, especially if treatment has already extended beyond the first trimester. Meanwhile, given the positive associations with cardiac defects indicated in some studies with all four commonly used SSRIs, we recommend that fetal echocardiography be offered to pregnant women who have been exposed to citalopram/escitalopram, fluoxetine, paroxetine, or sertraline during the first trimester of pregnancy. In addition, detailed prenatal ultrasound examinations during gestation should also be offered to monitor for other fetal abnormalities.

4 Late in Utero Exposure to SSRIs and Newborn Complications

4.1 Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn (PPHN) is a rare cardiac condition presenting as severe respiratory failure and occurring in 10–20/100,000 newborns [56]. In 2006, a large case–control study reported a sixfold increase in the risk of PPHN among infants born to mothers treated with an SSRI in late pregnancy [57]. As a result, the US FDA issued a public health advisory warning of the potential increased risk of PPHN in children of mothers treated with SSRIs in the second half of pregnancy [58]. The findings were similar in a large Swedish population-based study [20] and in a US Medicaid cohort study, which also controlled for depression [59], although the magnitude of the association was attenuated to odds ratios of 3.4 and 1.36, respectively. In the largest multi-national record-linkage study assessing PPHN risk associated with maternal-specific SSRI exposures in late pregnancy, the authors confirmed a twofold increased risk of PPHN among infants of mothers treated with citalopram, fluoxetine, paroxetine, or sertraline [60]. No association between SSRI treatment of the mother and PPHN in the infants was reported in smaller studies [61–63], which may not have had sufficient power to detect increased risks. The biological mechanism for such an association is not clear but may involve the possibility of higher circulating levels of serotonin in the fetus resulting in vasoconstriction and smooth muscle cell proliferation characteristic of PPHN [57] or various other mechanisms unrelated to serotonin that SSRIs have on cardiac conduction and cardiovascular function [64, 65].

4.2 Other Adverse Neonatal Outcomes

Late in utero exposure to SSRIs has been identified as a risk factor for impaired neonatal adaptation. Reported findings among newborn infants whose mothers had been treated with SSRIs prior to delivery include respiratory distress, temperature instability, feeding difficulties, jitteriness, restlessness, convulsions, rigidity, hypoglycemia, jaundice, and other symptoms of abnormal neonatal adaptation [17, 23, 66–71]. These symptoms appear to be especially common with high-dose maternal treatment late in pregnancy, particularly with paroxetine [72]. These problems, which usually present between birth and 2 weeks of age [72, 73], probably result from neonatal toxicity or from SSRI withdrawal in response to sudden cessation of treatment at birth.

Maternal use of SSRIs late in pregnancy has also been associated with an increased risk of delivering a premature baby (<37 gestational weeks) [74, 75], lower average gestational age at birth (which was dose related in one study) [76], low birth weight [17, 67, 68, 75], low Apgar scores [68, 69, 74, 77], Caesarean delivery [67, 78], and increased rates of neonatal intensive care unit (NICU) admissions [17, 40, 69, 70, 79]. However, no association of SSRI use in pregnancy with stillbirth or neonatal mortality was noted in the largest population-based cohort study from all Nordic countries [80]. Other neonatal behavioral alterations

reported with maternal use of SSRIs late in pregnancy include increased motor activity, tremulousness, altered sleep and rapid eye movement [81], and attenuated bio-behavioral reactivity to procedural pain [82]. In some studies, fetal neuro-behavioral effects of maternal SSRI treatment during gestation were seen, including reduced fetal breathing and increased motor movements on ultrasound observation [83–85]. A recent study has also shown a significant increase of Chiari I malformations in the children of mothers exposed to SSRIS during gestation [86].

5 Maternal SSRI Exposure and Long-Term Behavioral and Cognitive Outcome in Children

5.1 Autism Spectrum Disorders

Evidence from animal and human studies suggests that increased serotonergic activity during fetal brain development may be in the causal pathway leading to ASDs [87–89]. These observations have led researchers to hypothesize that maternal SSRI treatment during gestation may

Table 3 Epidemiological studies of maternal SSRI use in pregnancy and risk of Autism Spectrum Disorders (ASDs) and other long-term neurodevelopmental conditions

Study (year)	Design (country)	Cases/exposure (*n*)	Comparison group (*n*)	Findings	
				Autism spectrum disorders	Other neurodevelopmental conditions
Croen et al. (2011) [91]	Case–control (USA)	Children with ASD (298)	Children without ASD (1507)	First trimester exposure (OR 3.5; 95 % CI 1.5–7.9). Exposure in the year before delivery (OR 2.6; 95 % CI 1.5–5.4)	
Eriksson et al. (2012) [93]	Case–control (Sweden)	Children with ASD (208)	Children without ASD (119,183)	Exposure to SSRIs in pregnancy (OR 4.5; 95 % CI 2.19–9.05)	
Hviid et al. (2013) [95]	Record-linkage cohort (Denmark)	SSRI exposure 4 weeks before and throughout pregnancy (6068)	No SSRI prescription 2 years before pregnancy and through delivery (620,807)	No significant associations (RR 1.20; 95 % CI 0.90–1.61)	
Rai et al. (2013) [94]	Case–control (Sweden)	Children with ASD (1679)	Children without ASD (16,845)	Exposure to any SSRI during pregnancy in children with ASD without intellectual disability (OR 2.34; 95 % CI 1.09–5.06)	
Sorensen et al. (2013) [96]	Record-linkage cohort (Denmark)	Any SSRI prescription 30 days before conception to birth (7506)	No SSRI prescriptions 30 days before conception to the day of birth (55,015)	Exposure to SSRIs during the first trimester of pregnancy (HR 1.6; 95 % CI 1.3–2.0)	
Gidaya et al. (2014) [97]	Case–control (Denmark)	Children with ASD (5215)	Children without ASD (52,150)	Increased risk for SSRI exposure during pregnancy (OR 2.5; 95 % CI 1.7–3.7)	
Harrington et al. (2014) [92]	Case–control (USA)	Children with ASD (492) or developmental delay (154)	Children with typical development (320)	Increased risk for SSRI exposure any time during pregnancy in boys (OR 2.91; 95 % CI 1.07–7.93). First-trimester SSRI exposure in boys (OR 3.22; 95 % CI 1.17–8.84)	Increased risk for SSRI exposure during the third trimester among boys with developmental delay during pregnancy (OR 4.98; 95 % CI 1.20–20.62)
EL Marroun et al. (2014) [98]	Prospective cohort (Netherlands)	Exposed to SSRIs (69). Unexposed, depressive symptoms (376)	Unexposed, not depressed (5531)	Increased risk for SSRI exposure during pregnancy for pervasive developmental problems (OR 1.91; 95 % CI 1.13–3.47) and autistic trait (B 0.15; 95 % CI 0.08–0.22)	

ASD autism spectrum disorder, *B* beta, *CI* confidence interval, *HR* hazard ratio, *OR* odds ratio, *RR* rate ratio, *SSRI* selective serotonin reuptake inhibitor

increase the risk of having a child with ASD [90]. Recent studies suggest that such an association may exist (Table 3).

The first large population-based study specifically assessing this question used data from the California Childhood Autism Perinatal Study, a case–control study of potential risk factors for ASDs [91]. Among 298 case children with ASD, 20 (6.7 %) were reported with prenatal SSRI exposure compared with 50/1507 (3.3 %) in control children. A twofold increased risk of ASD was associated with maternal SSRI exposure during the year before delivery, and the association appeared strongest, with a threefold increased risk for ASD, when SSRI exposure occurred during the first trimester of pregnancy. A subsequent US case–control study using data from the CHARGE (Childhood Autism Risks from Genetics and the Environment) study reported significantly increased risks for ASD or developmental delay (DD) when the analysis was restricted to boys prenatally exposed to SSRIs; the greatest ASD risk was shown following first-trimester exposure [92].

A fourfold increased risk associated with maternal SSRI exposure in pregnancy was reported among 208 children with ASD in a case–control study in Sweden [93]. A larger nested case–control study based on the same population also reported an increase in risk of ASD related to SSRI exposure, but the association was statistically significant only among children with ASD without intellectual disability, after adjusting for maternal psychiatric disorder and other confounding factors [94].

Three large epidemiological studies of the risk of ASD following maternal SSRI treatment were performed in the Danish population. The first two used data from linked administrative national registers and found increased risks for ASDs with maternal SSRI exposure during pregnancy [95, 96]. In the first study, Hviid et al. [95] reported a rate ratio (RR) of 1.64 for ASD in children of women prescribed SSRIs in pregnancy, but the association lost statistical significance when fully adjusted for various factors including maternal psychiatric diagnoses before delivery. However, a statistically significant association was reported when SSRI exposure occurred between 2 years and 6 months before pregnancy, but not during pregnancy, which suggests that confounding by indication may play a role.

Sorensen et al. [96] reported associations of maternal SSRI exposure in pregnancy with ASD, which reached statistical significance when exposure was confined to the first trimester, and a dose–response relationship was noted, with a larger effect size reported for higher doses of maternal SSRI treatment. In an attempt to separate the effect of medication from that of the underlying disease, the authors restricted their analyses to children of women with a diagnosis of affective disorder and first-trimester exposure to antidepressants. The associations no longer showed statistical significance, suggesting that unmeasured genetic or lifestyle factors other than depression could be confounders. Paternal antidepressant use during the time of pregnancy was not associated with an increased risk of ASD; however, there was a 30 % increase when the fathers specifically took SSRIs. Both Danish studies shared similar inclusion criteria but, unlike the previous study [95], the authors in this study did not exclude children with genetic conditions [96].

The third Danish study was a case–control study involving 5215 children with ASD, each individually matched to ten children without an ASD by birth month and year [97]. The authors found significant associations between ASD in the children and maternal SSRI use in all exposure windows, including preconception, and in each trimester of pregnancy, but the association was strongest among women exposed to SSRIs in the third trimester (OR 2.5; 95 % CI 1.7–3.7). Similarly, when the analyses were restricted to women with a diagnosis of depression, a lower risk estimate with ASD was detected.

A recent prospective cohort study embedded in an ongoing population-based cohort in the Netherlands assessed the risk of autistic traits among the children of 69 mothers who had received prescriptions for an SSRI in pregnancy and 376 unexposed depressed mothers. The study found associations between SSRI use in the mother and childhood autism but not with other affective disorders, whereas prenatal depressive symptoms without treatment were associated with autistic traits and affective problems in children [98]. A limitation of this study was its reliance on parental ratings of their own and their children's mental status, rather than on clinical diagnoses or assessments.

The pooled summary results in a recent meta-analysis of the four main case–control studies looking at risk of taking SSRIs in pregnancy on ASD [91, 92, 94, 97] gave an adjusted OR of 1.81 (95 % CI 1.47–2.24) [100]. In all of the studies cited above, SSRIs were assessed as a group when examining risk for ASDs, which makes it impossible to determine whether one or more specific SSRIs was more strongly associated than others. Furthermore, the increase in ASDs could be due to a higher detection rate of ASD amongst the children of mothers exposed to SSRIs, who may receive more medical consultations and may be more likely to have their children assessed for neuro-behavioral abnormalities. Even if the association between SSRI exposure in pregnancy and ASD in the children is real, whether it is actually causal or confounded by the underlying depression in the mother has yet to be determined.

In a recent nested case–control study of linked healthcare data from a large healthcare system in the USA [99], the authors found associations between any antidepressant

exposure prior to and during pregnancy and ASD risk, but the risk of exposure during pregnancy was no longer significant after controlling for maternal depression. However, antidepressant exposure during pregnancy (but not prior to pregnancy) was more strongly associated with risk of attention-deficit/hyperactivity disorder (ADHD), even after adjustment for maternal depression (OR 1.81; 95 % CI 1.22–2.70). The authors suggested that the observed risk of antidepressants in pregnancy with ASD in the infant is probably confounded by the severity of maternal illness.

5.2 Other Neurodevelopmental Effects

Prenatal exposure to SSRIs has been associated with delayed psychomotor development and fine motor development in 31 children between 6–40 months of age [69] and in delayed gross motor development and altered social–emotional and adaptive behavior among 31 children at 10 months of age [101]. Furthermore, in a recent study of 110 mother–child pairs with 44 exposed to an SSRI in pregnancy, associations with sustained higher levels of internalizing behaviors in 3- to 6-year olds were evident, even when controlling for maternal depression [102]. However, several other prospective cohort studies with small sample sizes [103–108] and one larger retrospective cohort study [74] previously reported normal mental and psychomotor development in children following maternal SSRI treatment in pregnancy.

6 The Dilemma Regarding the Effect of SSRIs Versus the Underlying Disease

Depressive symptoms occur in about 20 % of women during their pregnancies, with 10 % going on to develop major depression [109]. Women with a diagnosis of depression in the past are more likely to relapse during pregnancy, especially if they have stopped using their antidepressant medications [55]. There is conflicting evidence on whether untreated maternal depression is a risk factor for adverse perinatal outcomes, with various studies reporting negative findings [110–112] and other studies showing an increase in risk. Maternal stress has been associated in some studies with higher rates of various congenital anomalies [113–115] and spontaneous abortion [116]. Gestational depression or anxiety has also been shown to be significantly associated with prematurity, low birth weight, NICU admission, and operative delivery [116–120]. Infants of mothers with higher depression symptoms were more likely to exhibit adverse neonatal effects, such as low motor tone, abnormal reflexes, lower activity levels, increased irritability, less endurance, and inferior orientation, than infants of mothers with lower depression scores in one study [121]. Furthermore, untreated maternal depression during pregnancy may be related to unhealthy lifestyle habits and other risk factors for adverse outcomes, such as poor nutrition, smoking, alcohol drinking, illicit drug use, as well as other maternal conditions, including diabetes [122] and pre-eclampsia [123]. Antenatal depression is an important risk factor for postpartum depression, which is associated with adverse outcomes for mothers and their children and is a major cause of maternal suicide. However, SSRIs are also prescribed for various other psychiatric conditions and non-psychiatric conditions. For example, in a recent study, maternal psychiatric disease (including anxiety, obsessive-compulsive disorder, and panic disorder) was associated with poor fetal growth [124]. Similarly, children of women who had high levels of anxiety during gestation displayed signs of ADHD and aggressive behavior at 9 years of age [125].

In reviewing the literature and in light of most epidemiological studies that have assessed risk of maternal SSRI exposure, we find it difficult to separate the effect of the underlying disease and/or related comorbidities, lifestyle, and other risk factors from the effect of medication used. In other words, we cannot attribute risk to one causal factor; it seems more likely that an interaction of the psychological status, pharmacological treatment, genetic factors, and other associated factors in each individual case determine the risk of an adverse outcome. It is also important to note that some adverse outcomes reported with either SSRI exposure or untreated depression in pregnancy are actually interrelated in their pathogenic pathway and could be considered a spectrum of various related outcomes over an extended developmental period, such as neonatal neurodevelopmental or "withdrawal" conditions being predictive of later-onset cognitive or behavioral disorders.

7 Conclusions

Whether to continue SSRI treatment or not remains a dilemma for many women with a history of mood or depressive disorders who are planning or undergoing a pregnancy. The current controversy over the risk of SSRIs in pregnancy and the uncertainty of some healthcare providers, more pressure is placed on some women, who may in fact face shame or guilt in deciding to continue (or discontinue) their treatment and may not receive support for their decision from their family or healthcare providers [126].

The revised US FDA Pregnancy and Lactation Labeling Rule [127] should provide clinicians with a more comprehensive narrative guide for communicating risk to their patients. Every woman, in consultation with her healthcare provider, must balance the possible risks of medication

against the severity of depression and the consequences of poorly or under-treated maternal illness. For many women affected with mild to moderate depression, or with other psychiatric illnesses, tapering off medication may be an option, and engaging in non-pharmacological types of therapy may be recommended. There are currently many non-drug treatments that may improve maternal depression and other psychiatric disorders, including cognitive and psychotherapy, omega-3 fatty acid supplements, exercise, or bright light therapy. It is advisable for women with non-psychiatric conditions to avoid SSRIs during their child-bearing years and choose other forms of therapy, if available, for their condition. However, for women with relapsing and severe depression, it is recommended that SSRIs, if that is the most or only effective treatment, be continued during pregnancy to avoid the potential adverse risks of untreated depression. Treatment with the smallest effective dose is advised. Based on currently available data in early pregnancy, avoidance of fluoxetine or paroxetine seems prudent if appropriate alternatives are available, because of their slightly higher, though still small, teratogenic risk compared with other SSRIs. The teratogenic potential of newer antidepressants, such as selective serotonin and norepinephrine reuptake inhibitors (SNRIs), remains undetermined, with very limited data available, so one should be cautious about switching treatment to them.

From a clinical perspective, while insufficient data are available to separate the effect of medication from disease, it is important to focus more on assessing the individual needs for each pregnant woman battling depression by providing comprehensive counselling and support, with all treatment options discussed on a case-by-case basis. From a public health perspective, it is crucial that the fetal and neonatal development of children of women treated with SSRIs in gestation is monitored, timely interventions are provided, and neurodevelopment is followed-up throughout childhood.

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