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# Do Individual Selective Serotonin Reuptake Inhibitors Used During Pregnancy Show Any Differences in The Risk of Neonatal and Childhood Outcomes: An Overview

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**ABSTRACT**

This review summarizes current data on the risk of neonatal and childhood outcomes associated with maternal use of individual selective serotonin reuptake inhibitors (SSRIs) during pregnancy. Research articles and meta-analyses published in English language and curated in PubMed between January 2005 and April 2020 were screened. Based on limited available data, compared to others, slightly higher risks associated with individual SSRIs are as follows: paroxetine for preterm birth, escitalopram for low birth weight, sertraline and paroxetine for spontaneous abortion, fluoxetine for persistent pulmonary hypertension and fluoxetine and paroxetine for poor neonatal adapdation syndrome. Sertraline for persistent pulmonary hypertension and sertraline and paroxetine for autism spectrum disorders may be relatively safer compared to the other SSRIs. The current evidence is inadequate for definitive conclusions. Futher multicenter comparative studies are urgently needed.

**Keywords:** Antidepressants, Pregnancy, Preterm Birth, Low Birth Weight, Spontaneous Abortion

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# Gebelikte Bireysel Kullanılan Seçici Serotonin Gerialım İnhibitörleri Yenidoğan ve Çocukluktaki Riskler Açısından Farklılık Gösteriyor Mu: Genel Bakış


## ÖZ

Bu derleme, hamilelik sırasında seçici serotonin geri alım inhibitörlerinin (SSRI'lar) annede bireysel kullanımıyla ilişkili yenidoğan ve çocukluktaki sonuçların risklerine ilişkin mevcut verileri özetlemektedir. Ocak 2005 ile Nisan 2020 arasında İngilizce ve PubMed'de yayınlanan araştırma makaleleri ve meta-analizler tarandı. Sınırlı mevcut verilere göre, diğerlerine kıyasla, bireysel SSRI'larla ilişkili biraz daha yüksek riskler şu şekildedir: erken doğum için paroksetin, düşük doğum ağırlığı için essitalopram, spontan düşük için sertralin ve paroksetin, kalıcı pulmoner hipertansiyon için fluoksetin ve zayıf yenidoğan adaptasyon sendromu olanlar için fluoksetin ve paroksetin. Kalıcı pulmoner hipertansiyon için sertralin ve otizm spektrum bozuklukları için sertralin ve paroksetin diğer SSRI'lara kıyasla nispeten daha güvenli olabilir. Mevcut kanıtlar kesin sonuçlar için yetersizdir. Daha fazla çok merkezli karşılaştırmalı çalışmalara acilen ihtiyaç vardır.


**Anahtar Kelimeler:** Antidepresanlar, Gebelik, Erken Doğum, Düşük Doğum Ağırlığı, Spontan Abortus


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## INTRODUCTION

Antidepressants are widely used for the treatment of many psychiatric diagnoses, especially depression and anxiety disorders. Epidemiological studies suggest that pregnant women are increasingly prescribed antidepressants (Damkier et al., 2018; Meunier et al., 2013; Munk-Olsen et al., 2012). Although the prevalence rate for the use of antidepressants during pregnancy is reported very differently in different geographical regions, a recent meta-analysis demonstrated a relatively frequent international use with about 4.0% (Molenaar et al., 2020). Pharmacotherapy in the treatment of some pregnant patients is clinially inevitable and the safety of antidepressants for the fetus or newborns is an important coercive factor in their selection during treatment. Despite low absolute risks, safety concerns related to the use of antidepressants during pregnancy continue due to controversial results reported in the literature.

One of the risks that is immediately associated with the use of antidepressants during pregnancy is the development of congenital malformation in the infant. However, other neonatal and childhood outcomes such as preterm birth, low birth weight and autism spectrum disorders are both frequent and important for long-term health. For example, preterm birth, which is frequently seen in the general population, is associated with 70% of neonatal deaths and up to 75% of neonatal morbidity (Wen et al., 2004). Moreover, meta-analyses have suggested that preterm birth and low birth weight negatively affect cognitive and academic performance in children (Aarnoudse-Moens et al., 2009; Allotey et al., 2018). On the other hand, available studies, systematic reviews or meta-analyses examining the relationship between antidepressants and neonatal outcomes are mostly focused on the use of general antidepressants or a class of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants rather than specific individual antidepressants. The current paper aimed to present current data on the effects of specific SSRIs used in pregnant women on birth outcomes other than congenital malformations.

### Methods

English language papers published in the PubMed electronic database between January 2005 and May 2020 were screened. The search words used were as follows: pregnancy, antidepressant, SSRI, citalopram, escitalopram, fuloxetine, paroxetine, sertraline, fluvoxamine, neonatal outcome, birth outcome, preterm birth, low birth weight, spontaneous abortion, persistent pulmonary hypertension, autism spectrum disorders, attention-deficit/hyperactivity disorder and poor neonatal adaptation syndrome. Clinical studies and meta-analyses but not reviews, case reports, letters to editor and experimental studies were included in this review.

### 1. Preterm Birth

Preterm birth is one of the major issues in perinatal health. It is defined as birth of the baby before 37 weeks of gestational (Tucker & McGuire, 2004). The prevalence rate of preterm birth estimated to be 5-10% in the general population (Frey & Klebanoff, 2016; Sharifi et al., 2017; Wen et al., 2004). Preterm birth could be triggered by multiple factors including infections, inflammation, uteroplacental ischaemia or haemorrhage. Gestational hypertension, intrauterine growth restriction, periodontal disease and a history of previous preterm birth are some risk factors (Goldenberg et al., 2008). Maternal use antidepressants during pregnancy appears to be

another risk factor for preterm birth. Meta-analyses have demonstrated that the prevalence of preterm birth in women exposed to SSRI antidepressants is 1.43-1.83 fold higher compared to the controls (Biffi et al., 2020; Eke et al., 2016; Huang et al., 2014).

Several studies have examined the relationship between maternal use of individual SSRIs and the risk of preterm birth in the infants. The reported prevalence of preterm birth in pregnant women using paroxetine was 8.7-20.0% (Costei et al., 2002; Diav-Citrin et al., 2008), fluoxetine was 4.1-14.3% (Chambers et al., 1996; Diav-Citrin et al., 2008), citalopram was 11% (Tucker & McGuire, 2004) and escitalopram was 11% (Klieger-Grossmann et al., 2012). This prevalence was 4-10% in the comparison groups including women unexposed to SSRIs. Simon et al. (Simon et al., 2002) revealed that perinatal outcomes with the use of sertraline, paroxetine and fluoxetine were similar. In a meta-analysis by McDonagh et al. (McDonagh et al., 2014), it was found that risk of preterm birth with citalopram or escitalopram was not significantly different from fluoxetine, paroxetine and sertraline. A more recent meta-analysis by Eke et al. (Eke et al., 2016) has suggested that women who used paroxetine had a similar risk of preterm birth to those who used fluoxetine (odds ratios=2.07 vs 1.91, respectively).

**2. Low Birth Weight**

Low birth weight is defined as birth below 2500 g and affects about 10% of infants. (Xu et al., 2014; Yonkers et al., 2014). Older maternal age, low economic level, disturbances in blood pressure and maternal anemia are the main risk factors for low birth weight (Figuerideo et al., 2018; Yadav & Lee, 2013). The relationship between low birth weight and maternal use of antidepressant during pregnancy is currently unclear due to the controversial study results (Grzeskowiak et al., 2012; Hayes et al., 2012).

The prevalence rate of low birth weight in infants exposed to fluoxetine and escitalopram was 11.5% and 9.9%, respectively, which was significantly higher compared to the controls (Chambers et al., 1996; Klieger-Grossmann et al., 2012). Klieger-Grossmann et al. (2012) also reported that the risk of low birth weight with maternal use of escitalopram was significantly higher than other antidepressants. The difference in mean birth weight between escitalopram and other antidepressants was 370 g. The mean birth weight in newborns exposed to fluoxetine was reported to be 160 g lower when compared to controls (Chambers et al., 1996). Other authors have reported that compared to the control non-exposed groups, the mean birth weight was lower by 180 g in paroxetine group and 100 g in citalopram group (Grigoriadis et al., 2018; Tucker & McGuire, 2004).

**3. Spontaneous Abortion**

The spontaneous termination pregnancy is an accepted definition of spontaneous abortion (Yonkers et al., 2014). Epidemiological studies indicate that spontaneous abortion is observed in 6-11% of pregnant womenin the general population (Hemels et al., 2005; Kjaersgaard et al., 2013). Its occurrence is particularly frequent secondary to congenital malformations. Therefore, spontaneous abortion is considered as one of the important indicators of embryotoxic effects of medications (Ellfolk & Malm, 2010).

The prevalence rate of spontaneous abortion in pregnant women exposed to specific SSRIs were reported as follows: 10-11.8% with fluoxetine, 11% with citalopram, 15% with

escitalopram, and 9.1% with paroxetine (Chambers et al., 1996; Diav-Citrin et al., 2008; Klieger-Grossmann et al., 2012; Sivojelezova et al., 2005). In a study by Diav-Citrin et al. (Diav-Citrin et al., 2008), the risk for fluoxetine (but not paroxetine) was significantly higher compared to the controls. On the other hand, Nakhai-Pour et al. (Nakhai-Pour et al., 2010) found that significantly elevated risk of spontaneous abortion was associated with paroxetine (n=84, odds ratio = 1.75) but not fluoxetine (n=22, odds ratio = 1.44), citalopram (n=19, odds ratio = 1.55), sertraline (n=28, odds ratio = 1.33) and fluvoxamine (n=5, odds ratio = 2.19); although the sample size was small in the study. Using a sample of 22,061 pregnancies exposed to antidepressants, Kjaersgaard et al. (2013) study reported that no individual SSRI could be related to spontaneous abortion. The risk ratios reported by these authors were 1.04 for fluoxetine, 1.43 for citalopram, 1.45 for paroxetine, 1.16 for sertraline and 1.65 for escitalopram, when compared to non-exposed women. The authors also analyzed the risk ratio in those patients with a diagnosis of depression and reported that the risk ratio for each of the SSRIs above was reduced around 1.00.

### 4. Persistent Pulmonary Hypertension

Persistent pulmonary hypertension in the newborn is characterized by elevated pulmonary vascular resistance that causes hypoxemia (Sharma et al., 2015). Its incidence rate is reported to be 1.8/1000 live births (Masarwa et al., 2019). Persistent pulmonary hypertension can lead to severe hypoxemia, cardio-pulmonary instability and mortality (Sharma et al., 2015; Yonkers et al., 2014). Asphyxia and meconium aspiration are the most common causes for persistent pulmonary hypertension. Premature birth, smoking, obesity, septicemia and cardiac malformation are the other risk factors (Occhiogrosso et al., 2012; Sharma et al., 2015; Yonkers et al., 2014). However, recent meta-analyses have suggested that maternal use of SSRI antidepressants during pregnancy is associated with an increased likelihood of persistent pulmonary hypertension in newborns (Grigoriadis et al., 2014; Masarwa et al., 2019; Ng et al., 2019).

Persistent pulmonary hypertension was reported to be observed in 0.35-1.9% of newborns exposed to sertraline in-utero. This prevalence rate was 0.39-1.1% for paroxetine, 0.27-0.8% for fluoxetine, 0.33% for citalopram and 0.18% for escitalopram (Chambers et al., 2006; Kieler et al., 2012). Källén and Olausson (2008) noted that while 15% of the patients used fluoxetine, 4 (36.4%) of 11 women who had infants with persistent pulmonary hypertension reported an exposure to fluoxetine during pregnancy. In this study, the use of paroxetine, sertraline and citalopram had similar weight in the study sample and in the patients whose infants had persistent pulmonary hypertension. A single published meta-analysis has reported pairwise comparison of individual SSRI antidepressants. Masarwa et al. (2019) reported that among SSRIs, sertraline was found most likely to have lowest risk for persistent pulmonary hypertension. When pairwise comparsions were considered, fluoxetine appeared to have a higher odds ratio compared to paroxetine, sertraline and escitalopram. Additionally, the odds ratio was lower for escitalopram than citalopram.

### 5. Autism Spectrum Disorders

Autism spectrum disorders are neurodevelopmental conditions that can cause persistent and severe impairment in soocial communication and interactions (Baxter et al., 2015; Modabbernia

et al., 2017). Autism spectrum disorders are observed in 7.6 per 1000 individuals and is associated with physical, mental, functional and other neurodevelopmental disorders (Baxter et al., 2015; Lord et al., 2018). Advanced maternal age, preterm birth, low birth weight, maternal infections, meconium aspiration and maternal diabetes are some of the risk factors for autism spectrum disorders (Lord et al., 2018; Modabbernia et al., 2017). In addition, it has been suggested that maternal use of SSRI antidepressants during pregnancy may increase the risk of autism spectrum disorders in the offspring (Andalib et al., 2017; Kaplan et al., 2016; Man et al., 2015).

Results of studies analyzing the effects of specific SSRIs on the risk of autism spectrum disorders are mixed. Victorin et al. (2017) reported that the risk of autism spectrum disorders in children of mothers using citalopram and escitalopram during their pregnancy was significantly higher compared to children of mothers who did not use these drugs (prevalence rate: 2.6%, relative risk =1.71). However, this risk did not retain statistical significance when maternal depression or anxiety disorders were considered. On the other hand, Brown et al. (2017) noted a lower hazard ratio of 1.76 for citalopram compared to other SSRIs (reported hazard ratios were 2.93 for fluoxetine, 2.48 for sertraline and 2.12 for paroxetine). In a study by Bérard et al. (2016), the hazard ratio for autism spectrum disorders was highest with the use of fluvoxamine (7.30) and fluoxetine (4.99) and lowest with sertraline (0.45). The hazard ratios for citalopram and paroxetine reported by these authors were 2.23 and 1.99, respectively. A recent meta-analysis (Halvorsen et al., 2019) that included data from Viktorin et al. (2017) and Brown et al. (2017) has demonstrated that maternal use of citalopram but not fluoxetine, sertraline and paroxetine, during pregnancy were associated with elevated risk of autism spectrum disorders in children. However, this meta-analysis included results of inverse probability of treatment-weighted analysis instead of crude analysis from by Brown et al. (Brown et al., 2017). The inverse probability of treatment-weighted analysis revealed very lower hazard ratios for paroxetine and fluoxetine compared to the crude analysis, which may have affected results of the meta-analysis by Halvorsen et al. (Halvorsen et al., 2019).

### 6. Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder is a neurodevelopmental disorder that affects 7.2% of children (Thomas et al., 2015). Genetic, biological and environmental factors such as low birth weight, smoking during pregnancy, exposure to alcohol in utero, infections, maternal stress and drug use during pregnancy play a role in its pathogenesis (Biederman, 2005; Sciberras et al., 2017). The avaliable evidence suggests that antenatal use of SSRI antidepressants by the mother increased the risk of attention-deficit/hyperactivity disorder in children by 1.33-1.50 folds (Halvorsen et al., 2019; Jiang et al., 2018). However, to date, no study examining the effect of use of specific SSRIs by the mother on attention-deficit/hyperactivity disorder in the child has been published in the literature (Uguz, 2018).

### 7. Poor Neonatal Adaptation Syndrome

Poor neonatal adaptation syndrome is seen in newborns following prolonged in utero exposure to drugs (Klinger & Merlob, 2008). The prevalence of this syndrome in newborns exposed and unexposed to SSRIs is about 30% and 5%, respectively (Kieviet et al., 2013; Lattimore et al., 2005). The etiology is unclear; however, a role of withdrawal or toxicity of the drugs in the

symtoms of this syndrome has been suggested. (Kieviet et al., 2013). Poor neonatal adaptation syndrome consists of central nervous system (e.g., restlessness, tremor, sleep disturbances, lethargy, agitation, weak cry, weak sucking and hypertonicity/hypotonicity), autonomic (e.g., temperature instability and excessive sweating), respiratory (tachypnea, dyspnea) and gastrointestinal (e.g., vomiting, diarrhea and feeding problems) symptoms (Kieviet et al., 2013; Klinger & Merlob, 2008). Poor neonatal adaptation syndrome is generally mild, of short duration, self-limiting without treatment, and rarely needs admission to a neonatal care unit (Kieviet et al., 2013).

Two meta-analyses reported a 4 - 5-fold increased risk of poor neonatal adaptation syndrome in newborns of women who were prescribed serotonergic antidepressants (Grigoriadis et al., 2013a; Lattimore et al., 2005). Poor neonatal adapdation syndrome was reported in 17.2-31.5 % of infants with exposure to fluoxetine and 20.4 % of infants with exposure to paroxetine (Chambers et al., 1996; Diav-Citrin et al., 2008). In a retrospective cohort study, it was reported that infants antenatally exposed to citalopram, sertraline and fluoxetine had similar prevalence rates of poor neonatal adaptation syndrome (Forsberg et al., 2014). On the other hand, Sanz et al. (2005) reported that out of 93 cases of SSRI-induced neonatal withdrawal syndrome, 64 were associated with paroxetine, 14 with fluoxetine, 9 with sertraline and 7 with citalopram. The authors concluded that paroxetine might have an elevated risk of neonatal withdrawal syndrome compared to other SSRIs.

## DISCUSSION

Principal factors in pharmacological treatment of psychiatric disorders during the perinatal period are efficacy and safety of the psychotropic drugs. The efficacy of a particular drug in the psychiatric disorder specific to the patient can retrieved from her history. However, if the patient experiences the symptoms during pregnancy, safety data on medications obtained from the literature are important. On the other hand, similar to non-perinatal patients, it is expected that clinical improvement in symptoms and adverse events secondary to the use of each antidepressant may vary between pregnant patients. Moreover, clinical features of psychiatric conditions such as severity, comorbidity, impairment in social, occupational and family relationship are not equal in all patients. It has been suggested that psychiatric conditions are associated with increased risk of preterm birth, low birth weight in infants, as wellas autism spectrum disorders and attention-deficit/hyperactivity disorder in children (Grigoriadis et al., 2018; Grigoriadis et al., 2013b; Grote et al., 2010; Kaplan et al., 2017; Man et al., 2018). Therefore, an individualized risk-benefit evaluation should be carried out prior to a decision on which medication will be administered (Cuomo et al., 2018).

According to the limited number of available studies, the prevalence rate of preterm birth in women using paroxetine appears to be slightly higher compared to fluoxetine, citalopram and escitalopram; however, comparative studies and meta-analyses revealed that difference between these SSRIs did not reach statistical significance. Current evidence suggests that among SSRIs maternal use of escitalopram is associated with the highest risk of low birth weight, although the reported prevalence rate is similar to the general population. No published study to date has examined the effects of sertraline and fluvoxamine on the risk of low birth weight. There is also no clear evidence suggesting a statistically significant elevated risk of the

use of an individual SSRI with spontaneous abortion. Nevertheless, two studies (Kjaersgaard et al., 2013; Nakhai-Pour et al., 2010) imply that compared to exposure to sertraline or fluoxetine, risk ratio/odds ratio for spontaneous abortion appear to be slightly higher in women using paroxetine or citalopram/escitalopram. Both studies, however, lack statistical comparative analysis. The available data suggest that the risk of persistent pulmonary hypertension may be lowest with sertraline and highest with fluoxetine. Although current study results regarding the risk of autism spectrum disorders with maternal use of individual SSRIs are controversial, relatively consistent results imply that sertraline and paroxetine to be slightly safer than other SSRIs. Lack of published studies prevents any firm comment on the risk of attention-deficit/hyperactivity disorder in children with maternal antenatal use of individual SSRIs Finally, based on the current evidence, paroxetine and fluoxetine may be more disadvantaged SSRIs with regard to poor neonatal adapdation syndrome in newborns. Overall, lowest risk of negative outcomes appears to be associated with sertraline while the highest risk is associated with fluoxetine. If these comments are confirmed by further studies, SSRIs with relatively higher risk than the others should be used with caution and at the lowest possible dose.

Ideally, studies on the safety of SSRIs in pregnant women should have a prospective controlled observational design that includes treated and non-treated patient groups who have matched diagnosis and severity of depression and anxiety disorders. However, such a desing has ethical and legal difficulties. This dilemma is an important reason why current scientific evidence is mostly based on electronic health registry databases and retrospective studies. The available studies are insufficient in completely excluding the effects of maternal depression and anxiety disorders, although some authors have considered them as confounders in their analyses. Data from several studies related to autism spectrum disorders (Viktorin et al., 2017) and spontaneous abortion (Kjaersgaard et al., 2013) suggest the importance of underlying maternal depression. Population based register database studies have relatively large samples of individual antidepressants, although the data on how many women took the medication as prescribed is unclear. However, these studies mostly include data on classes of antidepressant rather than individual drugs (Grigoriadis et al., 2013c). Additionally, most available studies do not assess the possible effects of the daily dose of antidepressants used. The range of therapeutic daily dose of antidepressants may vary by 4-fold, which can thereotically cause greater fetal exposure. Several studies have suggested that high daily dose of SSRIs can dramatically increase the risk of preterm birth (Roca et al., 2011; Suri et al., 2007). The relationship between other neonatal outcomes and dosing is unclear (Uguz, 2016). In addition to these limitations, the paucity of studies investigating effects of individual SSRIs on neonatal and childhood outcomes is another problem in interpreting the results. Current meta-analyses including individual SSRIs are based on very few studies. Nevertheless, the availability of studies with relatively large sample size and a prospective observational design is a considerable advantage (Diav-Citrin et al., 2008; Klieger-Grossmann et al., 2012; Sivojelezova et al., 2009).

## CONCLUSION

Owing to small number of studies with relatively small sample sizes and methodological limitations, the available scientific evidence is inadequate to convincingly determine which individual SSRI used in pregnancy has greater increased risk of neonatal or childhood outcomes

compared to others. Despite the limitations, the current review concludes that individual SSRIs which are slightly more disadvantaged than others for each outcome are as follows: paroxetine for preterm birth, escitalopram for low birth weight, sertraline and fluoxetine for spontaneous abortion, fluoxetine for persistent pulmonary hypertension, citalopram/escitalopram, fluoxetine and fluvoxamine for autism spectrum disorders, and fluoxetine and paroxetine for poor neonatal adapdation syndrome. However, multicenter comparative studies with large sample sizes that include data on the use of individual SSRIs are urgently needed to reach reliable and definitive conclusions for clinicians.

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