

## Safety profile between fluoxetine and sertraline as antidepressants for pregnant women with depression disorder

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### ABSTRACT

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Depression disorders are common in women of productive age, especially during pregnancy and peripartum period. Making a decision on the choosing of antidepressants is associated to the biggest concern about the risk of birth defects and major anomalies of their exposure. Decisions of antidepressant use not only involve considering the risks of medications exposure, but also the risks of untreated depression during pregnancy. Evaluation of the safety profile of selective reuptake inhibitors (SSRIs) which are commonly prescribed during pregnancy therefore urgently needed. This review aimed to compare two widely used SSRIs i.e. fluoxetine and sertraline as antidepressants for pregnant women with depression disorder. It is found that sertraline has more positive effects and more safe. Sertraline is well tolerated in pregnant women and breastfeeding mothers with depression disorder.

### ABSTRAK

Gangguan depresi sering terjadi pada wanita usia produktif, terutama pada masa kehamilan dan peripartum. Pengambilan keputusan untuk memilih antidepresan adalah berkaitan dengan kekhawatiran terbesar tentang risiko cacat lahir dan anomali utama paparanya. Keputusan penggunaan antidepresan tidak hanya mempertimbangkan risiko paparan obat, tetapi juga risiko depresi yang tidak diobati selama kehamilan. Evaluasi profil keamanan inhibitor reuptake selektif (SSRI) yang umumnya diresepkan selama kehamilan oleh karena itu sangat dibutuhkan. Review ini bertujuan untuk membandingkan dua SSRI yang banyak digunakan yaitu fluoxetine dan sertraline sebagai antidepresan untuk ibu hamil dengan gangguan depresi. Dilaporkan bahwa sertraline memiliki lebih banyak efek positif dan lebih aman. Sertraline ditoleransi dengan baik pada wanita hamil dan ibu menyusui dengan gangguan depresi.

## INTRODUCTION

Pregnant women commonly have complications like depression during pregnancy.<sup>1</sup> The prevalence of depression among late pregnancy women in China between the ages 25 and 29 years is 9.2%.<sup>2</sup> Some risk factors like artificial insemination, no exercise during pregnancy, low-self efficacy, poor sleep quality, anxiety symptoms,

and normal relationship with her mother-in-law give some influence in the risk of depression.<sup>2</sup> The symptoms of depression in pregnant women are having a lasting sad, anxious, or 'empty'; feeling of hopelessness or pessimism; feeling of guilt; worthlessness or helplessness; feeling of irritability or restlessness; loss of energy; concentration problem; difficult to sleep or sleeping too much; loss of appetite; suicidal thoughts; and

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aches or pains that do not get better by treatment.<sup>3</sup>

Some severe conditions of depression need antipsychotic relieve the symptoms. However, pregnant women with depression without treatment may have serious effects, not only to the mother, but also to the baby. Inadequate maternal weight gain, substance abuse, pre-eclampsia, preterm birth, low birth weight, fetal distress, increased risk of cesarean birth, increased risk of NICU admission are reported in pregnant women with depression without treatment.<sup>4</sup>

The antipsychotic drugs commonly used in treatment of depression are monoamine oxidase inhibitors (MAOI), tricyclic antidepressants (TCA), and selective serotonin reuptake inhibitors (SSRI). The most common prescriptions for pregnant women were sertraline (3.3%), bupropion (2.7%), citalopram (2.6%), escitalopram (2.5%), and fluoxetine (2.3%).<sup>4</sup> In Indonesia, two of SSRI are covered as antidepressants by Health Care and Security Agency i.e. sertraline and fluoxetine.<sup>5</sup> Sertraline and fluoxetine are more commonly

prescribed than other antidepressant drugs especially in pregnant women, because they have lower risk and are more preferred for pregnant women and also available in the market.<sup>5,6</sup> This review aimed to compare the safety profile between fluoxetine and sertraline as antidepressants for pregnant women with depression disorder.

### **MATERIAL DAN METHODS**

In this review, literature study as a method using various search engines was used. Keywords based on the PICO method with a publication range of 1996-2021 such as “antidepressants”, “depression disorder”, “pregnancy”, “breastfeeding”, “fluoxetine” and “sertraline” was used. Inclusion criteria as Randomized Controlled Trial, systematic review, retrospective cohort study, depression in pregnancy and/or lactation, use anti depression drugs there are sertraline and/or fluoxetine was established. Meanwhile, complications and use anti depression drugs other than sertraline and/or fluoxetine as exclusion criteria was used.

**TABLE 1. PICO Formulation**

Question part	Question Term
Population	Pregnant and/or Breastfeeding Women with Depression Disorder
Intervention	Fluoxetine
Comparison	Sertraline
Outcome	Safety profile

### **RESULTS**

A total of 175 articles was found and collected. The articles were then screened by applying inclusion criteria and found 38 articles with 20 articles

included in exclusion criteria. Therefore, 18 articles were analyzed as final references (TABLE 2). As for cause of exclusion are duplication references, articles can not be opened and not in the form of research or full articles.

TABLE 2. Comparison of pregnancy outcome between various literatures

Authors	Title of article	Conclusion (safety)		Conclusion
		Sertraline	Fluoxetine	
Gao, <i>et al.</i> <sup>16</sup>	Selective serotonin reuptake inhibitor use during early pregnancy and congenital malformations: a systematic review and metaanalysis of cohort studies of more than 9 million births	In nine studies show that the risk of major congenital anomalies in infants was RR 1.10 (95% CI: 0.99-1.22, I2 = 0; p= 0.69) and the risk of congenital heart defect was RR 1.42 (95% CI: 1.12-1.80; I2 = 63.9%; p= 0.001)	In eleven studies show that the risk of major congenital anomalies in infants was RR 1.17 (95% CI: 1.07-1.28, I2 = 0; p= 0.50) and the risk of congenital heart defects was RR 1.30 (95% CI: 1.12=1.53; I2 =29.3%; p=0.14).	The use of fluoxetine has a higher risk of major congenital anomalies in infants than Sertraline. But fluoxetine has lower risk of congenital heart defect than sertraline in infants with mothers history drugs used at early pregnancy.
Myles <i>et al.</i> <sup>15</sup>	Systemic meta-analysis of individual selective serotonin reuptake inhibitor medications and congenital malformations	Sertraline has lower risk of cardiac malformation in infants than other SSRIs (RR 0.93; 95% CI: 0.70-1.24)	Fluoxetine has high risk of major malformation in infants (RR=1.22; 95% CI: 1.01-1.04), and high risk of cardiac malformation (RR=1.25; 95% CI: 0.98-1.60)	Sertraline used in pregnant women has lower risk of cardiac malformation in infants than other SSRIs. Fluoxetine should be avoided in the first trimester, because it can induce major malformation in infants.
Kallen, <i>et al.</i> <sup>12</sup>	Maternal use of selective serotonin reuptake inhibitors in early pregnancy and infant congenital malformations	Risk of congenital malformation among infants whose mothers use sertraline in early pregnancy is 3.5%.	Risk of congenital malformation among infants whose mothers use fluoxetine in early pregnancy is 3.8%.	Risk of congenital malformation among infants whose mother used fluoxetine in early pregnancy is higher than sertraline.
Malm, <i>et al.</i> <sup>13</sup>	Selective serotonin reuptake inhibitors and risk for major congenital anomalies	Prevalence of major congenital anomalies in sertraline therapy during pregnancy is 457 of 10,000 [OR:1.26 (0.93-1.45)]	Prevalence of major congenital anomalies in sertraline therapy during pregnancy is 414 of 10,000 [OR:1.00 (0.71-1.39)]	Sertraline therapy during pregnancy has a lower risk of congenital anomalies than fluoxetine.
Reefhuis, <i>et al.</i> <sup>9</sup>	Specific ssris and birth defects: bayesian analysis to interpret new data in the context of previous reports	Sertraline treatment in pregnancy causes not significant birth defects (anencephaly, septal defects, anal atresia, any limb reduction, and omphalocele)	Fluoxetine treatment in pregnancy causes birth defects (ventricular septal defects, heart defects, right ventricular outflow tract obstruction, and craniosynostosis)	Fluoxetine treatment causes more significant birth defects in pregnancy than sertraline treatment.
Chambers <i>et al.</i> <sup>10</sup>	Birth outcomes in pregnant women taking fluoxetine	-	Exposure of fluoxetine during pregnancy in the first trimester was not associated with major fetal anomalies or risk of pregnancy loss, but in the third trimester exposure of fluoxetine can increase risk of complications in perinatal.	Exposure of fluoxetine during pregnancy in the first trimester was not associated with major fetal anomalies or risk of pregnancy loss, but in the third trimester exposure of fluoxetine can increase risk of complications in perinatal.

TABLE 2. Comparison of pregnancy outcome between various literatures (cont. )

Authors	Title of article	Conclusion (safety)		Conclusion
		Sertraline	Fluoxetine	
Nulman <i>et al.</i> <sup>23</sup>	Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study	-	Fluoxetine in pregnancy does not give effect in cognition, language development, or the temperament of preschool and early-school children	Fluoxetine in pregnancy does not give effect in cognition, language development, or the temperament of preschool and early-school children.
Riggin <i>et al.</i> <sup>11</sup>	The fetal safety of fluoxetine: a systematic review and meta-analysis	-	Women who take fluoxetine in the first trimester of pregnancy do not have increased risk of major fetal malformations.	Women who take fluoxetine in the first trimester of pregnancy do not have increased risk of major fetal malformations.
Long <i>et al.</i> <sup>24</sup>	Fetal exposure to sertraline hydrochloride impairs pancreatic $\beta$ -cell development	Use of sertraline can reduce $\beta$ -cell capacity at birth which can increase the incidence of metabolic disorders.	-	Use of sertraline can reduce $\beta$ -cell capacity at birth which can increase the incidence of metabolic disorders.
Heinonen <i>et al.</i> <sup>14</sup>	Sertraline concentrations in pregnant women are steady and the drug transfer to their infants is low	Transfer of sertraline plasma concentrations in infants from placenta is low and lowers the risk of severe withdrawal symptoms at birth.	-	Transfer of sertraline plasma concentrations in infants from placenta is low and lowers the risk of severe withdrawal symptoms at birth.
Berard <i>et al.</i> <sup>25</sup>	Sertraline use during pregnancy and the risk of major malformations	Use of sertraline in the first trimester of pregnancy appears to increase risk of atrial or ventricular defects and craniosynostosis.	-	Use of sertraline in the first trimester of pregnancy appears to increase risk of atrial or ventricular defects and craniosynostosis.
Shen <i>et al.</i> <sup>26</sup>	Sertraline use in the first trimester and risk of Congenital anomalies: a systemic review and Meta-analysis of cohort studies	Infants were at increased risk of cardiovascular-related malformations such as atrial and/or ventricular septal defects from maternal exposure in sertraline at first trimester.	-	Infants were at increased risk of cardiovascular-related malformations such as atrial and/or ventricular septal defects from maternal exposure in sertraline at first trimester.

TABLE 2. Comparison of pregnancy outcome between various literatures (cont.)

Authors	Title of article	Conclusion (safety)		Conclusion
		Sertraline	Fluoxetine	
Fumeaux <i>et al.</i> <sup>27</sup>	Risk-benefit balance assessment of ssri antidepressant use during pregnancy and lactation based on best available evidence: an update	Relative dose ingested by the child, n = 50: 0.5% (0.2-2.4%). Relative plasma concentration in the breastfed child, n = 50: 2% (0-15%). Reported effects in the breastfed child, n=100: diarrhea (n=1), decreased sleep and restlessness (n=6), normal weight gain (n=25); impaired response to pain (n=4); risk and causality not assessable. Relevant pharmacokinetic parameters, adult average half life: 22 - 36h metabolites with poor activity	Relative dose ingested by the child, n = 50 is 6% (1-12%), included active metabolite. Relative plasma concentration in the breastfed child, n = 50: 7% (0-10%) (included active metabolite). Reported effects in the breastfed child, n= 150: irritability (n=1), hyperglycaemia, and glycosuria (n=1), impaired response to pain (n=7); seizure (1; co-medication bupropion and carbamazepine) normal weight gain (n=60); normal developmental milestones (n=58); risk and causality not assessable. Relevant pharmacokinetic parameters, adult average half life: 4-6d fluoxetine and 4-16d active metabolite with good activity.	Fluoxetine and sertraline both have side effects in children who are breastfed, but the reported cases show that the ingested dose in children and the relative plasma concentrations in children who are breastfed on fluoxetine are higher than sertraline so that the risk of side effects caused by fluoxetine is higher than sertraline.
Pedersen, <i>et al.</i> <sup>17</sup>	Selective serotonin reuptake inhibitors in pregnancy and Congenital malformations: population based cohort study	Sertraline treatment for depression disorder in early pregnancy causes 1.9% cardiac malformation and 1.5% septal heart defect among children.	Fluoxetine treatment for depression disorder in early pregnancy causes 0.6% cardiac malformation and 0.6% septal heart defect among children.	Fluoxetine treatment has a lower risk of birth defect than sertraline treatment in early pregnancy women.
Schoretsanitis <i>et al.</i> <sup>18</sup>	The impact of pregnancy on the pharmacokinetics of antidepressants: a systematic critical review and metaanalysis	Pregnant women who used Sertraline has higher concentrations of the drug in the third trimester than baseline	Pregnant women who used Fluoxetine daily dose of 20 mg/day has lower concentrations of the drug in the third trimester than baseline	Fluoxetine shows a prominent decrease in dose-adjusted levels in the 3rd trimester, and the changes are considered negligible. For sertraline, there was a tendency towards increased dose-adjusted concentrations in pregnancy.

TABLE 2. Comparison of pregnancy outcome between various literatures (cont.)

Authors	Title of article	Conclusion (safety)		Conclusion
		Sertraline	Fluoxetine	
Field <sup>21</sup>	Breastfeeding and antidepressants	Concentrations of sertraline are not detectable in breast milk and currently considered as the antidepressants drug of choice for pregnancy.	Fluoxetine has relatively higher concentrations and do have detectable levels in breastmilk.	Sertraline should be considered as drugs of choice because of the not detectable concentrations in breast milk means the usage of fluoxetine will give few adverse effects in infants.
Sriraman, <i>et al.</i> <sup>22</sup>	Use of antidepressants in breastfeeding mothers	Although most SSRIs have been detected in breastmilk, sertraline usage is not exceeded the recommendation 10% of maternal level and usually undetectable in infant serum.	Use of fluoxetine in breastfeeding has exceeded the 10% of maternal level and increased adverse events in infants.	Sertraline is the most likely antidepressant to be prescribed with low to undetectable effects in breastmilk and offers a relatively safe profile in infants.
Westin, <i>et al.</i> <sup>19</sup>	Selective serotonin reuptake inhibitor and venlafaxine in pregnancy: changes in drug disposition.	Sertraline has higher plasma concentration than baseline in third trimester pregnancy (+68%; CI, +37%, +106%; p<0.001)	Fluoxetine has lower plasma concentration than baseline in third trimester pregnancy (-13%; CI, -36%, +19%)	Sertraline has higher plasma concentration in third trimester pregnancy, while fluoxetine concentration did not change significantly.

**DISCUSSION**

Risk of depression disorder elevated in women with reproductive age and associated with high risk of morbidity and mortality. Pregnancy is one of many conditions that can cause depression, therefore women should be screened for depression during pregnancy and perinatal period. Untreated depression disorders can have harmful effects on both the mother and the baby. However, the use of antidepressants during pregnancy can cause various side effects on mothers and development of the infants. Information concerning the safety of antidepressants therefore are important in order to give appropriate interventions.

**Antidepressants in pregnant women**

Current guidelines recommend use of antidepressants as treatment options for depression disorder cases

in pregnancy. The most widely used antidepressant in pregnancy is SSRIs. Numerous comparative studies have shown differences from various points of view between the most commonly prescribed SSRIs in pregnancy, including fluoxetine and sertraline.

Safety is a very important factor in the choice of antidepressant SSRI especially in pregnancy. That is because SSRI has several adverse effects that can happen in mothers and fetuses. Both sertraline and fluoxetine have been included in the pregnancy category C. Comparison of pregnancy outcome between various literatures is presented in TABLE 2.

*Pharmacokinetic*

Pregnant women experience many physiological changes during pregnancy and the changes can affect pharmacokinetic of some drug included 1). Gastric emptying during pregnancy will delay and increase pH of gastric. It



affects the bioavailability of medicine after oral administration. 2). Cardiac output during pregnancy will increase. It can increase hepatic blood flow and increase elimination for some drugs. 3). Total body water will increase during pregnancy. It affects the disposition of hydrophilic drugs. 4). Fat compartment will increase and affect the disposition of lipophilic drugs. 5). Renal blood flow and glomerular filtration rate will increase, and it can cause increased renal clearance during pregnancy. That is associated with increased elimination of drugs. 6). Concentration of plasma albumin will decrease during pregnancy. It can increase free fraction concentration of drugs. 7). Activity of CYP450 and UGT in hepar will change during pregnancy and it can affect the oral bioavailability and hepatic elimination of some drugs.<sup>7</sup>

These physiological changes must be considered in the selection of therapy and drug dosage in patients during pregnancy. Antidepressant SSRIs, especially sertraline and fluoxetine, were affected by physiological changes during pregnancy and can cross the placenta of the fetus. Sertraline may be exposed to the fetus estimated 29-73% in parent drug and 29-63% in drug metabolite. The estimate of exposure to fluoxetine parent drug and metabolite drug is 58-73% and 63-71%.<sup>8</sup> Both transfer placenta percentage is very large from mother to fetus. According to this percentage, the consumption of sertraline or fluoxetine in pregnancy could affect the fetus, one of them is birth defect.

#### *Risk of birth defect*

Some case controls have been discussed about the risk of birth defects caused by fluoxetine and sertraline. Reefhuis *et al.*,<sup>9</sup> reported that fluoxetine treatment causes more significant birth defects in pregnancy than sertraline treatment. Several birth defect caused by sertraline such as anencephaly, septal defects, anal atresia, any limb reduction, and omphalocele. Meanwhile, birth

defects that can occur by consumption of fluoxetine are ventricular septal defects, heart defects, right ventricular outflow tract obstruction, and craniosynostosis.<sup>9</sup>

Some studies show safety in women who take fluoxetine during pregnancy and were not associated with increased risk of spontaneous pregnancy loss and major fetal anomalies in the first trimester of pregnancy.<sup>10,11</sup> A few studies about fluoxetine and sertraline shows that women who are treated with fluoxetine during pregnancy have an increased risk of congenital malformation among infants in early pregnancy is higher than sertraline.<sup>12,13</sup>

The finding of safety from sertraline is consistent with the results that transfer of sertraline plasma concentrations in the fetus from placenta is low and lowers the risk of severe withdrawal symptoms at birth.<sup>14</sup> This results in line with results from other meta-analysis study that shows sertraline used in pregnant women has lower risk of cardiac malformation in infants than other SSRIs<sup>15</sup> and sertraline therapy during pregnancy has a lower risk of congenital anomalies than fluoxetine.<sup>13,16</sup>

In contrast, a cohort study reported that fluoxetine treatment has a lower risk of birth defect than sertraline treatment in early pregnancy women.<sup>17</sup> In a meta-analysis, Schoretsanitis *et al.*,<sup>18</sup> reported that the plasma concentration of sertraline in third trimester pregnancy is higher than fluoxetine, which can occur because of changes in physiology of pregnant women. Westin *et al.*,<sup>19</sup> reported that sertraline has significantly higher serum concentration than baseline in third trimester pregnancy (+68%; CI, +37%, +106%;  $p < 0.001$ ), while fluoxetine concentration did not change significantly. Sertraline plasma concentrations are known to be altered and extensively catalyzed by CYP2C19 and its variation. This activity may result in altered drug exposure.<sup>20</sup>

Overall results from various studies in articles present that sertraline has been shown to be superior to fluoxetine

in terms of safety, especially about birth defects in pregnancy. Although the plasma concentration of sertraline is higher in pregnant women than fluoxetine, the amount transferred to the fetus by placenta in sertraline is lower than fluoxetine. Various studies support the statement that risk of birth defect of fetus is lower in sertraline therapy than fluoxetine therapy.

### **Antidepressants in breastfeeding women**

Breastfeeding women have an additional route of drug excretion during lactation, that is excretion through breast milk. The excretion of the drug as parent drug or their metabolite can be excreted into breast milk and then enter into infants. Both fluoxetine and sertraline have side effects in infants who are breastfed. A study found that the relative dose ingested of sertraline and fluoxetine by the infant are 0.5% and 6%. Furthermore, the relative plasma concentrations of sertraline and fluoxetine in the breastfed infant are 2% and 7%. That study shows the ingested dose in infants and the relative plasma concentrations in infants who are breastfed on fluoxetine are higher than sertraline, therefore the risk of side effects in infants caused by fluoxetine is higher than sertraline.<sup>18</sup> This statement is supported by two other studies, Field<sup>21</sup> and Sriraman *et al.*,<sup>22</sup> reported that the sertraline does not get the concentration in breast milk, but they found the concentration of fluoxetine relatively higher in breast milk than sertraline. From that various studies, we can indicate that sertraline therapy is more safe in breastfeeding women than fluoxetine therapy to treat depression disorder.

Management of depression during pregnancy must depend on consideration of risk and benefit for patients-safety. Severity of depression disorder should be used as basic guidance to choose

the right treatment so that therapeutic targets can be achieved. For mild and moderate depression cases, non-pharmacologic treatment is selectable, meanwhile severe depression can be treated with antidepressants.<sup>28</sup>

Although numerous research and studies analyses about effectiveness and safety of antidepressants were carried out, heterogeneity in results about usage of fluoxetine and sertraline during pregnancy still existed, so further studies to determine side effects and fetal safety is needed. The results of this literature review can become a little help in the analysis of risk-benefit and can help the clinician to make decisions about choosing the right treatment of antidepressants in pregnancy.

### **CONCLUSION**

In conclusion, sertraline may have more positive effects and more safe. Sertraline is well tolerated in pregnant women and breastfeeding mothers with depression disorder. For breastfeeding mothers, sertraline is the most likely antidepressant from SSRIs to be prescribed, because the low to undetectable concentrations in breastmilk and this indicate relative safety profile in infants. Therefore, sertraline can be recommended as an antidepressant in pregnancy and breastfeeding women to treat their depression disorder. The SSRIs especially fluoxetine and sertraline are most commonly prescribed antidepressants drugs and widely accepted as the first line treatment for depression disorder during pregnancy, thus we need for further studies to evaluate the potential effects, side effects and safety in usage.

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