SIDE EFFECTS OF ANTIDEPRESSANT DRUG USE DURING PREGNANCY *LITERATURE REVIEW*

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Abstract

Depression in pregnant women can affect morbidity and mortality in both the mother and baby. It is also one of the risk factors for autism, low birth weight, prematurity, and postpartum hemorrhage. Depression is common during pregnancy, as is the increased use of antidepressant drugs during pregnancy. The purpose of this study was to identify the side effects of using antidepressant drugs during pregnancy. The research method used is to use a literature study approach with 20 journal sources systematically reviewed which have been selected based on the criteria determined by the researcher. In the results of the study, it is known that there are several unwanted side effects from the use of antidepressant drugs during pregnancy. Its side effects include psychiatric disorders, hypertension, low birth weight, short gestational age, congenital malformations, speech/language disorders, Hirschsprung's Disease, epilepsy, autism, and postpartum hemorrhage. In conclusion, the side effects of using antidepressant drugs during pregnancy such as psychiatric disorders, hypertension, low birth weight, short gestational age, congenital malformations, speech/language disorders, Hirschsprung's Disease, epilepsy, autism, and postpartum hemorrhage are known to be caused by the mechanism of action of antidepressant drugs, capable of crossing the placenta, thereby affecting fetal brain development. High serotonin levels with decreased growth hormone levels and can have a negative impact on the growth of fetus.

Keywords: Antidepressants, Side Effects, Depression, Pregnancy

Introduction

Pregnancy by definition is a condition of woman's womb in which there is an embryo or fetus. Pregnancy begins at the time of conception until the birth of the fetus, and the duration of pregnancy from ovulation to parturition is estimated to be around 40 weeks. Normal gestation period usually lasts for 40 weeks or 128 days until delivery. UNICEF (United Nations Children's Fund) estimates that at least 130 million babies are born each year, with some reports in the last 10 years putting the figure at 136 million, but it is difficult to know exactly how many babies are

born globally, as there are several children who not listed. The population growth rate (LPP) in Indonesia is still relatively high because there are 4.2 to 4.8 million newborns every year. (Badan Pusat Statistik, 2018).

In some pregnant women, the transition period can cause stress or depression. Depression is an emotional condition that is usually characterized by feelings of extreme sadness, feelings of worthlessness, and guilt. This condition can result in a person withdrawing, unable to sleep, losing appetite, interest and activities. The condition of depression has a very negative impact on pregnant women and the fetus they contain, because depressed pregnant women often do not have the strength or desire to take care of themselves and their womb. If depressed pregnant women do not get treatment, it can lead to malnutrition and suicidal ideation (Ahmed, et al., 2017). Depression conditions during pregnancy are estimated to be experienced by 2 out of 10 pregnant women in the world, while in Indonesia around 7 out of 10 pregnant women, so this requires treatment to overcome depression. (Tyas, Ma'rifah, & Triana, 2016).

Depression is common during pregnancy, and the use of antidepressant drugs during pregnancy has steadily increased in the last 20 years (Berard, Zhao, & Odile, 2016). The CDC (The Center for Disease Control and Prevention) says there are about 39% of pregnant women who use antidepressants to treat depression during their pregnancy. A study was also conducted in Indonesia and it was found that 14 of 44 pregnant women used antidepressant drugs (Tahta & Santik, 2019).

Based on the description of the background above, it can be concluded that the depression experienced by the mother during pregnancy will have an impact on the condition of the mother and the fetus in her womb. The use of antidepressant drugs is also still controversial, because several studies have shown side effects caused by the use of antidepressant drugs during pregnancy. This side effect is very detrimental for pregnant women with depression who use antidepressant drugs. Researchers are interested in the side effects that can be caused by the use of antidepressants during pregnancy, so the researchers feel that this study deserves to be studied in a Systematic Literature Review to find out the side effects that can be caused by the use of antidepressant drugs during pregnancy..

Method

The research method used is a systematic literature review. The systematic literature review method is a form of research carried out through searching by reading various sources, namely books, journals, and publications related to the research topic, to answer existing issues or problems. Systematic literature review method is a term used to refer to a particular research

methodology or research and development carried out to collect and evaluate related research on a particular topic focus. (Triandini, Jayanatha, Indrawan, Putra, & Iswara, 2019).

The literature sources used in this study were searched through Google Scholar, and pubmed using the keywords pregnancy, depression, antidepressants, and side effects. In determining the keywords using the PICO (Problem/Population, Intervention, Comparison, and Outcome) method. The literature sources used in this study were searched through Google Scholar, and pubmed using the keywords such as pregnancy, depression, antidepressants, and side effects. In determining the keywords using the PICO (Problem/Population, Intervention, Comparison, and Outcome) method. The criteria for the study materials used in this study include:

a. Inclusion Criteria
   - The articles searched are similar to the research topic
   - Articles that explore all possible side effects
   - The articles searched are the most recent literature retrieved in the last 5 years between 2016 and 2021
   - Covers national and international articles
   - Match between keywords and literature results
   - Articles with full text

b. Exclusion Criteria
   - Paid articles
   - Research in the form of proposal

Table 1: Literature findings

Data Based	Findings	Selected Literature
Pubmed	90	16
Google Scholar	31	4
Total	121	20

Results and Discussion

The results of the review of articles that have been carried out using the Systematic Literature review method, the researchers know the side effects that can result from the use of antidepressant drugs during pregnancy.

Table 2: Journal Review Findings

Author (Year)	Language	Sources	Purposes	Research Methods	Findings	Recommendations
(Liu, et al., 2017)	English	Pubmed	Investigating the relationship between exposure to	Kohort	Results: Of 905,383 children, 21,063 (2.3%) were born to mothers who used antidepressants	The results of this study should be of concern to clinicians.

Author (Year)	Language	Sources	Purposes	Research Methods	Findings	Recommendations
			antidepressants during pregnancy and the risk of psychiatric disorders		during pregnancy. Descendants with mental disorders, namely: • 8.0% (95% confidence interval) for the unexposed group • 11.5% for the discontinuation group • 13.6% for the advanced group, and 14.5% for new user groups. Advanced group antidepressants had an increased risk of psychiatric disorders (hazard ratio 1.27, 1.17 to 1.38), compared to the discontinuation group.	Assessment of the benefits and risks of choosing therapy is necessary. Psychological and/or herbal therapy suggested by medical personnel can be considered according to individual conditions, to prevent unwanted side effects.
(Zakiyah, et al., 2018)	English	Pubmed	Assessing the relationship between use of antidepressants during pregnancy and the risk of developing gestational hypertension	Kohort	Results: From 28,020 samples, 539 (1.92%) used antidepressants and the risk of gestational hypertension was doubled (aOR 2.00 95% CI 1.28–3.13, p value 0.002). SSRIs subgroup (aOR 2.07 95% CI 1.25–3.44, p value 0.009). Antidepressant exposure 30 DDDs (defined daily dose) (aOR 2.50 95% CI 1.55–3.99, p value < 0.001) and maternal age 30-34 years (aOR 2.59 95% CI 1.35–4.98).	Risk benefit assessment in the selection of therapy is very necessary. Psychological and/or herbal therapy recommended by medical personnel needs to be considered according to individual conditions, to prevent unwanted side effects.
(Rai, et al., 2017)	English	Google Scholar	Studying the relationship between antidepressant use during pregnancy and autism spectrum disorder (ASD) in offspring.	Kohort	The results of the study of 3342 children exposed to antidepressants during pregnancy, 136 (4.1%) had a diagnosis of autism. Exposure to antidepressants during pregnancy had a higher probability of a diagnosis of autism in offspring, compared with no antidepressants (aOR 1.45, 95% confidence interval ranging from 1.13 to 1.85)..	Assessment of the benefits and risks of choosing therapy is necessary. Psychological and/or herbal therapy suggested by medical personnel can be considered according to individual conditions, to prevent unwanted side effects.

Author (Year)	Language	Sources	Purposes	Research Methods	Findings	Recommendations
(Sasaki, et al., 2019)	English	Google Scholar	Investigating the use of antidepressants during pregnancy may increase the risk of autism spectrum disorder (ASD) in the offspring	Kohort	The results of this study showed that the prevalence of ASD in children at the time of analysis adjusted for the confounding effect of maternal depression during pregnancy, statistical significance was lost (OR, 0.76; CI, 0.27, 2.18, p value 0.61). After adjustment for confounders, no significant association was found between antidepressant use during pregnancy and ASD in Japanese children..	Medical treatment of pregnant women with antidepressants improves both the mental state of the woman and the development of the child. Clarification of the risks and benefits of taking antidepressants during pregnancy is helpful for both the patient and the clinician.
(Sujan, et al., 2017)	English	Pubmed	Evaluating alternative hypotheses regarding the relationship between the first trimester antidepressant exposure with birth and neurodevelopmental problems.	Kohort	The results of this study showed that among 1,580,629 births, there were 22 544 (1.4%) mothers who used antidepressants in the first trimester and compared with unexposed offspring (preterm birth [aOR], 1.34 95% CI, 1, 18–1.52), short gestational age (aOR, 1.01 [95% CI, 0.81–1.25]), autism spectrum disorder (aHR, 0.83 [95% CI, 0.62–1 ,13]), or attention-deficit/hyperactivity disorder (aHR, 0.99 [95% CI, 0.79-1.25]). Among offspring, there is a slight risk of preterm birth.	Assessment of the benefits and risks of choosing therapy is necessary. Psychological and/or herbal therapy suggested by medical personnel can be considered according to individual conditions, to prevent unwanted side effects.
(Molenaar, et al., 2020)	English	Google Scholar	Checking whether there is an effect of doses of serotonin reuptake inhibitors (SSRIs) during pregnancy on birth outcomes	Kohort	This study has 145 samples. SSRI dose at 36 weeks gestation was associated with birth weight (aß = -180.7, 95% CI -301.1; -60.2, p-value <0.01) as was the mean standard SSRI dose during total gestation (aß = -187.3, 95% CI -322.0; -52.6, p-value < 0.01). High daily doses of SSRIs during pregnancy are associated with low birth weight (180-190 g reduction in birth weight per single dose equivalent	Hasil penelitian ini perlu menjadi perhatian bagi para klinisi untuk menyarankan penggunaan SSRI pada masa kehamilan. Penilaian benefit risiko pemilihan terapi sangat diperlukan. Terapi psikologi dan/atau herbal yang disarankan oleh tenaga medis bisa dipertimbangkan

Author (Year)	Language	Sources	Purposes	Research Methods	Findings	Recommendations
					increase). There is no significant relationship between SSRI dose and gestational age or it is unlikely to be able to observe gestational age.	sesuai kondisi individu, untuk mencegah efek samping yang tidak diinginkan.
(Henriksen, et al., 2017)	English	Pubmed	Mengatasi pembaur tingkat keluarga dan genetik bersama untuk menyelidiki efek paparan SSRI prenatal dan depresi ibu pada berat lahir dan usia kehamilan.	Kohort	The results of the study of 27,756. Prenatal SSRI exposure was associated with a reduction in birth weight of 205 g (95% CI -372 to -38) and a decrease in gestational length of 4.9 days (95% CI -9.1 to -1.4) after prenatal exposure to SSRIs in two or more trimesters. There is no association between SSRI use in one trimester.	Assessment of the benefits and risks of choosing therapy is necessary. Psychological and/or herbal therapy suggested by medical personnel can be considered according to individual conditions, to prevent unwanted side effects.
(Huybrechts, et al., 2020)	English	Pubmed	Evaluating the risk of harm to mother and baby after exposure to duloxetine during pregnancy.	Kohort	Research result: • exposed vs unexposed, the risk was 1.11 (95% CI, from 0.93 to 1.33) for congenital malformations and 1.29 (0.99 to 1.68) for cardiovascular malformations. • Premature risk 1.01 (0.92 to 1.10) for early exposure and 1.19 (1.04 to 1.37) for late exposure. • Gestational age at risk 1.14 (0.92 to 1.41) and 1.20 (0.83 to 1.72) for early and late pregnancy exposure, • Pre-eclampsia 1.12 (0.96 to 1.31) and 1.04 (0.80 to 1.35). • Risk of postpartum hemorrhage 1.53 (1.08-2.18). Duloxetine is not a major teratogen but may be associated with an increased risk of postpartum hemorrhage and a slightly increased risk of heart disease malformations.	Penilaian benefit risiko pemilihan terapi sangat diperlukan. Terapi psikologi dan/atau herbal yang disarankan oleh tenaga medis bisa dipertimbangkan sesuai kondisi individu, untuk mencegah efek samping yang tidak diinginkan.
(Man, et al., 2017)	English	Pubmed	Assessing the potential	Kohort	The results of the study were 190,618 children,	In other studies reported that there

Author (Year)	Language	Sources	Purposes	Research Methods	Findings	Recommendations
			relationship between Antidepressant use during pregnancy and the risk of attention deficit/hyperactivity disorder (ADHD) in offspring.		1,252 whose mothers during pregnancy used antidepressants. 5659 children (3.0%) were diagnosed with ADHD or received treatment for ADHD. The risk of ADHD in children of mothers with psychiatric disorders was higher than that of children of mothers without mental disorders even if the mothers had never received antidepressant therapy (1.84, 1.54 to 2.18, P < 0.01). There was no difference in the risk of ADHD in those exposed to antidepressants during pregnancy and those not exposed during pregnancy (0.54, 0.17 to 1.74, P = 0.30). This study found that mothers in the negative control group and mothers in the prenatal care group were at the same increased risk for having ADHD . offspring.	is an increased risk of ADHD due to the use of antidepressants during pregnancy, so this is still debated. Decision-making about the use of antidepressants in pregnancy is important and requires an assessment of the risks and benefits in the context of the individual woman and her family.
(Bérard, et al., 2017)	English	Pubmed	Determining the association between first-trimester antidepressant exposure and risk of major congenital malformations in the depression/anxious woman group.	Kohort	Research result: • Paroxetine risk of heart defects (aOR 1.45, 95% CI 1.12 to 1.88), and ventricular/atrial septal defects (aOR 1.39, 95% CI 1.00 to 1.93); • Citalopram risk of major congenital malformations (aOR 1.36, 95% CI 1.08 to 1.73; 88 cases exposed), risk of musculoskeletal defects (aOR 1.92, 95% CI 1.40 to 2.62), and craniosynostosis (aOR 3.95, 95% CI 2.08 to 7.52); • TCA of eye, ear, face, and neck defects (aOR 2.45, 95% CI 1.05 to 5.72), and digestive defects (aOR 2.55, 95% CI 1.40 to 4.66); and	Assessment of the benefits and risks of choosing therapy is necessary. Psychological and/or herbal therapy suggested by medical personnel can be considered according to individual conditions, to prevent unwanted side effects.

Author (Year)	Language	Sources	Purposes	Research Methods	Findings	Recommendations
					• • Respiratory distress venlafaxine (aOR 2.17, 95% CI 1.07 to 4.38).	
(Lupattelli, Wood, Lapane, Spigset, & Nordeng, 2017)	English	Pubmed	Describe the early and late risk of preeclampsia during pregnancy exposure to antidepressants and to evaluate the impact of time and duration of exposure to antidepressants on pregnancy, particularly selective serotonin reuptake inhibitors (SSRIs), in preeclampsia	Kohort	The results of the study of 5,887. SSRI exposure compared with no treatment in mid and late pregnancy had an adjusted RR for late-onset mild preeclampsia of 0.76 (95% CI, 0.38-1.53. There was no evidence that SSRI exposure in early or mid-pregnancy increased risk of late-onset preeclampsia.The small sample size precluded conducting a customized analysis and further exploring this potential association.	This information can help clinicians evaluate the risks of treatment with SSRIs compared to depression without treatment.
(Momen, et al., 2017)	English	Pubmed	Evaluating whether exposure to antidepressants during pregnancy increases the risk of cancer in childhood.	Kohort	The results of this study revealed that 21,488 (2.4%) used antidepressants during pregnancy and 28 children were diagnosed with cancer. During pregnancy or before not associated with cancer risk; HRs were 1.14 (95% CI, 0.83–1.57) and 1.15 (95% CI, 0.78–1.72), compared with unexposed children. When data were restricted to the 1.03 antidepressant group (95% CI, 0.63 to 1.68), compared with children born to mothers who stopped antidepressants before pregnancy. When analyzed in women with at least 2 antidepressant prescriptions during pregnancy, the results remained unchanged.	Based on this research it is known that the use of antidepressants during pregnancy is not associated with cancer in the offspring or if so, the effect is small, as well as on leukemia or tumors of the nervous system. An analysis with 2 prescription antidepressants during pregnancy was also carried out, and the results remained unchanged.
(Brown, et al., 2016)	English	Pubmed	Examine whether SRI exposure during pregnancy is	Kohort	The results of the study of 56,340 infants for speech / language disorders in offspring:	Assessment of the benefits and risks of choosing therapy is

Author (Year)	Language	Sources	Purposes	Research Methods	Findings	Recommendations
			associated with speech/language, scholastic, and motor impairment in offspring through early adolescence.		• SSRI-exposed and untreated groups, (HR, 1.20; 95% CI, 0.97-1.49; P=0.10). • 2 purchases of SSRIs in the SSRI-exposed group with the group not given medication and not exposed by adjusted analysis (2 purchases or more vs no drugs: HR, 1.37; 95% CI, 1.11-1.70; P= 0.004; 2 or more purchases vs not exposed: HR, 1.63; 95% CI, 1.37-2.01; P<0.001). There was a risk of motor impairment for children of mothers with 2 SSRI purchases compared to offspring in the unexposed group (HR, 1.39; 95% CI, 0.98-1.96; P=0.06). There were no significant differences in the risk of other disorders between offspring in the SSRI-exposed and non-drug groups. Offspring of mothers who used SSRIs twice during pregnancy were 37% more at risk of significant speech/language impairment compared to offspring in the no-treatment group. The cumulative hazard of speech/language impairment was 0.0087 in the SSRI-exposed group vs. 0.0061 in the untreated group.	necessary. Psychological and/or herbal therapy suggested by medical personnel can be considered according to individual conditions, to prevent unwanted side effects.
(Viktorin, Uher, Reichenberg, Levine, & Sandin, 2017)	English	Pubmed	Examined the association between use of antidepressant drugs during pregnancy and ASD in offspring, investigated antidepressant medication, and specific	Kohort	The results of this study showed 2379 children (1.3%) were born to mothers with a single antidepressant dispensation during pregnancy, and 3982 (2.2%) were born to mothers with two antidepressant dispensations during pregnancy. In children of	Judging from these findings, the risk of ASD in the offspring should not be a consideration for withholding treatment with commonly used antidepressant drugs from pregnant women,

Author (Year)	Language	Sources	Purposes	Research Methods	Findings	Recommendations
			antidepressant drugs.		mothers with two antidepressant dispensations with unexposed children the adjusted RR was 1.23 (95% CI 0.96–1.57). Analysis of children of mothers with at least one diagnosis of depression or anxiety and with two or more antidepressant dispensations during pregnancy with an adjusted RR of 1.07 (0.80-1.43). Treatment with antidepressants during pregnancy is not associated with an increased risk of ASD in the offspring.	because the condition of depressed pregnant women without treatment is also harmful to the mother and fetus..
(Lupattelli, et al., 2018)	English	Pubmed	Evaluating the effect of prenatal exposure to selective serotonin reuptake inhibitors (SSRIs) on behavioral, emotional, and social development in children at 5 years of age, and over time from 1.5 years of age.	Kohort	The results of the study of 8,359 samples. Children exposed to SSRIs in late pregnancy had an increased risk of anxiety/depressive behavior compared to children who were not exposed (adjusted =0.50, 95% CI= 0.04, 0.95, $p<0.05$). children of mothers who used SSRIs in late pregnancy were at greater risk for anxiety/depressive behavior problems. Prenatal SSRIs do not increase the risk for greater behavior in preschool-aged children or for temperamental problems in terms of emotionality, sociability, activity, or shyness, and this is consistently seen across multiple exposure windows..	There is no evidence for a substantial effect of prenatal SSRIs on externalizing, social, and emotional problems with antidepressant use in early, mid and late pregnancy. Assessment of the benefits and risks of choosing therapy is necessary. Consider the risks of untreated depression with your doctor before making treatment decisions during pregnancy
(Singal, et al., 2017)	English	Pubmed	Determine whether a selective serotonin reuptake inhibitor (SSRI) or selective	Kohort	The results of the study of 3048 children, 21.43% of children in the exposed group were assessed as susceptible in 2 or more domains compared to 16.16% of children in the unexposed group (aOR =	Assessment of the benefits and risks of choosing therapy is necessary. Consider the risks of untreated depression with

Author (Year)	Language	Sources	Purposes	Research Methods	Findings	Recommendations
			serotonin norepinephrine inhibitors (SNRIs) are associated with developmental susceptibility children whose mothers were diagnosed with a mood or anxiety disorder during pregnancy.		1.43; 95% CI 1.08 –1.90). Children in the exposed group had a significant risk of vulnerability in language and/or cognitive development (aOR = 1.40; 95% CI 1.03–1.90). Exposure to SSRIs or SNRIs during pregnancy is associated with an increased risk of developmental susceptibility and deficits in language and/or cognition.	your doctor before making treatment decisions during pregnancy. Psychological and/or herbal therapy suggested by medical personnel can be considered according to individual conditions, to prevent unwanted side effects.
(Nielsen, Ljungdalh, Nielsen, Nørgård, & Qvist, 2017)	English	Google Scholar	Investigating the relationship between prescription and SSRI in the period from 1 month before conception to the end of the first trimester of pregnancy and have a child with a diagnosis of HD (*Hirschsprung's disease*)	Kohort	Out of 1,256,317 children, 19,807 children were born to women who had one or more SSRI prescriptions 30 days before conception until the end of the first trimester. In the exposed group, 16 of 19,807 (0.08%) children were diagnosed with HD, with an aOR for HD of 1.76 (95% CI 1.07–2.92). Analysis showed that one SSRI prescription was associated with a 1.3-fold increased risk of HD, and at least two prescriptions was associated with a 2.3-fold increased risk, suggesting that SSRI dose was associated with the development of HD..	Assessment of the benefits and risks of choosing therapy is necessary. Psychological and/or herbal therapy suggested by medical personnel needs to be considered according to individual conditions, to prevent unwanted side effects.
(Park, Hanley, Guhn, & Oberlander, 2020)	English	Pubmed	Checking progress at kindergarten age, to investigate the impact of prenatal antidepressant exposure on behavior and development, which may reflect overall health from the normal development of children.	Kohort	The results of the study of the entire sample, 3,661 children (3.87%) were exposed to antidepressants during pregnancy. The exposed children had a lower mean gestational age (38.4 vs 38.9 weeks) and less ESL (English as a second language) status (7.3 vs 21.7%) of the children - unexposed children. Mothers exposed and unexposed in the diagnosis of mood and anxiety disorders (64.2 vs 8.9%). Prenatal antidepressant exposure	Penilaian benefit risiko penggunaan antidepresan selama kehamilan sangat diperlukan, terapi psikologi dan/atau herbal yang disarankan oleh tenaga medis perlu untuk dipertimbangkan sesuai kondisi individu, untuk mencegah efek samping yang tidak diinginkan.

Author (Year)	Language	Sources	Purposes	Research Methods	Findings	Recommendations
					was associated with susceptibility to physical independence (OR, 1.14; 95% CI, 1.00–1.30), social exploration (OR, 1.64; 95% CI, 1.23–2.20), and anxious behavior (OR, 1.30; 95% CI, 1.01–1.66). The development of children of mothers who continued antidepressants during pregnancy to those who discontinued, with anxiety behavior (OR, 1.32; 95% CI, 1.01–1.72) and an almost significant association with physical independence (OR, 1.14; 95% CI, 0.99–1.32). Effects are also due to the severity of maternal mental illness or other unmeasured confounding factors.	
(Mao, et al., 2016)	English	Pubmed	Estimating the association between prenatal exposure to antidepressants and the risk of childhood epilepsy, taking maternal depression into account.	Kohort	The results of the study were 734,237 children, 5829 (0.8%) children diagnosed with epilepsy. Children who had been exposed to antidepressants during pregnancy had a 27% higher risk of epilepsy with (aHR: 1.27; 95% CI: 1.05–1.54) than children in the reference group. Children whose mothers took antidepressants in early pregnancy had an increased risk of epilepsy (aHR: 1.34; 95% CI: 1.04–1.74) compared to those who were not exposed. The estimated association was 1.71 (95% CI: 1.10-2.66) if their mother was also diagnosed with depression in the 6 months before pregnancy or during pregnancy and 1.14 (95% CI: 0.91-1.43) if their mother does not have a diagnosis of depression. Children of mothers who took antidepressants from	Risk benefit assessment in the choice of therapy. Psychological and/or herbal therapy suggested by medical personnel needs to be considered according to individual conditions, to prevent unwanted side effects.

Author (Year)	Language	Sources	Purposes	Research Methods	Findings	Recommendations
					2 to 6 months before pregnancy had an increased risk of epilepsy (aHR: 1.36; 95% CI: 1.07–1.73) compared with children whose mothers did not take antidepressants during pregnancy and in the 6 months before pregnancy..	
(Bérard, et al., 2017)	English	Pubmed	Use of selective serotonin reuptake inhibitors (SSRIs) with an increased risk of persistent pulmonary hypertension in the newborn (PPHN). Data are limited regarding the risk of PPHN with serotonin norepinephrine reuptake inhibitors (SNRIs). We aim to measure both associations.	Kohort	Results of the study of 143,281 pregnancies; SSRI use during the second half of pregnancy was associated with an increased risk of PPHN [(aOR) 4.29, 95% CI 1.34, 13.77] compared to non-use at the same time. The use of SNRIs at the same time was not statistically associated with the risk of PPHN (aOR 0.59, 95% CI 0.06, 5.62), exposure to SNRIs protected against the risk of PPHN. Use of SSRIs (aOR 0.37, 95% CI 0.11, 1.22) and SNRIs (aOR 1.88, 95% CI 0.49, 7.14) before the 20th week of gestation was not associated with the risk of PPHN.	Assessment of the risk-benefit of the choice of therapy is still needed. Psychological and/or herbal therapy recommended by medical personnel needs to be considered according to individual conditions, to prevent unwanted side effects.

Discussion

In the review of the journal above, it is known that the use of antidepressants during pregnancy can result in several side effects, namely:

a. Mental Disorder

A mental disorder is a syndrome characterized by clinically significant disturbances in an individual's cognition, emotion regulation, or behavior that reflect dysfunctions in the psychological, biological, or developmental processes that underlie mental function. The results of the study (Liu et al, 2017) found that the risk of mental disorders among offspring in the continuation group of antidepressant use during pregnancy was higher than in the discontinuation group (HR 1.27, 95% confidence interval 1.17 to 1.38). Continuing antidepressant medication during pregnancy is associated with significant anxiety behavior (OR, 1,32; 95% CI, 1,01-1,72) (Park et al, 2020).

b. Hypertension

Prolonged antidepressant exposure appeared to significantly increase the likelihood of gestational hypertension, with aORs of 2.13 (95% CI 1.36–3.34), 2.36 (95% CI 1.35–4.12) and 2.66. (95% CI 1.52–4.65) each for exposure in the 0–10 week gestation period including women with and without sustained exposure, 11–20 weeks gestation, and both periods (Zakiyah et al, 2017). The use of antidepressants in the first 20 weeks of pregnancy and the use of SSRIs during the second half of pregnancy are associated with an increased risk of PPHN (pulmonary hypertension of the newborn) (aOR 4,29, 95% CI 1,34, 13,77) (Bérard et al, 2017).

c. Birth Weight and Gestational Age

Research (Sujan et al, 2017) found preterm birth ([OR], 1.34 [95% CI, 1.18-1.52), and from a study from (Molenaar, 2020) it was found that SSRI dose was significantly associated with birth weight = -180.7, 95% CI -301.1; -60.2, p-value < 0.01) as mean standard SSRI dose during total pregnancy = -187.3, 95%CI -322.0;-52.6, p-value < 0.01. Research from (Henriksen et al, 2017) also reported that infants exposed to SSRIs during two or more trimesters lost 205 g (b: -205 g, 95% CI -372 to -38), and also known exposure to SSRIs for two or more more trimesters born 4.9 days earlier (b: 4.9 days, 95% CI -9.1 to 1.4).

d. Congenital Malformations

Research conducted by (Bérard et al, 2016) found that infants have an increased risk of heart, musculoskeletal, craniofacial, digestive and respiratory defects. In a study conducted by (Huybrechts et al, 2020) it was also known that there was a relationship between the use of antidepressants (duloxetine) during pregnancy and congenital malformations, the relative risk between exposed and unexposed was 1.11 (95% confidence interval 0.93 to 1.33) for congenital malformations overall and 1.29 (0.99 to 1.68) for cardiovascular malformations.

e. Speech/Language Disorder

Research (Singal et al, 2020) reports that children of mothers diagnosed with mood or anxiety disorders who use SSRIs or SNRIs during pregnancy are at risk for developmental susceptibility to language and cognitive difficulties. Research conducted by (Brown et al, 2016) found that the offspring of mothers who bought SSRIs at least twice during pregnancy had a 37% increased risk of speech/language disorders.

f. Diagnosis of HD (*Hirschsprung's Disease*)

Research (Nielsen et al, 2017) showed a significantly increased risk of HD (Hirschsprung's Disease) after the mother was exposed to SSRIs with an aOR for HD of 1.76 (95% CI 1.07–2.92). The increased risk of HD is still not clearly understood.

g. Epilepsy

Research (Mao et al, 2016) reported that children exposed to antidepressants during pregnancy had a 27% higher risk of epilepsy (aHR: 1.27; 95% CI: 1.05-1.54) compared to children in reference group.

h. Autism

Research from Rai et al (2017) reported that exposure to antidepressants during pregnancy had a higher probability of diagnosing autism in offspring, compared to those without antidepressants (aOR 1.45, 95% confidence interval ranging from 1.13 to 1.85).

i. Postpartum haemorrhage

A study from Huybrechts et al (2020) reported that compared with unexposed women, the risk of postpartum hemorrhage in women exposed to duloxetine increased after full adjustment for relative risk of 1.53 (95% confidence interval 1.08-2.18).

Conclusion

Side effects of using antidepressant drugs during pregnancy such as psychiatric disorders, hypertension, low birth weight, short gestational age, congenital malformations, speech/language disorders, Hirschsprung's Disease, epilepsy, autism, and postpartum hemorrhage are known to be caused by the mechanism of action of antidepressant drugs capable of crosses the placenta, thereby affecting fetal brain development. High serotonin levels are associated with decreased growth hormone levels and can have a negative impact on fetal growth.

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