Journal of
Controversies in Obstetrics & Gynecology and Pediatrics

Review

DOI: 10.51271/JCOGP-0005

Therapy options for psychiatric disorders in pregnancy

İbrahim Söylemez

Psychiatrist, Private Clinic, İstanbul, Turkey

Cite this article: Söylemez İ. Therapy options for psychiatric disorders in pregnancy. *J Controv Obstetr Gynecol Ped.* 2023;1(1):21-25.

Submit Date: 05/01/2023 **Accept Date:** 17/01/2023 **Corresponding Author:** İbrahim Söylemez, dribrahimsoylemez@gmail.com

ABSTRACT

While psychotherapy is often preferred in treating mild psychiatric disorders, drug and other non-drug options are adopted in treating moderate and severe conditions during pregnancy. In addition, cognitive behavioral therapy (CBT) has become prominent among psychotherapies. Regarding antidepressants, Sertraline, Citalopram, and Escitalopram are recommended as the first choices. Benzodiazepines are not recommended unless necessary; they are prescribed in the minimum dose and duration if highly needed. Mood stabilizers are considered risky and should be carefully used. Moreover, the expectant mother should be required for fetal follow-up more frequently and in detail when such drugs are prescribed. The safest among them is considered Lamotrigine. If antipsychotics are to be prescribed, the expectant mother's blood glucose, weight, and blood pressure should be followed up frequently. Due to the possible side effects to occur in the infant following delivery, antipsychotics may be considered to be discontinued immediately before birth and restarted after delivery. It is argued that there is no notable difference between the first and second generations. Besides, electroconvulsive therapy (ECT) is recommended in cases of suicidal depression, manic attack, psychotic attack, and catatonia where rapid response is required. Although promising results were previously reported about transcranial magnetic stimulation (TMS) and bright light therapy, their utilization areas are still limited.

Keywords: Pregnancy and psychiatric disorders, medication, non-drug therapy options

INTRODUCTION

Therapy options for psychiatric disorders during pregnancy are often divided into drug and non-drug therapies. While antidepressants, anxiolytics, mood stabilizers, and antipsychotics are presented as medication options, psychotherapy, electroconvulsive therapy (ECT), and transcranial magnetic stimulation (TMS) are adopted as non-drug therapies. They have also welcomed bright light therapy (phototherapy) oriented to depression in recent years. The level of the disorder is settled as mild, moderate, and severe by how much the psychiatric disorder disrupts functionality and daily life and by symptom severity. Psychotherapy often becomes prominent in mild conditions, while other drug and non-drug options are considered, as well as psychotherapy, in moderate and severe disorders.

DRUG THERAPY IN PSYCHIATRIC DISORDERS DURING PREGNANCY

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) are often the first choice when deciding antidepressants.[1] The literature hosts a plethora of studies on the use of these drugs for depression in pregnancy, and they were previously shown to be efficient. Despite conflicting findings on teratogenicity, the prevailing view is that they can be used at the minimum effective dose in case of indication; the risk of teratogenicity increases with increased doses.[2] A meta-analysis study concluded a 1.36-fold increase in the risk of a septal defect in the infants of 6.5 million expectant mothers using Sertraline in the first trimester, despite no association with other anomalies.[3] The previous research reported an increased risk of premature birth, persistent pulmonary hypertension, and neonatal adjustment syndrome both in sertraline use and untreated pregnancy depression.[4] In addition, the risk of neonatal seizures was found to be higher when using tricyclic antidepressants.[5] However, there is growing evidence that Sertraline, Citalopram, and Scitalopram are relatively safe. Paroxetine was found to be riskier for cardiac anomalies. Fluoxetine is, on the other hand, a drug with a long half-life. Therefore, these two drugs are not recommended as the first choice but can be started after informing the expectant mother and her relatives in the case of no response to the others and a history of response to them.[6]

It is suggested that tricyclic antidepressants should not be the first choice because of the risk of teratogenicity and side effects.[7]

Despite not satisfying data on Mirtazapine, it is suggested to be used in the case of hyperemesis, insomnia, anorexia, and weight loss.[8]

Some studies reported no increase in the risk of anomalies related to Venlafaxine and Duloxetine, the members of SNRIs, but further research is needed on this subject. Venlafaxine may increase the risk of hypertension; therefore, it should be avoided in high-risk pregnancies in terms of preeclampsia-eclampsia.[9]

In the postpartum period, the first choice for breastfeeding mothers is Sertraline and Paroxetine, which are known to pass into milk the least. Other SSRI drugs can also be used in the case of no response to the above-mentioned options or emerging intolerable side effects.[10]

Anxiolytics

Benzodiazepines cross the placenta. The use of Benzodiazepines during pregnancy was found to be associated with anal atresia and cardiac anomaly,[11] low birth weight and preterm birth,[12] drowsiness, reduced muscle tone, and decreased feeding when used close to birth and neonatal withdrawal syndrome, somnolence, irritability, difficulty sucking, tremor, tachypnea, gastrointestinal symptoms, hypoglycemia, and hypothermia among ¼ of babies during late pregnancy.[13,14] Although it was considered a teratogen for a while until further research on the grounds that it might cause cleft lip and palate,[15] the current studies established no relationship between major malformations and Benzodiazepine use. While some studies suggested that Benzodiazepines should be gradually tapered and discontinued until delivery to avoid possible postpartum complications, some others opposed such a suggestion because the mother's anxiety symptoms may also increase.[16] As a result, the use of benzodiazepines is not recommended during pregnancy. Only limited use is recommended for the lowest dose and duration in severe anxiety attacks and sleep disorders that do not respond adequately to non-drug therapies and antidepressants.

Since the data on the use of beta-blockers during pregnancy were obtained from expectant mothers using them for hypertension and cardiovascular reasons, it is unclear whether the fetus-specific effects are due to medical reasons or drugs.[17] Yet, they are accepted as non-teratogens.[18] Some studies suggested they are associated with feeding problems, hypoglycemia,[19] low birth weight, and hemodynamic disorders in infants.[20] Overall, although they are not considered teratogens, it is proposed that they may have adverse effects on the infant in the postnatal period.

Antihistamines are used for allergy and hyperemesis during pregnancy, and those with low sedation effects are preferred. The literature lacks research on its use for anxiolytic and hypnotic purposes.[21] Diphenhydramine, Cetirizine, and Hydroxyzine were not found to be associated with a malformation.[22]

Although it was shown that the use of Pregabalin and Gabapentin during pregnancy does not contribute to the risk of malformation, they are not recommended to be used because not only was the number of relevant studies limited but also a study with a smaller sample concluded contrasting findings study.[23,24]

Mood Stabilizers

Lithium is a drug with placental transfer used as a maintenance therapy during remission to alleviate acute attacks (hypomania, mania, depression) and prevent attacks in bipolar disorder. The blood lithium level is the same in the mother and the fetus, but its half-life is longer in the fetus since the fetus' renal clearance will not be sufficient; therefore, it should be considered that lithium may reach toxic levels in the fetus. Ebstein Anomaly was found 400 times more in babies exposed to lithium in the first trimester.[25] Its use between 2-6 weeks was found to be riskier, and subsequent studies concluded the risk to be 20-40 times lower.[26,27] Another study discovered a three-fold increase in all congenital malformations and an eight-fold increase in cardiac anomalies.[28] On the other hand, a relatively recent review mentioned that it would not contribute to the risk of major malformations.[29] In the literature, complications that are uttered to be linked with lithium use during pregnancy are listed as preterm birth, high birth weight, nephrogenic diabetes insipidus, hydramnios, floppy baby syndrome, transient neurodevelopmental defects, poor newborn reflexes, apnea and respiratory distress, feeding difficulties, bradycardia, thyroid dysfunctions, and low birth weight. High-resolution ultrasonography and fetal echocardiography are recommended for expectant mothers using lithium between 16-20 weeks of pregnancy. Since the blood volume may decrease, reducing the lithium dose before delivery is also recommended to prevent possible toxic effects in pregnant women using lithium. Another recommendation is to discontinue lithium two days before delivery and restart it after delivery.[30] Overall, a considerable number of studies recommend that lithium should not be used in the first trimester unless mandatory and should be discontinued just before delivery and restarted after delivery.[31]

A meta-analysis study on valproic acid showed an increased risk of spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis when it is used in the first trimester of pregnancy. Even the risk increases much more when the daily dose exceeds 1000 mg.[32] Irritability, feeding problems, reduced muscle tone, liver toxicity, coagulopathy, and hypoglycemia were previously reported in infants exposed to valproic acid close to birth.[33] Intramuscular vitamin K should be administered just before delivery to reduce the risk of coagulopathy.[34] Overall, it can be asserted that the use of valproic acid should be avoided during pregnancy if possible. If only valproic acid has benefited so far and the symptoms increase when discontinued, patients are recommended to use it at a lower dose.[31] Moreover, starting folic acid supplementation before pregnancy is recommended to reduce the risk of neural tube defect development among patients with a pregnancy plan who are recommended to continue with valproic acid during pregnancy.[34]

Carbamazepine was formerly considered a teratogen; nevertheless, current data propose vice versa. It increases the risk of congenital anomaly (3-6%) but is thought to be safer than valproic acid.[34] Neural tube defects, cleft palate, cleft lip, cardiovascular anomaly, products system anomaly, short nasal root, hypertelorism, and fingertip hypoplasia

were reported in the case of Carbamazepine use.[35] Folic acid supplementation is also recommended for expectant mothers to use Carbamazepine.[31]

Lamotrigine is safer than other mood stabilizers; the risk of malformation is 2-3%. Although an increased risk of cleft palate and lip, hypospadias, and gastrointestinal defects were mentioned, no dose-dependent relationship was previously detected.[36]

Antipsychotics

Apart from the possible teratogenic effects related to the use of antipsychotics during pregnancy, another risk that may arise in all antipsychotics, particularly those of the second generation, may be the complications such as increased appetite, weight gain, insulin resistance, hyperglycemia, hypertension, obesity, and gestational diabetes.[37]

In the second generation, Clozapine and Olanzapine are the riskiest drugs for gestational diabetes. However, Risperdal carries a relatively lower risk. Moreover, the previous research could not conclude a relationship between risky situations in pregnancy and the use of Amisulpride, Aripiprazole, Quetiapine, Sertindole, and Ziprasidone.[38]

Although the use of first-generation antipsychotics is gradually decreasing, Haloperidol and Chlorpromazine are still preferred and have been used safely at low doses for years in the treatment of hyperemesis gravidarum. In addition, no risk of teratogenicity was mentioned in the literature.[39]

A study on the use of antipsychotics during pregnancy reported an increased risk of gestational diabetes, preterm birth, and low birth weight. In the same study, it was mentioned that the use of antipsychotics during early pregnancy may cause an increase in the risk of atrial and ventricular septal defects and that any relationship could not be established clearly due to confounding factors such as concomitant use of other drugs.[40]

Two recent reviews on the subject complained about insufficiency and reported no relationship between the use of antipsychotics during pregnancy and congenital anomalies.[41]

The British Association for Psychopharmacology's guide on the use of psychotropics during pregnancy mentions a moderately increased risk of complications (e.g., congenital anomalies, preterm birth, developmental disorders, and newborn adjustment problems) among women using antipsychotics during pregnancy than healthy women. It also reports a low degree of risk when compared to pregnant women who have a psychiatric disorder but do not use medication. Besides, it utters no difference between the first- and second-generation antipsychotics by fetal risk when considered at the class level or individually.[42]

In another study, the authors reported no relationship between the use of antipsychotics during pregnancy and a major congenital anomaly. Neurodevelopmental and behavioral disorders were significantly more common in the infants of women having used antipsychotics compared to those of women who did not. Yet, the statistical significance was lost when confounding factors (e.g., smoking, alcohol, substance use, and concomitant use of other drugs) were controlled.[43]

A previous meta-analysis study revealed a relationship between antipsychotic use during pregnancy and congenital anomalies, preterm birth, low birth weight, and elective curettage but noted that this relationship might be doubtful due to confounding factors. However, the authors could not conclude such a relationship between the first- and second-generation antipsychotics and highlighted that and the multitude of confounding factors (e.g., smoking, alcohol and substance use, obesity, socio-economic problems, concomitant use of other drugs and excess medical comorbidities) among expectant mothers using antipsychotics limited the research findings.[44]

A reasonable order among antipsychotics by placental transfer may be as follows: Olanzapine > Haloperidol > Risperidone > Quetiapine.[45]

Extrapyramidal manifestations were observed in the infants of mothers having used antipsychotics close to delivery. Due to the risk of neutropenia in the infants of mothers using Clozapine, it is recommended to follow up hemogram once a week in the first month and then once a month for six months after delivery.[38]

NON-DRUG THERAPIES FOR PSYCHIATRIC DISORDERS DURING PREGNANCY

Cognitive Behavioral Therapy (CBT)

CBT is one of the main schools of psychotherapy and has become widespread worldwide in the last 50 years. It is also among the leading non-drug therapies for expectant mothers with mild depressive and anxiety disorders with no severe symptoms. The relevant literature hosts a plethora of studies showing its efficacy and safety. It is an evidence-based and structured psychotherapy method and the first-choice therapy for those afraid of drug exposure and with drug rejection. While it can be administered to expectant mothers already exhibiting mild symptoms, it can also be preferred prophylactically for women expecting pregnancy with a history of depression and anxiety disorder. Interventions with CBT for distorted cognitions (e.g., inadequacy, guilt, inability to cope, and catastrophizing) are recommended to prevent or mitigate the disorder that may occur during pregnancy. It was consistently shown to be as effective as medication in depression with mild symptoms and no psychotic symptoms.[46]

Electroconvulsive Therapy (ECT)

It is the stimulation of the brain with a low electrical current and having a seizure. Although the mechanism of action of which has not been clarified despite being utilized in psychiatry for a long time, it is a reliable therapy with a rapid response, proven efficiency in some psychiatric disorders, and several advantages in terms of side effects.

ECT is indicated in cases with moderate and severe depressive episodes (unipolar or bipolar disorder), no response to the drug, suicidal risk, insufficient nutrition (malnutrition or dehydration), psychotic symptoms, signs

of agitation and catatonia, no cooperation, and treatment rejection. According to a meta-analysis, ECT was found to be more effective than drug therapy and imitation ECT in depression.[47]

Apart from this, manic episodes (bipolar disorder), psychotic exacerbation (schizophrenia, schizoaffective disorder), and catatonic symptoms for whatever reason, bear ECT indications during pregnancy.

The most common side effects in the mother following ECT during pregnancy are transient and mild nausea-vomiting, muscle pain, and headache. The most prominent undesirable side effects are uterine contractions and premature birth, observed at a frequency of 3.5%. The current does not pass through the uterus, which is thought to be related to oxytocin release during ECT. Its side effects on the fetus are reported as transient cardiac arrhythmias, and its relation with congenital anomalies was not reported before.[48]

Drugs increasing the seizure threshold (e.g., benzodiazepines and mood stabilizers) should be discontinued a few days before ECT.

Transcranial Magnetic Stimulation (TMS)

Whereas it lacks enough data to be utilized as the first-choice therapy, it can be considered in selected cases. It is a novel method deployed leading to neurotransmitter release by stimulating neurons with magnetic stimulation (neural depolarization) in various neurological and psychiatric disorders. Concerns about drug exposure and myths about ECT have highlighted this method in recent years. The literature hosts only three studies conducted so far showing its efficacy and safety in the treatment of depression in pregnancy, and any of these studies reported no serious side effects. The most common side effect was reported to be a headache at a rate of 40%, and all infants were born healthy.[49] Previous research on the non-pregnant anxiety disorder population demonstrated that it can be reliably utilized in anxiety disorder during pregnancy despite no study yet on its efficacy and safety among expectant mothers.[50]

CONCLUSION

Psychiatric disorders often occur in the reproductive age between 18-45 years in women. Therefore pregnancy is a period of increased susceptibility to psychiatric disorders such as anxiety disorders, depression, eating disorders, and psychosis for many women. In this article, psychiatric disorders in pregnancy and lactation period and treatment options are reviewed in light of current treatment guidelines. The benefits, teratogenicity risks of psychopharmacological treatment during pregnancy should be considered carefully. The lowest effective dose and single medication should be used, and fetal / infant must be closely monitored during pregnancy.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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İbrahim Söylemez

I graduated from Ankara University Faculty of Medicine in 2005. I am a psychiatrist. I am working in the fields of Psychotherapy, General psychiatric applications, Gambling Addiction, and Cognitive Behavioral Therapy, Couples Therapy, Emdr in the fields of diseases.