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Review Article

Pharmacotherapy of Affective Disorders in Pregnancy: Current Updates

Taliha Harika Aydın and Ozgur Devrim Can*
Department of Pharmacology, Anadolu University, Turkey

***Corresponding author:** Ozgur Devrim Can, Department of Pharmacology; Anadolu University, 26470, Eskisehir, Turkey

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Abstract

Affective disorders are common among women of reproductive age. In a pregnant women, affective disorders can cause congenital malformations and various psychomotor behavioral disorders in newborns. These disorders even can cause premature birth, low birth weight, and unplanned abortion. Appetite loss, inadequate maternal weight gain, sleep disturbances, and poor self-care observed in a depressed pregnant can lead some developmental deficits on baby. Further, increased smoking and/or alcohol consuming also damage to the baby. Harmful effect of affective disorders both on the mother and baby, requires to produce suitable treatment algorithms for this diseases in pregnant population. Although psychotherapy is the first consideration in treatment, antidepressant therapy may still be necessary if these regimens are unsuccessful or inaccessible. Indeed, antidepressant therapy may become mandatory, especially in severe cases threating the life of pregnant woman and her unborn child. Selective Serotonin Reuptake Inhibitors (Ssris) are generally considered first-line in pregnancy. Among the SSRIs, fluoxetine has been reported to prescribe frequently since long term using of this drug is not related with any developmental sequel detected in children. Citalopram/escitalopram or sertraline are also preferable SSRIs. Tricyclic antidepressants are just relatively safe for the fetus. Unfortunately, a mood stabilizer such as lithium and carbamazepine is known to increase congenital malformation risks. Conventional antipsychotics are relatively safer for the fetus than atypical ones. Benzodiazepines are known as teratogenic agents, and in high dosage have been associated with withdrawal symptoms, hypotonia and agitation in the newborn.

Keywords: Affective disorders; Antidepressants; Mood stabilizers; Pregnancy; Teratogenic

Abbreviations

SSRIs: Selective Serotonin Reuptake Inhibitors; SNRIs: Serotonergic Noradrenergic Reuptake Inhibitors; FDA: Food and Drug Administration

Introduction

The morphological architecture for a human is laid down during the embryonic period, and the structures simply grow in size and develop normal physiologic function during the fetal period. Congenital anomalies can be induced during the fetal period through a fetal effect, although they are usually induced during the critical embryonic period [1]. Unsuitable drug use during pregnancy is one of the main causes inducing congenital malformations and developmental retardations in newborn.

Unfortunately, drug use during pregnancy is a frequent event. Almost two-thirds of pregnant women take at least one medication during pregnancy. While using of some drugs such as vitamins or iron is necessary during gestational period, a significant number of medications is known to cause some serious harmful effect on developing embryo or fetus [1,2]. Nevertheless, during gestational period, some conditions such as chronic maternal illnesses, pregnancy induced complaints, and pregnancy-specific diseases may make medication use mandatory. Common reasons of drug use in pregnancy were displayed in the Table 1 [3,4]. Affective disorders can also be added to this table, since considerable part of the pregnant women have been suffered from this type of complaints [5,6]. It is known that, 15% and 20% of women experience affective disorders during their pregnancy [7]. Further women, ranging from 5 to 10 percent, consume some type of psychoactive agent during pregnancy [1]. Food and Drug Administration (FDA) also underlies the importance of "the baby blues", "depression during pregnancy" and "postpartum depression" for the health of mother and advice

Table 1: The main situations requiring use of drugs during pregnancy.

Causes of using drugs in pregnancy	Situations for drug using
New conditions developed with pregnancy	Nausea-vomiting Gastric burn Constipation Hemorrhoid Coagulation disturbances
Diseases specificfor pregnancy	Gestational hypertension Gestationaldiabetes
Prepartum chronic diseases	Diabetes Thyroid disorders Hypertension Epilepsy Asthma HIV
Others	Flu Common cold Rheum

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the treatment of this emotional disorder with the help of healthcare providers [8].

Depression, an affective psychiatric disorder, is common during pregnancy. It affects up to 14-18.4% of pregnant women [9,10]. More than one-quarter of pregnant women describes symptoms of depression [1]. The incidence increases especially in the first and third trimester. Depression relapses during pregnancy, in about 50%of women with depression history. 70% of the pregnant women interrupting their psychiatric treatment confronts with disease recurrence, especially in the first trimester [11].

Anhedonia and depressed mood are two major diagnostic criteria for depression. Depressed women experienced some physical symptoms such as sleep disturbances, altered appetite, altered activity, low energy and fatigue. Sleep and appetite disturbances and energy reduction, which can also been seen in a healthy pregnant, may mislead the physician and depression symptoms of pregnant women may overlook [11]. Ruminative guilty thoughts, suicidal ideation, poor concentration, and indecision are the cognitive symptoms observed in the depressive patients [1,12].

Affective disorders are known to effect pregnant women in a negative way. Loss of appetite and inadequate maternal weight gain, sleep disturbances, and poor self-care behavior may lead deficits in the development of baby. Increased smoking and/or alcohol consuming of depressed pregnant also damage the baby [10]. Preeclampsia incidence may increase as a result of depression. Worse, major depression complicated with a delusional component in pregnant women may lead to the mother attempting suicide and infanticide [13].

As a mental disorder, depression, it adversely affects fetal development. Moderate to severe depression may cause increase in the risk of premature birth, low birth weight, unplanned abortion, lower Apgar scores, and smaller head circumference [7,10,14]. Further, prenatal depression causes decrease in motortone, increase in abnormal reflex response, irritability, atypical frontal electroencephalogram patterns, emotional and other psychomotor behavioral disorders. Depression-like behavior is seen in the newborns of depressed mothers. Some of these problems have been associated with the impaired function of hypothalamic-pituitary-adrenal axis and enhancement in cortisol amount. Depression scores have been found closely related with increased cortisol and decreased brain dopamine and serotonin levels [10,11,14].

Depression can also be bipolar. Patients with bipolar disorders have periods of mania and depression [1]. In a majority of women with pre-existing bipolar disorder, relapse arises in pregnancy [15,16]. About 80% of women with bipolar disorders experienced a mood episode also in the postpartum period, as well as their pregnancy. Pregnant women may experience first episode or relapse of bipolar illness dramatically, as a result of unsuitable diagnosis or lack of treatment [16,17].

The mentioned harmful effect of affective disorders both on the mother and baby, requires to produce suitable treatment algorithms for these diseases in pregnant population. Psychotherapy seem as a first choice for treatment of depression during pregnancy in order to avoid possible destructive effect of the psychotropic drugs. Therefore, management of depression during pregnancy should be undertaken in consultation with a psychiatrist and/or psychologist [1,18]. Although psychotherapy is the first consideration in treatment [19,20], antidepressant therapy may still be necessary if these regimens unsuccessful or inaccessible [11,20,21]. Besides, necessity of long time for the success of psychotherapy may also become a disadvantage in some cases. Indeed, antidepressant therapy may become compulsory, especially in severe cases threating the life of pregnant woman and her unborn child [1,18,20]. The key point of prescribing a medicine for pregnant women's health, is performing a careful risk assessment and preventing her embryo or fetus from damage probability, as much as possible. While treating a pregnant patient, physician should take into account risk of teratogenicity on fetus, postnatal toxicity and withdrawal syndrome, and long-term behavioral outcomes. On the other hand, safety of drugs is questionable or unknown in many cases [1,11,22].

FDA has established five risk categories (A, B, C, D and X) to indicate the potential of a drug to cause birth defects if used during pregnancy. The categories are determined by the reliability of documentation and the risk to benefit assessment. For the drugs listed in Category A, adequate and well-controlled studies have failed to exhibit a risk to the fetus in the pregnancy. Drug has listed in Category B, if animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Drugs listed in category C have shown an adverse effect on the fetus in animal reproduction studies and there are no adequate and well-controlled studies in humans. Drugs belong to Category D cause human fetal risk. For the drugs listed in Category X, both preclinical and clinical studies have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk. These drugs are not recommended for use during pregnancy [8]. Many of the psychotropic drugs listed as FDA category C agents.

With the present state, current limitations of the FDA categories make difficult to decision making for choosing of an appropriate medication for pregnant women. Therefore, FDA projected some major revisions to prescription drug labeling to more completely inform the use of drugs during pregnancy, in May 2008. The proposed regulations abolish the traditional pregnancy categories A, B, C, D, and X due to limitations in their ability to accurately and consistently convey risk and benefit. Writing and clearance process of Final Rule still continue [23].

Antidepressants, mood stabilizers, antipsychotics, and anxiolytics are some of the psychotropic agents indicated for treatment of various affective disorders [1]. Therefore, pregnant women with an affective disorder may use one of these drugs and her baby may suffer from the usage of them. Unfortunately, none of the psychotropic drugs is completely safe in pregnancy [11]. This article was prepared with the aim of providing a perspective for appropriate managements for maternal affective disorders, in the light of current literatures.

Treatment of Affective Disorders in Pregnancy

Pharmacotherapy

Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs) are the most often prescribed drugs in pregnant women, followed by

Table 2: FDA categories of frequently used antidepressant drugs.

Drugs	Categories	Drugs	Categories
SSRIs			
Depoxetine	B	Sertraline	C
Escitalopram	C	Citalopram	C
Fluoxetine	C	Paroxetine	D
Fluvoxamine	C		
SNRIs			
Duloxetine	C	Milnacipran	*
Venlafaxine	C		
MAOIs			
Moclobemide	B	Tranylcypromine	C
Phenelzine	C		
TCAs			
Opipramol	B	Protriptyline	C
Amoxapine	C	Trimipramine	C
Desipramine	C	Amitriptyline	D
Doxepine	C	Imipramine	D
Clomipramine	C	Nortriptyline	D
Newer Antidepressants			
Agomelatine	B	Nefazodone	C
Mirtazapine	C	Bupropion	C
Trazodone	C	Mianserine	*

*: No studies

Serotonergic Noradrenergic Reuptake Inhibitors (SNRIs), tricyclic antidepressants and infrequently monoamine oxidase inhibitors [24]. FDA categories of well-known anti depressants was displayed in the Table 2 [25].

SSRIs: Nowadays, physicians frequently prescribe SSRI antidepressants because of their strong therapeutic efficacy as well as reliable side effect profile.

Early studies have not suggested any augmented risk of major congenital malformations with in utero exposure to SSRIs [10] and large portion of evidence documents their safety during pregnancy [26]. However, since 2005, data on possible congenital malformations induced by the use of individual SSRIs, have been inconsistent [27].

Recent studies indicated that, exposure to SSRIs has been reported to increase the risk of neurobehavioral disturbances such as altered motor activity, tremors and stress/pain regulation [7]. Increased risk for respiratory distress syndrome, temperature regulation disorder, endocrine and metabolic disturbance, hypoglycemia, anencephaly, omphalocele, craniosynostosis, convulsion, jaundice, earlier delivery and lower birth weight, congenital malformations, and lower Apgar Scores have also been reported with related to antenatal exposure to these drugs [10,14,28-32]. Besides, exposure to SSRIs after the 20th gestation week has been reported to increase the risk ofprimary pulmonary hypertension of newborn [14,29]. Moreover, reports indicated some problems in neonatal adaptation [1,33,34] and symptoms of a neonatal withdrawal syndrome [35] for the infants exposed SSRIs in late pregnancy.

Among the SSRIs, paroxetine has become the most complicated one in terms of reported risks. Several reports have been pointed out that antenatal paroxetine exposure induces cardiac anomalies particularly atrial and ventricular septal defects [14,28-38]. Moreover, some individual reports have been suggested some malformations induced by fluoxetine, sertraline and citalopram. Hypertrophic stenosis [39], spontaneous abortion, pulmonary hypertension, congenital heart defects and general malformations have been reported depending on antenatal fluoxetine exposure [9,14,30,31,36,38,40]. Moreover, sertraline use has been associated with omphalocele, anencephaly and cardiovascular malformations especially cardiac septal defects, in newborns [14,30,40-42] Similarly, citalopram exposure has been suggested to induce omphalocele, congenital heart defects, and neural tube defects [38,40-42]. Escitalopram has not been associated with risk of major malformation [38,41,43].

At this point, it is necessary to underlie the fact that afore-mentioned individual studies may not be adequate to reveal an association between antenatal SSRI exposure and congenital malformations. Because, results of severalmeta-analyses revealed no increased risk for congenital anomalies among infants whose mothers took SSRIs in the first trimester [1,10,44].

SNRIs and other non-SSRI antidepressants: There is a very limited number of paper investigating the SNRIs exposure during pregnancy. Some studies examining the effect of venlafaxine, suggested

an increase in the risk of spontaneous and therapeutic abortion and major malformations [9,26]. However, some other reports have not supported this data [1,45]. Exposures to venlafaxine have been associated with poor neonatal adaptation including respiratory stress, feeding difficulties and tachypnea [29]. In a recent study, *duloxetine*, another SNRI, has been associated with an increased risk of abnormal pregnancy outcomes [46].

Bupropion, mirtazapine, nefazodone and *trazodone* are newer antidepressants, not commonly used during pregnancy [9]. It has been reported that about 0.3% of antidepressant-exposed women uses mirtazapine during pregnancy. Exposureto this drug in pregnancy have been associated with the risk of spontaneous abortions and congenital malformations [9,10,14]. Trazodone and nefazodone, have been reported to use by 6.1% and 2.2% of the antidepressant-exposed pregnant women, respectively. Prevalence of spontaneous abortion has been found about 12-15% when trazodone used with other drugs such as benzodiazepines [9].

Some other papers have suggested nefazodone or mirtazapine as safe drugs. Antenatal use of them have not been associated with any increase in the risk of congenital malformations [45,47-49].

An increased risk of spontaneous abortion, congenital abnormalities and congenital heart defects has been suggested for first timester bupropion exposure, in both of the retrospective and prospective reports [9,10,50]. However, some other studies have not been supported this information and not demonstrated any augmented risk with the use of bupropion [10]. Exposure to bupropion has also been associated by poor neonatal adaptation [29].

Frequency of congenital anomalies has not been reported to increase by mianserin, amineptine, and viloxazine administrations during the first trimester of pregnancy [1]. Currently existing data are limited to let a significant risk evaluation of the use of agomelatine during pregnancy [14,29]. Nevertheless, agomelatine listed in FDA category B.

Tricyclic antidepressants: Currently, tricyclic antidepressants are not frequently preferred drugs, because of safer side effect profile of the newer antidepressants [51]. Tricyclic antidepressants are not totally safe drugs in pregnancy. Nortriptyline and amitriptyline use has been associated with structural malformations, congenital cardiac malformations, respiratory distress syndrome, endocrine and metabolic disturbance, hypoglycemia, temperature regulation disorder, convulsion, jaundice and spontaneous abortion [9,24,28,52]. FDA listed nortriptyline as category D drug [9].

Recent data have shown an increased risk of dysmelia, cardiovascular malformations, preterm delivery and decreased birth weight induced by antenatal *clomipramine* exposure [9,14,29].

Monoamine Oxidase Inhibitors: Among the monoamine oxidase inhibitors, use of phenelzine and tranylcypromine are not suggested during pregnancy due to their side effects [9]. Datais inadequate for the evaluation and monoamine oxidase inhibitors should be avoided during pregnancy [14].

Mood Stabilizers: FDA categories of frequently used mood stabilizers were displayed in the Table 3 [25].

Table 3: FDA categories of frequently used mood stabilizers.

Mood Stabilizers	
Drugs	**Categories**
Lamotrigine	C
Oxcarbazepine	C
Lithium	D
Valproate	D
Carbamazepine	D

Lithium is a gold standard in pharmacological defense against bipolar disorder. However, there are only a few notable studies on the use of lithium during pregnancy. Reports have been indicated that lithium exposure causes birth complications such as polyhydramnios and pre-eclampsia. In addition, many case reports of neonatal lethargy, hypotonia, poor oral feeding, respiratory distress syndrome, cyanosis, jaundice, diabetes insipidus, floppy baby syndrome, thyroid disturbance, weak suck and Moro reflexes have been published. Further, risk of congenital cardiac malformation, specifically Ebstein's anomaly have been shown to noticeably increases in babies exposed to lithium in utero [1,14,17,28,29,32,53-55].

In utero exposure to carbamazepine, the most preferred alternative of lithiumfor treatment of bipolar disorder, has been associated with an increased risk of microcephaly, mid-facial abnormalities, orofacial clefts, spina bifida, cardiac defects, transient hepatic toxicity, neonatal bleeding (caused by vitamin K deficiency), and growth retardation in newborns [29,32,55,56].

Exposure to *valproate* in utero has been shown to related with harmful effect on infant's neurodevelopment and increased risk of autism spectrum disorders. In utero valproate exposure, termed 'fetal valproate syndrome', has been well documented to produce a consistent facial appearance, several other characteristic anomalies and dysfunction of the centralnervous system [32]. Central nervous system anomalies, principally neural tube defects and spina bifida, as well as facial dysplasia, dysmelia, a fibrinogenemia, hypoglycemia, liver atrophy, cholestasis, cardiac and urogenital malformations have been reported as the majority of structural abnormalities induced by the valproate exposure [17,29,32,53-55]. Both of the valproate and carbamazepine must be avoided during early pregnancy, because of their potential for interfering with folate metabolism [53].

Lamotrigine has also shown to increase the risk of orofacial cleft in newborns [29,53]. In addition, newborns who exposed the lamotrigine in utero, have been reported to suffer from neonatal adaptation problems including apnea, decreased muscle tone and sedation [29,55].

Oxcarbazepine is a newer mood stabilizer and a structural analogue of carbamazepine but they have different metabolic profiles. Oxcarbazepine has been reported to possess a better tolerability than carbamazepine and to poorly characterize with teratogenicity [32].

In clinic, antidepressants and a mood stabilizer drugs can be used for bipolar depressive patients, however, there is no study demonstrating the benefit/safety of this type of combination in the pregnant patients [57].

Antipsychotics

Antipsychotics are used to treat psychosis of any cause,

Table 4: FDA categories of frequently used antipsychotics.

Antipsychotics	
Drugs	**Categories**
Clozapine	B
Risperidone	C
Quetiapine	C
Ziprasidone	C
Phenothiazines	C

including psychotic depression, bipolar disorder, substance induced hallucinations, or delirium-induced psychosis. They are also used to augment the effects of antidepressant and anxiolytic drugs. Some of the antipsychotics are known to cause sedation, anticholinergic effects or extrapyramidal side effects (akathisia, Parkinsonism, tardive dyskinesia etc). Their neonatal side effects can be listed as withdrawal symptoms and extrapyramidal dysfunction such as hand posturing, tremors, and irritability [1].

Exposure to phenothiazines, traditional antipsychotics, have been found to associate with a small increase in the relative risk of malformations. Cholestatic jaundice has also been reported to be related with phenothiazine exposure [29].

Olanzapine is an atypical antipsychotic medication indicated for acute mania [55]. Exposure to olanzapine in utero has been shown to induce abortions, cleft lip, encephalocele and aqueductal stenosis. Olanzapine as well as clozapine have been associated with increase in the risk of gestational metabolic complications and heavier birth weight. *Clozapine* have also been shown to increase the risk of spontaneous and therapeutic abortions [32].

Increased in the risk of spontaneous and therapeutic abortions have also been reported for other atypical antipsychotics q*uetiapine* and *risperidone* [32]. Moreover, ventricular septal defects, cardiovascular malformations and kidney alterations have been reported depends on the z*iprasidone* exposure [58]. There is no information about the risks of *asenapine*.

FDA categories of frequently used antipsychotics were displayed in the Table 4 [25].

Exposures to antipsychotic plus anticonvulsant combination have been reported to increase the risk of malformations and ventricular septal defect [57].

Anxiolytics

Benzodiazepines have been reported to cause facial cleft malformations, general delay in mental development, floppy infant syndrome which is qualified by sedation, hypotonia, hypothermia and low Apgar scores. Exposure to *diazepam, alprazolam, oxazepam, lorazepam, clonazepam, medazepam, tofisopam* and *nitrazepam* in utero has been associated with teratogenicity [32].

FDA categories of frequently used anxiolytics were displayed in the Table 5 [25].

Electroconvulsive therapy

Electroconvulsive therapy, by following expanded clinical guidelines (presence of an obstetrician during treatment, Doppler ultrasonography of fetal heart rate, low-voltage etc.) is considered as a safe strategy for the treatment of some psychiatric disorders in a pregnant woman [1,5].

Table 5: FDA categories of frequently used anxiolytics.

Anxiolytics			
Drugs	**Categories**	**Drugs**	**Categories**
Benzodiazepines			
Diazepam	D	Lorazepam	D
Alprazolam	D	Medazepam	*
Clonazepam	D	Oxazepam	*
Clorazepate	D	Nitrazepam	*
Clordiazepoxide	D	Tofisopam	*
Prazepam	D		

*: No studies

Nevertheless, uterine contractions, vaginal bleeding, and miscarriage have been reported for pregnant women taking electroconvulsive therapy. Furthermore, some case reports have been pointed out transient benign fetal cardiac arrhythmias, hydropsfetalis and meconium peritonitis in the baby [1].

Conclusion

Detrimental effect of maternal affective disorders both on the pregnant women and her unborn baby, requires to plan appropriate treatment strategies. However, preparing a general treatment algorithm valid for all pregnant women is quite difficult since, ethical rules forbids double blind placebo controlled clinical studies in the pregnant population. Therefore, each case should be evaluated separately and appropriate treatment strategy should be planned considering benefit: risk ratio [11].

Indeed, affective disorder of pregnant women should be treated. Also, relapse during pregnancy should be prevented. For mild and moderate depression psychotherapy may be first option. However, drug therapy should be planned for moderate to severe depression cases, especially for the patients having suicide or infanticide risk.

While deciding a treatment, physicians should consider potential risks of not only psychotropic medication but also untreated maternal psychiatric illness. If the treatment benefits outweigh the risks, then the medication should be prescribed based on an individualized risk/benefit assessment. Medication history of the patient may lead to the physician. Using an efficacious drug for individual women may provide to avoid treatment failure or need of more than one antidepressant. Previous success with symptom remission, and women's preference should guide to treatment decisions. Further, treatment should be initiated and maintained with minimal effective dose. Clinician also should be aware of the residual depression possibility under the antidepressant treatment, which cause dual exposures of both medication and illness. Combined drug therapies should also be avoided, unless there is a clear indication for the polypharmacy [10,59].

SSRIs are generally considered as first-line in pregnancy [60]. Although their reliability has not been proven, information obtained from the clinical studies has not shown any major malformation on the fetus exposing SSRIs during pregnancy [10,11,59]. Among the

SSRIs, fluoxetine has been reported to be prescribed frequently since long term using is not related with any developmental sequel detected in children [61]. Citalopram/escitalopram or sertraline are also considered as safe SSRIs. If citalopram or sertraline are not adequate in treating depressive symptoms, bupropion and venlafaxine can be considered with the necessary caution [29]. Tricyclic antidepressants are just relatively safe drugs [59].

Conventional antipsychotics are relatively safe for the fetus. Women taking atypical antipsychotics should be exchanged to conventional antipsychotics before they conceive. Unfortunately, mood stabilizers such as lithium, sodium valproate, carbamazepine and lamotrigine have been associated with increased congenital malformations. Similarly, benzodiazepines in the first trimester have been reported as teratogenic, and at high dosage withdrawal symptoms, hypotonia and agitation have been displayed in the newborn [59]. Electroconvulsive therapy may be an option in suitable conditions [1].

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