CURRENT DILEMMAS IN TREATING THE DEPRESSED PREGNANT PATIENTS

Vesna Pirec

UDK: 615.214.06:618.2-085-06

University of Illinois at Chicago, United States of America

Summary

Treatment of depressive illness in peripartum is a challenging task. Both treated and untreated depressive illness carries risks for mother, baby and the entire family. It is crucial to establish the adequate diagnosis and suggest the proper treatment. Treatment should be tailored towards particular person and risks vs benefits should be discussed with the patient and ideally the baby’s father as well. For mild to moderate depressive symptoms, treatment of choice is psychotherapy, among which Individual Psychotherapy and Cognitive Behavioral therapy has showed the best results so far. In the more severe cases, psychotropic medications are often used. This review discusses only unipolar non psychotic depression, and consequently the treatment options for this clinical presentation. Currently, most commonly used antidepressants are Serotonin reuptake inhibitors (SSRIs), as well as Serotonin Norepinephrine reuptake inhibitors (SNRIs). Lack of double blind placebo controlled trials leaves us to build our opinion and expertise on less ideal data sets. However, available data on use of SSRIs and somewhat less of SNRIs in peripartum are numerous. Despite some reports indicating potential teratogenicity of those agents, data are inconclusive and no specific malformation is linked to a specific medication leading us to rely on our clinical judgment and detailed discussion of risks vs benefits with each patient.

Key words: antidepressants, pregnancy, teratogenicity
INTRODUCTION

Depressive disorders are the most common psychiatric disorder in women. The increased incidence in women compared to men becomes apparent after puberty and continues until the fifth decade [1]. Pregnancy is an important phase in the female reproductive cycle and approximately two-thirds of women with a psychiatric diagnosis become mothers. Despite some existing myths, pregnancy is not a protective factor for new onset or the recurrence of previous psychiatric illnesses. For example, it is estimated that major depression occurs in 10–16% of pregnant women. During pregnancy, mood symptoms can induce a remarkable impairment in functioning, either presenting as Minor or Major Depressive Disorder. Screening for peripartum mood disorders have become paramount of good quality medical care and in some parts of US has been mandated by law. Detecting vulnerable women allows better assessment and adequate treatment of this patient population.

EPIDEMIOLOGY

In a prospective community-based study, O’Hara demonstrated similar rates of depression among gravid and non-gravid women [2]. A more recent study demonstrated that depression persists in 10–14% of untreated women throughout pregnancy [3]. The discontinuation of previous treatments for depression poses a significant risk for relapse. In a recent, prospective, longitudinal community-based study, Cohen et al. reported that discontinuation of antidepressants proximate to conception was associated with a 68% relapse rate [4]. Half of those women relapsed during the first trimester and 90% relapsed by the end of the second trimester.

Untreated depression in pregnant women has a negative impact on adaptation and performance in children exposed to the illness in utero. One study demonstrated increased externalizing behaviors (e.g., defiance, aggressiveness, noncompliance), conduct disorder, oppositional defiant disorder, attention deficit disorder, and other behavioral problems in 27-month-old children of mothers with untreated depression during pregnancy [5]. Furthermore, these children were followed on the first day of school and demonstrated poor adaptability to a new and stressful situation. Another prospective study found an increased risk of major depression, anxiety spectrum disorder, and substance abuse in the offspring of depressed parents followed for 20 years [1]. These children were also more likely to suffer from various chronic medical conditions.

Diagnosis of depression in peripartum

Some changes that occur during pregnancy could be mistaken for depressive symptoms and vice versa. Physiological changes that are often present during pregnancy are decreased libido, fatigue, and alterations in sleep and appetite. It is crucial to first distinguish those from symptoms of depression, and to establish an adequate diagnosis of either recurring symptoms or of new onset illness. Symptoms such as anhedonia, hopelessness, helplessness, feelings of guilt and thoughts of suicide can lead into diagnosis of depression. The most common way to identify women at risk is to
administer validated screening tools such as Edinburgh Postnatal Depression Scale-EPDS [6] and Patient Health Questionnaire- PHQ9 [7] and then, if screening positive, provide further assessment and treatment.

When and how to treat Peripartum Depressive Disorders in Peripartum

Symptoms of depression may be mild, moderate, or severe. For mild and moderate cases, non-pharmacological treatments should be attempted first. Psychotherapies, especially interpersonal therapy and cognitive behavioral therapy, are effective in antenatal depression as well as in prevention of postpartum depression [8,9]. Other methods such as a daily exercise and omega fatty acids may also provide potential benefit in mild to moderate depression [10, 11].

When a clinician encounters a patient with more severe depressive symptoms, and diagnosis of univocal depression has been established, antidepressants are most likely inevitable. General considerations during the decision process for and against medication use in pregnancy are the following:

- Ideally, pregnancy would be planned and all treatment decisions should be made well in advance;
- Treatment should be individualized for each patient;
- Risk and benefits of taking antidepressants while pregnant should be discussed with the patient and her partner, if possible;
- Start the antidepressant, which produced a positive response in the past, even if that medication is less well studied; and
- Pregnancy is not a good time for experimentation with medication.

Administering medications during pregnancy is not an ideal situation, yet untreated depression is equally if not more risky for the mother and developing fetus. Depressed mothers tend to have irregular prenatal care, are more prone to use of illicit substances to “self medicate” and are also more ambivalent about the pregnancy itself [12, 13]. Women who go untreated usually have more pregnancy-related complications ranging from preeclampsia, placental abruption, fetal distress, neonatal complications, and premature delivery [14-16]. Women who do not receive treatment of their depressive symptoms during pregnancy are at greater risk of developing postpartum depression [17].

Fear of potential teratogenicity, often leads to abrupt discontinuation of medication once conception is achieved or as soon as a woman starts family planning. Some strategies encourage discontinuation of medications during the first trimester to avoid organ malformations. Studies indicate that women with a history of severe depression, however, have a tendency to relapse three to four months after medication discontinuation [4]. Therefore, the decision to discontinue an antidepressant during the first trimester might possibly work for highly fertile young women who are planning their conception. This decision can be risky if the conception does not take place within a certain timeframe, a situation which frequently occurs in older women. It is important to emphasize that the reintroduction of antidepressants later in the pregnancy tends to attenuate the risk of depressive relapse. This group of women is still at a higher risk for suffering symp-
toms during the pregnancy, however, compared to those who choose continuous treatment. By contrast, a recent study demonstrated that women treated with antidepressants throughout pregnancy were equally prone to suffer from depressive and anxiety symptoms during pregnancy, compared to depressed women not treated with medication [14]. It is difficult to interpret these disparate findings at this time. This study looked at women with mild and moderate symptoms of depression, so it is possible that the outcomes would differ in women with more severe symptoms. It is also possible that these women were undertreated since there is a general tendency to prescribe lower medication doses for pregnant women. Further, women in the second trimester of pregnancy actually need higher doses, due to the increased volume of distribution and other pharmacokinetic changes (change in gastric absorption, increased GFR-Glomerular Filtration Rate, increased hepatic metabolism). It is crucial to approach each case independently and weigh the risks vs. benefits for each treatment approach carefully.

The following issues should be considered when medications are used during pregnancy:

- Effects on timing of labor;
- Altered maternal effects due to altered pharmacokinetic and pharmacodynamics;
- Physical teratogenicity;
- Fetal and neonatal side effects and withdrawal; and
- Behavioral teratogenicity.

Due to obvious ethical reasons, it is not feasible to conduct prospective randomized, double-blind trials. Therefore, we accumulate our knowledge from different sources, such as:

- Prospective (non-randomized, unblinded, no placebo) controlled trials;
- Retrospective studies using large databases such as national birth registries or insurance company registries;
- Self-reported drug registries including the WHO (World Health Organization);
- Drug company registries; and
- Animal studies.

**PHYSICAL TERATOGENICITY**

The Food and Drug Administration (FDA) has created categories which guide our use of medications in pregnant patients. However, there is no FDA-approved psychotropic medication for use in pregnant women. Regarding the medication risk during pregnancy, the FDA recognizes the following categories:

- Category A: Human controlled studies showed no risk;
- Category B: No risk in animals or risk in animals not shown in human controlled studies;
- Category C: Risk in animals; no human controlled studies or studies not available;
- Category D: Positive evidence for risk; need for drug has to justify known risk; and
- Category X: Contraindicated in pregnancy.

It is a common assumption that medications found in category B are safer than those found in the category C, but when there is not enough data about a certain medicine, it may be classified in a higher (“safer”) category. The medicat-
ons tend to downgrade when more information is available (such as paroxetine going from category C to D or buproprion from category B to C). **Basically, there is no medication that can be labeled as “safe or risk free” when used during pregnancy.** The decision of how to treat should be based solely on the principle of measuring risks vs. benefits for a particular individual.

Today, the most frequently used antidepressants are the selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Both groups are also used for treatment of various anxiety disorders. All easily cross the placental barrier exposing the fetus to their direct effects. We now know that the concentrations of specific medication in the amniotic fluid differ, yet the interpretation of the absolute amounts found in the fetus is still unclear. Serotonin plays an important role in neonatal development and its levels increase in fetal tissue during the in utero exposure to SSRIs. In the developing fetus, serotonin has multiple roles such as neurotransmitter-related regulation of cardiac function, respiratory function, and arousal. It also serves as a trophic signal for the developing brain. In addition, serotonergic neurons are present throughout important regions of the brainstem, which regulates respiration, central chemoreception as well as motor regulation. The effect of increased serotonin levels in fetal tissues is not well understood. Avoiding medication just to protect the fetus from unknown potential effects is not always a good solution. Therefore, treatment is an ongoing dilemma, which has become even more complex with some studies indicating potentially severe problems with the SSRIs in this population.

For many years, studies did not demonstrate a statistically significant increased risk for miscarriage or congenital malformations in women taking antidepressants during pregnancy. Several prospective studies evaluated the rate of congenital malformation in fluoxetine exposed infants and no teratogenicity was found [19, 20]. Additional studies also support the reproductive safety of various SSRIs [21-24]. In the Erickson and Whilhom study, citalopram was the most commonly used drug. A large study using the Swedish birth registry data included 4291 SSRI-exposed pregnancies and found a 2.9% congenital malformation rate similar to the 3% rate in the nonexposed population [25]. They also extrapolated data for paroxetine and reported that the rate of congenital malformations increased to 3.4%, which was not significantly higher when compared to the control group. For years, fluoxetine, sertraline, and paroxetine were the most frequently prescribed antidepressants in pregnant women and considered relatively safe. More recent studies, however, are suggesting some potential teratogenicity with the use of SSRIs early in pregnancy. In 2006, a Danish population-based cohort study by Wogelius et al. reported that infants exposed to SSRIs early in pregnancy were at increased risk for developing nonspecific congenital malformations [26]. This group also noted that the illness factor was not considered and depression itself could possibly induce some malformations observed in newborns. This study was based on prescriptions written, but not necessarily filled or used. Further, the use of illicit drugs, alcohol and/or ciga-
rettes was not taken into account. Therefore, it is hard to conclude with certainty that SSRIs were responsible for the higher rate of congenital malformations in that group. Additional studies suggest that paroxetine might induce congenital anomalies, especially cardiac. GlaxoSmithKline, the manufacturer of paroxetine (Paxil®), did an epidemiological database review to examine the risk of birth defects in babies with first trimester in utero exposure to different antidepressants [27]. Paroxetine appeared to induce significantly more congenital malformations compared to other antidepressants. Although not statistically significant, there was a trend for paroxetine to induce cardiovascular malformations, specifically ventral septal defects. GlaxoSmithKline consequently posted a warning for paroxetine and potential cardiovascular malformations during pregnancy. Another epidemiological review of the Swedish Medical Birth Register reported that exposure to paroxetine in the first trimester doubles the risk of congenital malformations compared to other SSRIs used in the same time-period. The most frequently described anomalies in that study were atrial and ventricular septal defects. Due to these recent findings and the potential teratogenicity of paroxetine, the FDA moved this antidepressant in category D [27]. However it is important to emphasize that the current data on SSRI exposure show no consistent information to support specific morphological teratogenic risks.

The Committee on Obstetrics Practice of the American College of Obstetricians and Gynecologists has published recommendations for the use of SSRIs and SNRIs in pregnancy. They suggest an individualized approach during the decision making process for a choice of antidepressant. In addition, the same committee recommended that paroxetine use in pregnancy and among women planning to become pregnant should be avoided if at all possible. A study by Berard et al. reported that paroxetine may induce cardiovascular malformations only if used in doses higher then 25 mg per day during the first trimester [28]. Two other recently published studies reveal additional potential teratogenicity with SSRIs. Contrary to those findings Meta Analysis performed by Mother-Risk group did not reveal any correlation between the first trimester exposure to paroxetine and cardiovascular malformations in fetus [29]. Alwan et al. [30] used the National Birth Defects Prevention Study which is an ongoing, multisite, case-control study of environmental and genetic risk factors for more than 30 selected categories of birth defects. The most commonly used medications were sertraline, fluoxetine, paroxetine, and citalopram. The study demonstrated a link between the first trimester exposure to SSRIs and an increased risk of anencephaly, craniosynostosis, and omphalocele. Among those exposed to SSRIs, obese women were more likely to have an infant with cardiac tract outflow defects as well as septal defects. When analyzing individual SSRIs, paroxetine was associated with anencephaly, right ventricular tract obstruction defects, omphalocele, and gastroshisis. Fluoxetine was associated with an increased risk for craniosynostosis and sertraline an increased risk of anencephaly. While none of these findings were statistically significant, associations were observed. This study did not control for depression severity or antidepressant dose and there was a poten-
tial for recall bias. By contrast, another epidemiologically-based, case-control study showed no association with first trimester exposure to SSRIs and craniosynostosis, omphalocele, or heart defects in newborns [31]. A correlation between sertraline and omphalocele and septal defects, as well as paroxetine and right ventricular outflow tract obstruction defects has been reported. Additionally, cumulative reports that describe the reproductive safety of SSRIs are recently reviewed [33, 34]. Furthermore, a data from prospectively collected cases of women exposed to SSRIs during the first trimester have not found any association with increased malformation beyond the baseline. In addition, no SSRI was link to a specific malformation [35]. While data for antidepressants such as venlafaxine, nefazodone, trazodone, buproprion, and mirtazapine are limited, they do not reveal a potential for teratogenicity with the prenatal exposure [36-38].

Only one relatively recent case control study demonstrated relation between exposure to buproprion in first trimester and increased risk of left outflow heart defect [39]. To this date these data have not been reproduced.

**FETAL AND NEONATAL TOXICITY AND WITHDRAWAL**

Another aspect of medication safety during pregnancy is the presence of neonatal toxicity and perinatal symptoms. These include various physical and behavioral manifestations of a newborn exposed to a medication at or around the time of delivery. The most commonly described symptoms in neonatal syndrome are increased muscle tone; tremulousness; and difficulties with respiration, feeding and disturbed sleep patterns [40]. Neonatal manifestations are well documented and describe a transient neonatal distress syndrome associated with either in utero exposure or acute withdrawal from these medications upon delivery [41-43]. In 2004, concerns about neonatal symptoms led the FDA and Health Canada to issue a warning regarding the use of SSRIs in the third trimester of pregnancy.

While the neonatal syndrome related to SSRI exposure has been described as short-lived and relatively benign, recent studies suggest more severe consequences. One large study using population health data demonstrated an increased risk of respiratory distress in children exposed to SSRIs (primarily paroxetine, fluoxetine, and sertraline) in utero [44]. This study took into account maternal severity of depression but did not control for other psychiatric comorbidities, including substance abuse. These findings may be explained by animal studies which demonstrate that fetal lung serotonin is directly associated with pulmonary artery smooth muscle proliferation and consequent pulmonary hypertension. Similar mechanisms of action could occur in the human fetus. Furthermore, Chambers et al. demonstrated that in a case control study design, in utero exposure to SSRIs occurring after 20 gestational weeks increased the risk of pulmonary hypertension in newborns by 5–6 times [45]. The validity of this study is questionable, however, since it is retrospective and recall bias is highly possible. In addition, the number of exposed in-
fants was small, underlining the need for additional studies. Of note, this study found that 99% of women exposed to an SSRI during pregnancy delivered babies unaffected by PPHN. Furthermore, a recent review of cohort studies found that 1 in 313 full term newborns exposed to SSRIs had severe respiratory difficulties that required intubation but PPHN was not mentioned as a cause [45]. Similarly, another more recent retrospective study did not demonstrate correlation between late exposure to paroxetine and PPHN in newborns [46]. The most recent study found a correlation between the type of delivery, namely cesarean section, with increased risk of PPHN, rather then the SSRI use [47]. To date, data indicating link between late pregnancy exposure to SSRIs and PPHN have never been replicated.

Neonatal syndrome after exposure to SSRIs is real. It peaks within 48 hours after delivery and babies have to be monitored closely. Discontinuation of medications in this time period is not suggested because of the high depression relapse rates. In addition previously suggested tapering the dose of SSRIs to 50% of the regular dose after 35 weeks of gestation was not found to be beneficial, but rather increase risk of relapse of depression is susceptible patients.

BEHAVIORAL TERATOGENICITY

Studies are limited and most report mixed results. A prospective controlled, cohort trial followed children age 15 months to 6 years following in utero exposure to either a TCA or flexitome [48]. No adverse effects on intelligence quotient (IQ) score, language, or behavioral development were found. In contrast, another prospective study showed lower Bayley Psychomotor Developmental Index scores, specifically body control, fine motor skills, and coordination in 31 children exposed to SSRIs in utero throughout pregnancy [49]. Similarly, recent studies demonstrated some delay in early (up to 6 months) fine motor movement in children exposed to SSRIs in utero, yet that difference was no longer evident at 19 months [50].

EFFECTS ON TIMING OF LABOR

Conflicting data exists regarding the affect of in utero antidepressant exposure on preterm labor. Several studies reported no effect of antidepressant exposure on duration of pregnancy [20, 42 - 44]. Some of these studies were limited by small sample sizes or minimal exposure to medication. More recent studies, however, indicate that exposure to most antidepressants in utero reduced the gestational age at birth [49, 51, 52] The most recent study done by Suri et al. [14] employed a prospective naturalistic design to demonstrate that exposure to antidepressants during the last half of pregnancy led to an increased risk of lower gestational age and preterm birth. In addition, this study reported that higher doses induced a lower gestational age at birth (such as preterm birth).

Interestingly, despite the lower gestational age, these babies did not have a lower weight or lower APGAR score.
compared to the control groups. Therefore, these findings may be of a particular value for women with other risk factors for adverse obstetrical outcomes.

**CONCLUSION**

There is no “safe” antidepressant during pregnancy. Being aware that data regarding the use of SSRIs in pregnancy is still limited, one should carefully consider the necessity of prescribing antidepressants in this population. Conversely, untreated depression has multiple consequences for the mother and developing fetus. It is important to remember that randomized, double-blind, placebo-controlled trials are not ethically possible in this population. Taking into consideration the risk-benefit ratio, as well as individual preference is crucial. The conceptual model created by Wisner et al. serves as helpful guideline in this decision making process [17].

When making the decision to use medication for depression in pregnant women, SSRIs are first line treatments. If previous trials with SSRIs were unsuccessful or there is a history of a positive response to TCAs, nortryptiline is the best choice due to its low anticholinergic effects and ability to measure plasma levels. When deciding to use an SSRI, fluoxetine has the most data and no teratogenicity has been observed. It is not recommended, however, if breastfeeding is planned due to its long half-life and the possibility of accumulation in infant serum. While citalopram has been studied more than sertraline, it accumulates more in the fetus (i.e., higher fetal to maternal serum ratio). Therefore, it should be a second line choice treatment, used in women who have responded well to it in the past, or for those who had an undesirable side effect on either fluoxetine or sertraline.

Paroxetine should probably be avoided if pregnant or planning a pregnancy, however data are not consistent. If it is the only helpful medication, explain that paroxetine can increase the possibility for congenital malformations by 1% (from 3 to 4%) which is more then with other SSRIs. If one chooses to stay on paroxetine during pregnancy, high resolution ultrasound conducted in 16-17 gestational week could detect potential cardiac malformation.

The SSRI dose might need to be raised as the pregnancy progresses due to an increased volume of distribution and increased metabolic rates. Occasionally splitting the dose might be a reasonable approach to reduce in utero exposure to medication. One should address that option on case to case basis. Depressive symptoms should be monitored closely to avoid under medicating. The antidepressant should be administered for at least one year post partum and then reassessed for ongoing necessity.
Sažetak

Tretman depresije u periodu peripartuma je izazovan zadatkom. Primena terapije i njen izostanak nose svoje rizike za majku, bebu i celu porodicu. Od krucijalnog značaja je postavljanje adekvatne dijagnoze i predloganje najboljeg terapijskog pristupa, koji bi trebalo da bude individualno prilagođen, a rizici i koristi terapije razmotreni sa majkom, idealno i sa ocem deteta. Za blage i umerne depresivne simptome terapija izbora je psihoterapija, individualna psihoterapija i kognitivno bihevioralna su pokazale do sada najbolje rezultate. U najtežim slučajevima indikovana je primena neptrofnih medikamenata. U radu se razmatraju terapijske opcije u sklopu unipolarne nepsihotične depresije. U sadašnje vreme, najpreispisivanijsi antidepressivi su inhibitori preuzimanja serotonina (SSRI) kao i inhibitori preuzimanja serotonina i noradrenalinena (SNRI). Nedostatak duplo slepih placebom kontrolisanih studija ostavlja prostor za formiranje stava u ovom domenu na osnovu manje validnih podataka. Ipak brojni su podaci dostupni o primeni SSRI a u manjoj meri i SNRI u periodu peripartuma. Uprkos tome da neki izveštaji ukazuju na potencijalnu teratogenost ovih lekova, podaci su nepotpuni i ni jedna specifična malformacija nije povezana za specifični antidepressivni medikament, što nas upućuje na oslanjanje na kliničku procenu i detaljno razmatranje rizika vs. koristi za svakog pacijenta ponaosob.

Ključne reči: antidepressants, pregnancy, teratogenicity

References:


