

## WHAT IF DEPRESSED AND PREGNANT?

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### SUMMARY

*Depression is the most prevalent mood disorder among pregnant women. Only 50% of women seek intervention during gestation. Untreated during pregnancy, depression can induce obstetric and neonatal complications, most commonly, anhedonia, suboptimal weight gain, suicidal behavior, pre-term birth, and/or spontaneous miscarriage. The babies more often suffer cognitive deficits, low birth weight, and growth delay. The mothers subsequently also experience an increased risk for significant degrees of postpartum depression. Those with relatively milder cases of depression should initially receive psychotherapy. Otherwise, there are many antidepressant medications available for the pharmacotherapy of depression. However, treating pregnant females with depression is a challenge because of potential teratogenic effects caused by many pharmaceuticals. Physicians should know the recommended guidelines for treating depressed women during a time of gestation. It is crucial to identify women suffering from depression during pregnancy, and electing those that warrant pharmacotherapy while picking the best and safest medication is a complex process with paramount significance. Before prescribing an antidepressant drug, explain the advantages and disadvantages of the interventions. Whenever prescribing during these circumstances, more than conventionally close obstetric, emotional, and medication monitoring is to be provided. This would also include an emphasis on diet, exercise, psychotherapy, and avoidance of any non-critical medicinal or other substance exposures.*

**Key words:** depression - antidepressive agents - drug therapy – pharmacotherapies – pregnancy – fetus - congenital abnormalities

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### INTRODUCTION

#### Why treat unipolar depression during pregnancy?

Unipolar depression is common among women during pregnancy and the postpartum period; yet, treatment recommendations for that are less consistently addressed (Vigod et al. 2016). The prevalence of depression during pregnancy is 7% and approaching 9% during the postpartum period (Ko et al. 2012, Vesga-Lopez et al. 2008). There is a high risk of morbidity and mortality for mothers and children associated with depression during pregnancy (Susser et al. 2016). Antenatal affective disorders are associated with detrimental lifestyle decisions, such as inadequate diet or prenatal care, smoking, and abuse of drugs and/or alcohol. Well-recognized problems affecting the baby include congenital malformations, altered neurological development, pre-term birth, increased cortisol, and decreased dopamine levels. These complications result in more frequent neonatal intensive care issues (Susser et al. 2016, Muzik & Hamilton 2016). Growth delays, deficits in attention, and mood disorders are long-term consequences (Muzik & Hamilton 2016). Furthermore, mothers with depressive symptomatology who discontinue antidepressant medications during pregnancy are at high risk of relapse, with adverse effects on their progeny (Susser et al. 2016).

Psychotherapies like cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) are usually the

first treatment choices recommended for depressed women during pregnancy and postpartum. Pharmacotherapies, including selective serotonin reuptake inhibitor (SSRI) drugs, serotonin-norepinephrine reuptake inhibitors (SNRI), and tricyclic antidepressants (TCA), can be safely prescribed during pregnancy. Exercise, social activation, a balanced diet, and adequate sleep are also helpful in mitigating depressive feelings (Bowen et al. 2014, Dennis & Dowswell 2013).

#### What are the challenges?

For ethical reasons, there is a reluctance to conduct randomized controlled trials during gestation, resulting in a dearth of pharmacotherapy outcome evidence. In lieu of conclusive data, the following are the suggested practice guidelines (Susser et al. 2016, NICE 2014). Since many localities lack adequate access to psychiatric services, primary care doctors and obstetricians are often responsible for recognizing and treating women with perinatal unipolar depression. Screening for mood disorders and providing intervention has good efficacy (Susser et al. 2016).

### DISCUSSION

#### What are the types of practice guidelines?

Various practice guidelines for screening depression are as follows: a) The US Preventive Services

Task Force (USPSTF) guidelines help depression screening during pregnancy (Dennis & Dowswell 2013). b) The American College of Obstetricians and Gynecology (ACOG) guidelines recommend that all women should be screened for depression in the perinatal period, especially in their second trimester (Muzik & Hamilton 2016). c) The United Kingdom National Institute of Health and Care Excellence (NICE) guidelines suggest that all patients with a previous history of depression should be screened for depression and that psychotherapy is initially indicated instead of pharmacotherapy in women with milder cases of unipolar depression (NICE 2009). d) The Department of Veteran Affairs (VA) endorses screening for depression on an annual basis (US VA 2017). e) The American Psychiatric Association (APA) approves the prescribing and/or continued use of antidepressant medications for women who are moderate to severely depressed during pregnancy (Gelenberg et al. 2010).

### **What does USPSTF suggest?**

The USPSTF has recommendations on managing unipolar depression in adults, including those who are pregnant or during postpartum (Dennis & Dowswell 2013). They report that screening and prescribing antidepressant medications during pregnancy has positive outcomes. The risk of fetal malformations during the use of these drugs is not significantly different from that of other pregnancy outcomes (Dennis & Dowswell 2013).

Risk factors inducing depression in gestational and postpartum women include child-care stress, decreased social support, prenatal anxiety, a previous history of postpartum depression, poor self-esteem, single parenting, and unintended pregnancy. According to the USPSTF, along with assessing risk factors, the Edinburg Postnatal Depression Scale (EPDS) is useful during pregnancy and postpartum to screen for a mood disorder. Patients having a positive screening should be assessed for the severity of depression and other psychological or medical co-morbidities. Once the diagnosis is confirmed, depending on the severity, psychotherapy, pharmacotherapy, or a combination can be made available (Dennis & Dowswell 2013).

Systematic reviews revealed that when research investigators compared the use of EPDS with other instruments, the sensitivity of this test was at 0.67 to 1, the specificity of 0.90, and it had a positive predictive value between 47-64% (Siu et al. 2016, O'Connor et al. 2016). Screening patients for unipolar depression during the postpartum period had a 28-59% reduction in depression severity compared to routine care (NICE 2014). EDPS scores declined by 5-10 points when intervention and screening of these subjects were completed as compared to a 2-6 point decrease when not following these practices (O'Connor et al. 2016).

### **Which pharmacotherapy?**

The initial perinatal treatment is educating the mothers on the relative risks and benefits of pharmaco-

therapy and non-pharmacological interventions. The severity of the depressive episode is always considered (NICE 2014). When required, the most common first choice antidepressant medicine choices are among the SSRI group (Susser et al. 2016).

Sertraline, citalopram, escitalopram, and fluoxetine are the most commonly prescribed drugs during the first trimester of pregnancies (Zoega et al. 2015). Reportedly, sertraline has a low risk of teratogenicity and can also be safely prescribed during lactation (Hayes et al. 2012). Citalopram and sertraline are often preferred during pregnancy; however, both have been linked to postpartum hemorrhage in one study. Less evidence is available to evaluate some of the other SSRI drugs (Hayes et al. 2012). Duloxetine and venlafaxine are reported to be the safest SNRI selections for prescribing during pregnancy; current research reveals no risk for teratogenicity or congenital malformations. Other antidepressant medicines that are considered to be safe for treating unipolar depression during gestation include bupropion, duloxetine, mirtazapine, and tricyclic antidepressant drugs (Byatt et al. 2013).

Pharmacotherapy prescribing should consider these facts. a) Providing psychotherapy alone is the best initial approach for patients with mild depression. b) A combination of psychotherapy with pharmacotherapy is usually more effective for treating unipolar depression than pharmacotherapy alone. c) Psychological interventions should always be provided (NICE 2014). d) There is risk associated with exposure to any medication; there are also dangers resulting from untreated depression (Susser et al. 2016). e) SSRI monotherapy is advised as one way to reduce pharmacotherapy exposure (Susser et al. 2016, Muzik & Hamilton 2016). f) The lowest clinically effective dosage in treatment aims to limit the amount of medication exposure and should help avoid under-treatment (Susser et al. 2016). g) Use the medicine with proven efficacy. Although SSRIs are the most commonly chosen drug, TCA and/or other related medications can also be effective, especially if the mother has previously responded well to a specific one (Susser et al. 2016, Muzik & Hamilton 2016). h) Switching medications might be helpful. Physicians should sometimes consider changing to an alternately effective pharmaceutical with the fewest known adverse effects on patients and the unborn (NICE 2014). i) If tapering off of medications is appropriate, do so in the pre-pregnancy stage. It minimizes the risk of added danger by the affective illness and/or drug exposures (Susser et al. 2016). j) SSRI blood levels usually decrease in the second and third trimesters, and thus on a clinical basis, the dosage might need to be increased (Susser et al. 2016). k) Identify high-risk women, such as those with a previous or family history of depression or who have experienced depressive episodes within the recent months before conception. Such individuals often have a high relapse rate, irrespective of current stability (Muzik & Hamilton 2016, Pearlstein 2015).

## What are the fetal concerns?

The primary concern when prescribing antidepressant medications during pregnancy is the risk of teratogenicity or congenital malformations. Some of the main fetal concerns are as follows:

### *Poor Neonatal Adaptation Syndrome*

Prescribing SSRI in the third trimester is associated with poor neonatal adaptation syndrome (PNAS) (US VA 2017). Symptoms include respiratory distress, apnea, and irritability. PNAS occurs in between 5-85% of infants following SSRI or SNRI exposure in utero (Grigoriadis et al. 2013a). Drug discontinuation late during gestation may not consistently alleviate this risk. Clinical manifestations are usually mild and resolve within weeks. Since TCAs can induce neonatal symptoms similar to toxicity or withdrawal, medicines with minimal anticholinergic effects (e.g., nortriptyline or desipramine) are frequently preferred (Susser et al. 2016, Pearlstein 2015).

### *Miscarriage*

Evidence regarding the rate of miscarriage in the first trimester is controversial (Susser et al. 2016). SSRI exposure might lead to miscarriage and fetal loss; yet, discontinuing SSRIs prior to pregnancy may increase the risk of miscarriage as well (Susser et al. 2016, Vigod et al. 2016). The risk of spontaneous abortion is slightly higher with venlafaxine, duloxetine, and TCA drugs, as compared to that with an SSRI (Lassen et al. 2016, Kjaersgaard et al. 2013).

### *Congenital Malformations*

There is no known significant association between congenital malformations and first-trimester SSRI exposure, except for prescribing paroxetine (Zoega et al. 2015). The evidence about paroxetine as an established cause of cardiac malformations to a fetus exposed in utero is noted but is not substantiated nor recommended during gestation (Zoega et al. 2015). A meta-analysis indicated that babies within Utero fluoxetine exposure had an increased risk of teratogenicity and congenital cardiac malformations (e.g., right ventricular outflow tract obstruction) (Reefhuis et al. 2015). Associations with teratogenicity, especially of cardiac malformation occurrences, are inconsistently reported and might be attributed to confounding factors, including the severity of depression, maternal age, and/or ingestion of other substances. SNRI and TCA drugs are not linked to congenital malformations (Susser et al. 2016, Muzik & Hamilton 2016, Zoega et al. 2015, Pearlstein 2015).

Antidepressant medications can induce an increased risk for congenital defects, but the baseline incidence suggests that the absolute risk is low, reportedly at “minimal” clinical significance (Muzik & Hamilton 2016). A meta-analysis of 13 studies compared infants who developed cardiac malformations with those who did not know when all the mothers

were exposed to antidepressant drugs during pregnancies. This study revealed that infants born with heart abnormalities when their mothers were treated with antidepressant medications experienced about a 1.4 fold increased risk, with a confidence interval of 1.1-1.7, over those who were not so exposed. This translates to an increase of two cases per 1,000 live births (Grigoriadis et al. 2013b).

A study by Hata et al. assessed the effect of psychotropic drugs on fetal behavior and found no significant adverse impact on fetal behavioral development in utero due to psychotropic medications (Hata et al. 2019). In this case-control study, Kurjak’s antenatal neurodevelopmental test (KANET) and 4D ultrasound were used during 28 and 36 weeks of gestation in pregnant women. The case group consisted of pregnant women who took psychotropic medications during pregnancy. A total KANET score of 10 to 16 is considered normal, the borderline score is 6 to 9, and 5 or below considered abnormal. The score was determined based on eight fetal parameters consisted of isolated hand movements or hand to face movements, finger movements, perception of general movement, isolated eye blinking, isolated head anteflexion, cranial sutures and head circumference, and facial alteration or mouth opening, or isolated leg movement. Even though in the case group, three neonates were born with total anomalous pulmonary venous return (TAPVR), esophageal atresia, and meconium aspiration syndrome (MAS), the findings were not statistically significant, and the study failed to find the association of psychotropic drugs with fetal abnormal behavioral and anomalies (Hata et al. 2019).

### *Persistent Pulmonary Hypertension of the Newborn*

The effect of third trimester SSRI exposure precipitates a risk of persistent pulmonary hypertension of the newborn (PPHN), ranging up to a six-fold increase. However, no data is suggesting which SSRI is associated with causing more PPHN. The general population incidence is 1-2 live births per 1,000.4. Due to the lack of evidential consensus, this is to be discussed with patients, but often without recommending changes in treatment. TCAs and SNRIs are not known to cause PPHN (Pearlstein 2015).

### *Pre-Term Birth and Low Birth Weight*

There is evidence that SSRI exposure causes pre-term birth (PTB) and low birth weight (LBW) (Jarde et al. 2016, Cantarutti et al. 2016). Pregnant women who are depressed are prone to deliver pre-term and low birth weight babies irrespective of antidepressant medication intake (Yang et al. 2017). SSRI exposure in utero at 2-4 weeks is associated with prematurity (Lennestål & Källén 2007). The National Pregnancy Registry study notes that venlafaxine is associated with pre-term birth in pregnant women treated with antidepressant medication as compared to other pregnancies (Brown et al. 2016). However, TCA drugs have been linked to both concerns (US VA 2017).

## Autism Spectrum Disorders

SSRI drug exposures could lead to speech and language delays and an association between autism spectrum disorders (ASD) and such exposure is postulated (Cantarutti et al. 2016, Boukhris et al. 2016, Brown et al. 2017). The risk may be higher for boys than girls, but existing research did not always adjust for confounding variables; with control of these issues, an association is reportedly not present or might of less significance (Muzik & Hamilton 2016, Yang et al. 2017, King 2016). Always balance this against the risk of untreated maternal mental illness, also linked to ASD (Gentile 2015). However, there is no evidence showing an association between SNRI and TCA drug exposure with ASD (Gadot & Koren 2015).

## What are the maternal concerns?

There is some association between maternal SSRI exposure and gestational hypertension and pre-eclampsia (Muzik & Hamilton 2016). Pre-eclampsia incidence following SSRI patient usage during gestation is 3.7%, compared to that of 2.4% in non-exposures (Pearlstein 2015, Kim et al. 2016). For those treated for longer than only the first trimester, the incidence of pre-eclampsia is over 15%, perhaps related to the effect of serotonin on vascular modifications (Miller 1994). There are confounding issues such as depression severity, body mass index, and socioeconomic factors, which could also influence the outcome. Evidence about postpartum hemorrhage as a potential complication of SSRI, SNRI, or TCA exposure is unclear (Kim et al. 2016, Miller 1994). Some investigations cite an increased risk, but the significance is said to be small; yet, there is an increased occurrence of such hemorrhages once fluoxetine or sertraline are prescribed (Kim et al. 2016).

## What if pharmacotherapy is not effective?

Electroconvulsive therapy (ECT) can be very effective for patients who do not respond well to multiple pharmaceutical trials of medications or who decline medicinal use during a time of gestation. Research involving 300 pregnant subjects who received ECT revealed no evidence of fetal malformations or developmental defects in those children exposed in utero (Miller 1994). Transcranial magnetic stimulation (TMS) is also reported to be a safe, effective alternative treatment during pregnancy (Kim et al. 2011).

## CONCLUSION

Psychotherapy is indicated for women in mild cases of depression and/or in more severe instances, together with pharmacotherapy. The risk-to-benefit ratio of antidepressant drug prescribing to women during pregnancy remains without consensus. It makes prescribers wary of recommending antidepressant medication management during the peripartum. Untreated depression during gestation can result in a detrimental effect on mothers and children. Treatment options for depression amongst preg-

nant patients must be determined at the individual level, after in-depth weighing and discussing risk-benefit ratio to improve and optimize healthcare outcomes.

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Tina Thomas: Conceptualization, design, investigation, methodology, literature search, visualization, approval of the final version of the manuscript, original draft writing & editing.

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Steven Lippmann: Conceptualization, project administration, supervision, validation, visualization, original draft writing, reviewing, and editing.

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