DEPRESSION IN PREGNANCY: SCREENING, DIAGNOSIS
AND TREATMENT OPTIONS

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Perinatal depression occurs in 8-25% of pregnancies in the United States (Field, Diego & Hernandez-Reif, 2006). It is a disorder that can cause adverse consequences to the mother, fetus, neonate, and family unit. In order to properly diagnose perinatal depression, use of an objective screening tool is recommended. The Edinburgh postnatal depression scale (EPDS) has been found to be highly sensitive and specific when screening for depression in pregnant women (Hayes, 2010; Milgrom, Ericksen, Negri, & Gemmill, 2005). Upon diagnosis, treatment of depression is crucial to avoid the sequelae of depression. For mild to moderate depression, psychotherapy, either cognitive behavioral therapy or interpersonal psychotherapy can be considered a first line treatment (Spinelli & Endicott, 2003). The efficacy of acupuncture, massage therapy, and bright light therapy are thought to have some positive effects, but requires further research to determine proper use (Misri & Lusskin, 2013). For moderate to severe depression, antidepressant medication is recommended.

Keywords: Depression, pregnancy, perinatal, antidepressant, Edinburgh Postnatal Depression Scale
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Depression in Pregnancy: Screening, Diagnosis, and Treatment Options

Major depressive disorder is a condition that affects up to 14.8 million Americans, or 6% of the population within any given year (National Institute of Mental Health, 2013). The prevalence of this condition within a person’s lifetime is over 16% (Kupfer, Frank & Phillips, 2012). The criteria for diagnosis include five or more of the following symptoms: depressed mood; loss of interest in activities; weight loss or gain; insomnia or hypersomnia; decreased concentration; decreased energy; feelings of worthlessness or guilt; psychomotor agitation or retardation; and suicidal ideation. In addition, it is required that one of the symptoms is either depressed mood, or loss of interest in one’s usual activities, and the symptoms must be present for 2 weeks or greater (DoD Deployment Health Clinical Center, 2009).

There are several theories regarding the pathophysiology of depression. The neurotransmitter theory was proposed after observations that the medication imipramine reduced the neuronal reuptake of a vital neurotransmitter, norepinephrine. This caused an increase of norepinephrine within the neuronal synapse, which resulted in decreased depression. Serotonin and dopamine are additional neurotransmitters thought to cause depressive symptoms when levels are depleted (Hasler, 2010; Takahashi, 2010).

Another theory thought to contribute to the pathophysiology of depression is related to the neuroendocrine system. Many symptoms of depression are due to hypothalamic dysfunction and the hypothalamic-pituitary-adrenal (HPA) axis (Worthington III & Rauch, 2009; Takahashi, 2010). The HPA axis involves the relationship and release of hormones by the hypothalamus,
pituitary and adrenal glands (Forshee, Clayton & McCance, 2010). This axis can be overly activated by the body's perception of stress, which causes hypothalamic production of corticotropin-releasing hormone leading to excessive levels of cortisol in the body. Overabundance of cortisol has been shown to be responsible for symptoms of depression including sleep disturbances, appetite changes, and psychomotor dysfunction (Worthington III & Rauch, 2009). Stress from environmental factors may be related to the susceptibility of an individual for depression. Surrounding influences can include work, childcare, financial concerns as well as relationship troubles (University of Maryland Medical Center, 2009). However a genetic component is thought to be more closely related to the development of depression than one’s environment (Worthington III & Rauch, 2009).

Depression affects women twice as much as it does men (Kupfer, Frank & Phillips, 2012). Studies have shown that women are physiologically more susceptible to perceived stress, which activates the HPA axis (Hasler, 2010). In women, hormonal changes related to puberty, pregnancy, post-partum, and menopause have been implicated in an increased rate of depression during these periods (University of Maryland Medical Center, 2009).

Perinatal depression encompasses major or minor depressive episodes during the perinatal period, which is the time from when a woman becomes pregnant lasting up to a year after the pregnancy ends (Perinatal mood, 2013). For the purposes of this review, perinatal depression will be discussed as related to the time period during pregnancy only, as there are many distinct concerns related to post-partum depression. The prevalence of major depressive disorder during pregnancy is 3.1-4.9 % (Gaynes et al., 2005; Misri & Lusskin, 2012). The prevalence of suffering from any depressive episode, major, or minor during pregnancy is as
great as 8.5-25 %. (Field, Diego & Hernandez-Reif, 2006; Misri & Lusskin, 2012). There are several risk factors for perinatal depression including a previous history of depressive episodes and family history of mental illness or substance abuse. Many social factors including relationship and financial stress as well as difficulties with previous pregnancies, births, or miscarriages can contribute to perinatal depression (Perinatal mood, 2013). Lack of desire and/or ambivalence towards the current pregnancy is also a risk factor (Misri & Lusskin, 2012).

Research has demonstrated that there might be an increased risk for depression during certain periods throughout the pregnancy. One study reported the incidence of depression is greatest during the second trimester, while other studies have demonstrated that both the second and third trimesters are particularly vulnerable times (Misri & Lusskin, 2012).

The effects of perinatal depression can have grave physiologic adverse effects on the pregnant mother. Complications that occur during the pregnancy of a depressed mother are numerous and can include placental dysfunction, placental abruption, pregnancy induced hypertension, preeclampsia, spontaneous abortion or premature delivery (Misri & Lusskin, 2012; Field, Diego & Hernandez-Reif, 2006). Sequelae of perinatal depression include gastrointestinal conditions such as irritable bowel syndrome, cardiovascular conditions, as well as changes in the brain structure, such as dilated ventricles and decreased size of the hippocampus (Bowen & Muhajarine, 2006).

One study found that mothers suffering from perinatal depression had high cortisol levels and norepinephrine and low dopamine and serotonin levels. In this study, it was also noted that these mothers were more likely to deliver prematurely than their non-depressed counterparts (Field, et al., 2006). Additional results of this study indicated increased cortisol had a direct
effect with an increased incidence of premature delivery, and increased norepinephrine levels with increased risk for preeclampsia and low birth weight (Field, et al., 2006).

Symptoms associated with depression can cause drastic behavior changes, which are detrimental to the woman. She is more likely to have poor nutritional habits, which can prevent adequate weight gain throughout the pregnancy (Misri & Lusskin, 2012). Altered sleep habits and decreased compliance in following prenatal advice are likely consequences of untreated maternal depression. A pregnant woman who is depressed is also more likely to use alcohol, drugs, and/or tobacco as a coping mechanism (Misri & Lusskin, 2012; Spinelli & Endicott, 2003).

Untreated depression can put a woman at an increased risk for worsening symptoms, which can lead to psychosis, as well as manifestations of other mental health disorders (Misri & Lusskin, 2012). Anxiety and panic disorders are the most frequent co-morbid conditions associated with depression. (Misri & Lusskin, 2012) Other outcomes of untreated depression can include consequences lasting into the post-partum period. This includes difficulty bonding with the infant and a much greater risk for post-partum depression and post-partum psychosis. (Misri & Lusskin, 2012).

Self-harm and suicidal ideation poses a substantial threat to those suffering from perinatal depression (Spinelli & Endicott, 2003). Suicidal ideation is present in up to 40% of depressed pregnant women (Bowen & Muhajarine, 2006). One study reviewed causes of maternal death during pregnancy. Upon evaluating all reported cases of death during pregnancy, the risk of death for the general population is 17.8 per 100,000. Of these deaths, 12% were due to unspecified psychiatric causes and 10% were the result of suicide (Oates, 2003). This makes
suicide the second leading cause of death in pregnant women, after thromboembolisms (Oates, 2003). This study also reported violent methods were more likely used to commit suicide, such as hanging or jumping (Misri & Lusskin, 2012; Oates, 2003).

Gandhi et al. (2006) compared women in California between 1991 and 1999 who attempted suicide during pregnancy to a control group of pregnant women who did not attempt suicide. They found the risk of a suicide attempt in pregnant women to be 0.4 in 1,000 after the 19th week of pregnancy. In this study, 86% of women attempted suicide by overdosing on medications or ingested poisonous material. This study did not include suicide attempts that were not hospitalized, which indicates that the rate of attempts might be higher than reported. From the population studied, women who attempted suicide during pregnancy were generally less than 30 years old, were of low income, low education, had a history of substance abuse, and were African American (Gandhi et al., 2006).

Appleby (1991) conducted a retrospective study from 1973 to 1983 in England and Wales to discover more about suicide during pregnancy. The population studied were women age 15-44 who committed suicide while pregnant or in the year after birth compared to pregnant women who did not commit suicide. The mortality ratio was found to be 0.17. However, in the case of a poor pregnancy outcome such as stillbirth, the suicide rate was increased six times. It was also demonstrated that the risk for suicide in pregnant adolescents was five times the risk of suicide in pregnant women in any other age group. Another important discovery from that study was that 57% of the suicides recorded occurred during the second trimester of pregnancy (Appleby, 1991).
Not only does depression affect the pregnant mother, but it can lead to consequences for the fetus as well. When a pregnant woman is depressed, it has been observed on ultrasound that the fetal heart rate is increased and greater fetal activity has been detected as opposed to non-depressed pregnant women. This was observed as early as the fifth month of the pregnancy, which indicates that maternal depression can negatively affect the fetus as early as the second trimester (Field, et al., 2006). It is thought that the increased fetal activity and heart rate could be related to the increased cortisol levels in a depressed mother. Elevated levels of cortisol have been seen at birth in infants born to depressed mothers (Field, et al., 2006). Animal studies using primates, mice and sheep found that increased maternal cortisol could lead to decreased development of fetal lungs, heart and brain. It also has been shown to decrease placental size and cause uterine artery constriction which results in reduced fetal blood flow (Field, et al., 2006). Placental dysfunction causes a limited availability of oxygen and nutrients to the fetus, which is directly associated with premature birth and decreased fetal growth (Field, et al., 2006). Due to the increased occurrence of prematurity, infants born to depressed mothers are more likely to need intensive care following birth for a variety of complications. The most common concerns are ventricular hemorrhaging, and respiratory distress leading to bronchopulmonary dysplasia (Field, et al., 2006). Perinatal depression is also associated with the infant being small for gestational age (SGA). One of the central causes for fetal death and disease is due to SGA (Field, et al., 2006). In addition, the fetus is at risk for the harmful effects of smoking, alcohol, and drugs if a mother uses them to self-medicate depression symptoms (Misri & Lusskin, 2013).

Besides obvious physiologic concerns, there are psychosocial and developmental consequences to the fetus associated with perinatal depression. Studies have shown a potential
for increased fussiness and negative affect during maternal-infant interactions, which indicate impaired bonding. Perinatal depression has been shown to lead to delayed growth and development (Field, et al., 2006). Increased irritability and decreased variation in facial expressions is also noted in infants who are born to depressed mothers (Stewart, 2011). Many of these children have decreased language skills, delayed physical and mental development, and reduced cognitive function in their early childhood (Toohey, 2012). One study showed neonatal electroencephalogram (EEG) changes similar to patterns noted in their depressed mothers. Increased stimulation was noted in the right lobe of the brain, indicating decreased ability to regulate emotions and high incidence of depression (Field, Diego & Hernandez-Reif, 2006). This change is also associated with lower vagal tone, and neurobehavioral dysfunction (Field, et al., 2006; Toohey, 2005).

The entire family unit is likely to be affected by perinatal depression as well. If a partnership is unstable, it can worsen the effects of depression and cause further damage to the family (Misri & Lusskin, 2013). The strain of perinatal depression can also be associated with domestic violence (Misri & Lusskin, 2013). In a study conducted in Brazil between June 2006 and April 2007, 712 pregnant women were assessed for domestic violence and depression during pregnancy. Using an abuse assessment screening tool, 18.2% of these women reported domestic violence during their current pregnancy. Of these women 28% reported the presence of depressive symptoms as well (Manzolli et al., 2010).

While an obstetrician-gynecologist will follow most pregnant patients, it is likely that the primary care provider may come into contact with these patients at some point during their pregnancy (Barrio & Burt, 2000). Women who have an established relationship with a primary
care provider may return to this trusted individual with concerns of depression (Harvey, Fisher & Green, 2012). For many women, recognizing their symptoms of depression may be difficult, therefore presentation to primary care for somatic concerns is likely (Barrio & Burt, 2000). This provides a vital opportunity for primary care providers to screen for perinatal depression. While many primary care and perinatal care providers realize the importance of diagnosing and treating perinatal depression, one study discovered that as many as 48-64% of primary care providers identify a lack of knowledge and tools to appropriately diagnose and treat this disorder (Olson et al., 2002; Shade et al., 2011).

Perinatal depression continues to be under diagnosed and undertreated (Misri & Lusskin, 2012; National Institute of Mental Health, 2013). This may be related to somatic concerns associated with both depression and pregnancy including changes in sleep, appetite, weight, and energy level, which can prevent the provider and the patient from recognizing perinatal depression (Misri & Lusskin, 2012). It is clear that depression during pregnancy causes disruptive and potentially lethal outcomes to the mother and infant, which can negatively impact the family unit (Earls, 2010; National Institute of Mental Health, 2013). It is of the utmost importance to properly diagnose and treat depression that occurs during the perinatal period to ensure the health and well-being of the infant, mother, and family. The aim of this review is to increase knowledge about the diagnosis of perinatal depression and the use of diagnostic tools such as the Edinburgh postnatal depression scale. The benefits and risks of depression treatment during pregnancy using psychological therapy, exercise programs, alternative treatments, and medications will also be discussed. Post-partum depression will not be addressed in this paper as there are many distinct concerns regarding that diagnosis.
Literature Search Strategies

Washington State University’s database was accessed to search for literature. The Cumulative Index to Nursing and Allied Health (CINAHL) and PubMed were the primary databases used to search for English language articles from 1982 to the present. The initial search terms included pregnancy and depression. These searches retrieved over 4,000 articles from CINAHL and 9,000 articles from PubMed. In order to narrow the results, additional searches were conducting using the above phrases combined with search terms including: pathophysiology, treatment, diagnosis, selective serotonin reuptake inhibitor, tricyclic, antidepressant, screening, diagnostic tools, perinatal, acupuncture, exercise, massage therapy, Edinburgh postnatal depression scale. Articles were selected from these searches based on content. When researching diagnostic tools and screening, the Edinburgh postnatal depression scale was the most discussed screening tool, and therefore was selected for a central topic discussed in screening.

Literature Review

Screening

It is recommended that pregnant women undergo routine depression screening, as the effects of untreated depression can have severe consequences on the entire family unit (Leigh & Milgrom, 2007). Signs of depression can be easily missed in routine appointments. If a provider uses an interview method to acquire information regarding depressive symptoms, it is more likely to be undetected or misdiagnosed. Goodman & Tyer-Viola (2010) recommended consistently utilizing a screening tool to ascertain information on every pregnant patient rather than relying on a subjective interview technique. At this time it is estimated that providers
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caring for pregnant women only screen their patients with an objective screening tool 25-40% of the time (Breedlove & Fryzelka, 2011).

One of the tools frequently recommended to screen for depression in pregnancy is the Edinburgh postnatal depression scale (EPDS). The EPDS was originally designed as a systematic screening tool for women at risk of post-partum depression (Tandon, Cluxton-Keller, Leis, Le & Perry, 2013). It is a ten-item questionnaire that addresses cognitive and affective depressive symptoms that have been noted over the prior week (Tandon et al., 2013). This tool is unique in that it omits somatic concerns commonly associated with pregnancy and the post-partum period, so as to not confuse common physical complaints of pregnancy such as fatigue, change in sleep habits and changes in weight and those associated with depression, as they are comparable (Tandon, et al, 2013).

The EPDS has proven to be an effective diagnostic tool for post-partum depression (Breedlove & Fryzelka, 2011). Despite its initial indication as a postnatal depression tool, it has been found to be consistently accurate in women across the perinatal period (Hayes, 2010). It has demonstrated to possess a positive predictive value when used to screen pregnant women of all socio-economic statuses for depression (Tandon et al., 2013). Since being developed in 1987, it is still the mostly widely used screening tool for perinatal depression, internationally (Hayes, 2010). It has been found to be 100% sensitive and 89% specific in depression screening, although false positives and false negatives can occur (Hayes, 2010; Milgrom, Ericksen, Negri, & Gemmill, 2005). Women who score positive for prenatal depression are most likely to also score positive for post-partum depression. This screening tool can be utilized sequentially during visits throughout the patient’s pregnancy and within the year after birth to track depression
occurrence and intensities. Consistent use of this tool can be beneficial in aiding the primary
care provider in screening and evaluating depression across the perinatal period (Goodman &
Tyer-Viola, 2010).

It is important to note that the Edinburgh Postnatal depression scale is merely a screening
tool. It allows providers to address the issue of depression among pregnant women in an
objective manner while only spending approximately five minutes to do so (Breedlove &
Fryzelka, 2011). There are 30 allotted points for this questionnaire. If a woman scores 0-9, the
likelihood that she is experiencing depression is low. If she scores between 10-12, it is probable
that she has mild to moderate depression. If a patient scores above 12, severe depression is
expected. If a woman’s score is between 10 and 12, then it is recommended she be rescreened in
2 weeks (Hayes, 2010). Other sources state that if a woman scores 9 or less initially, she should
be rescreened in her second and third trimester and in unspecified intervals after birth as the
incidence of depression is higher during these times (Michigan State University, n.d.; Bowen &
Muhajarine, 2006). It is important to pay particular attention to the last question of the EPDS,
which addresses self-harm. If this answer indicates concerns of self-harm, it must be
immediately addressed, regardless of the patient’s total score (Hayes, 2010). In the case that a
patient scores positive initially, the provider needs to perform a more thorough assessment
(University of California, San Francisco, n.d.).

A complete evaluation will provide consideration that depressive symptoms can be
related to organic causes such as hypothyroidism, electrolyte imbalances, diabetes, substance
abuse, nutritional deficiencies and more (Worthington III & Rauch, 2009). In order to
thoroughly rule out organic conditions, it is recommended that basic lab work be obtained,
including a complete blood count (CBC), thyroid stimulating hormone level (TSH), and a metabolic panel including kidney and liver functions tests (Misri & Lusskin, 2013).

**Treatment**

While most providers will agree that depression in pregnancy must be treated, there continues to be a large variation in treatment methods for this condition. There are many considerations for treatment including the risks to the mother and fetus of the selected treatment versus the risks of untreated depression. In primary care, it is important to consider referral of these patients to psychiatric specialty providers, especially if the symptoms are severe, unresponsive to treatments, or involve suicidal ideation (Barrio & Burt, 2000). It is also critical to remain in contact and coordinate care with the patient’s obstetrician if these services are not being provided by the primary care clinic (Toohey, 2012).

**Psychotherapy.** It is thought that mild to moderate depression in pregnancy can be successfully treated with interpersonal psychotherapy (IP) or cognitive behavioral therapy (CBT) (Spinelli & Endicott, 2003). If a pregnant woman’s depression is worsened by conflict with her partner, family therapy may be indicated as an adjunct (Misri & Lusskin, 2013). The risks to the mother and fetus with these types of treatment are very low, and the potential benefits are numerous. If a mother is suffering from severe depression, initiating treatment with psychotherapy alone may be unsuccessful as she may not be prepared or capable to put forth the effort necessary to benefit from psychotherapy due to the severity of her depression symptoms (Toohey, 2012).

IP is a specific type of therapy that is evidence-based and time-limited, allowing for improvements in depression within 12-16 weeks (Markowitz & Weissman, 2004). It is designed
to help a patient connect their depressive symptoms with specific life events (Markowitz & Weissman, 2004). For depression during pregnancy common topics discussed include role transitions, undesired pregnancy, medical and obstetrical health issues and other concerns (Spinelli & Endicott, 2003). One study has shown that women who had 16 weeks of IP had an improvement on the EPDS from 20 points to 12 points (Spinelli & Endicott, 2003).

Similar to IP, CBT also takes an evidenced-based short-term therapeutic approach (Association for Behavioral and Cognitive Therapies, 2010). It is a general term for therapy that uses the patient’s present situation as well early life experiences to evaluate their thinking processes and subsequent behaviors. The goal of CBT is to provide the patient with tools to achieve the goals set forth at the beginning of the treatment, which in this case would be a reduction in depressive symptoms. As there may be limitations to a patient accessing a behavioral counselor, there are also online options for CBT (Association for Behavioral and Cognitive Therapies, 2010).

Exercise. In several studies, exercise during pregnancy has shown to be moderately effective in treating mild to moderate depression (Shivakumar et al., 2011). It is thought that exercise may have an antidepressant effect due to its ability to facilitate the uptake of dopamine and serotonin (Shivakumar et al., 2011). In one study using a convenience sample of 53 pregnant women, it was demonstrated that those who participated in aerobic exercise (N=31) were more likely to have higher self-esteem as compared to the control group (N=22) measured by a self-report questionnaire (Shivakumar et al., 2011). Moderate exercise has been shown to increase both self-esteem and feelings of well being, which leads to less depressive symptoms. Other
exercises studied which may have some antidepressant effect as well include group walking, independent walking, jogging, and cycling (Shivakumar et al., 2011).

Several studies have indicated that moderate to vigorous exercise during a depressive episode in a non-pregnant patient may be as helpful as psychopharmaceuticals and psychotherapy combined (Demissie et al., 2011). Although data are limited, some studies have also shown these results to be true during pregnancy (Demissie et al., 2011). Between 2001 and 2005, 1,220 pregnant women participated in a study assessing for an association of moderate to vigorous exercise and decreased depression symptoms. In this cohort study, women between 17 and 22 weeks pregnant were interviewed about their physical activity the week prior to the interview (Demissie et al., 2011). These women were also asked to perform a self-administered depression scale at less than 20 weeks, and then again between 24-29 weeks. Women who performed greater than 0 and less than 2.67 hours weekly of moderate to vigorous activity demonstrated reduced depressive symptoms with an odds ratio of 0.56 (Demissie et al., 2011).

As exercise has not demonstrated adverse affects on the fetus and it is likely to be beneficial, it is a recommended treatment option (Spinelli & Endicott, 2003). For women who are not physically active prior to pregnancy, attempting to perform at least 150 minutes a week of moderate intensity exercise is advised. For women who are highly active and physically fit prior to pregnancy, it is recommended to continue the same pre-pregnancy level of activity (Demissie et al., 2011).

**Alternative treatments.** One study reported that pregnant women reported decreased depressive symptoms following a series of acupuncture treatments (Field, et al., 2006). Manber et al., (2010) randomly assigned 150 women diagnosed with major depressive disorder to a
control acupuncture group, acupuncture for depression group, or massage group. Participants received a total of 12 treatments over 8 weeks. Their depression symptoms were scored using the Hamilton rating scale for depression prior to treatment, at 4 weeks, and again at 8 weeks. The acupuncture for depression group reduced their score 53% from their initial score, an average of 11 points reduction. The control acupuncture group reduced their score by less than 9 points. The massage group reduced their score by less than 10 points, indicating that massage may also be beneficial (Manber et al., 2010).

Massage therapy has been studied in the treatment of depression (Pearlstein, 2008). One study reported that massage therapy not only decreased a mother’s symptoms of depression, it also decreased cortisol and norepinephrine levels and increased dopamine and serotonin levels. A group of 84 pregnant women were assigned to control groups, or a group receiving two 20 minutes massage weekly for 16 weeks during the pregnancy (Field, Diego, Hernandez-Reif, Schanberg, & Kuhn, 2004). After the sessions, participants completed a self-report depression assessment. The massage group not only demonstrated less depression symptoms, but also showed average cortisol level of 252 at the end of treatment, down from 328 prior to the start of treatment, they also had higher dopamine and serotonin levels, and lower levels of norepinephrine. (Field, et al., 2004). The control group in this study had no treatment and was found to have an increase in their cortisol levels from 326 to 332 check these numbers throughout the course of the study (Field, et al., 2004). Compared to the control group who did not have massage therapy, the massage group also experienced fewer premature and low birth weight infants (Field, et al., 2006).
Some research has indicated that alternative treatments using bright light therapy may have some efficacy, although more studies are needed (Pearlstein, 2008). One small study (n=27) compared treatment with a 7000 lux white light to a 70 lux red light in pregnant women diagnosed with depression. A greater reduction in depression symptoms was noted in the group that had treatment with the white light, 69% compared to 36% who were treated with the red light (Misri & Lusskin, 2013).

**Medications.** Medication for the treatment of depression in pregnancy is a highly debatable topic due to lack of information and recommendations in this area. Available research is often conflicting, inaccurate or unreliable due to the ethical issues associated with performing studies on pregnant women (Drapkin Lyerly, Namey, Gray, Swamy, & Faden, 2012; Misri & Lusskin, 2013). Many of the studies available are not randomized and controlled, and are retrospective and observational (Barrio & Burt, 2000; Misri & Lusskin, 2013). When deciding to start psychopharmaceuticals, many factors must be considered. It is important to include the wishes of the patient and the family when considering the available options. The Federal Drug Administration labels all medication with a pregnancy category rating in order to help providers choose the safest option of medication for pregnant patients based on available studies and information, which can be limited. At this time there is an updated pregnancy category proposal being considered but is not currently in use (Howland, 2009). Table 1 defines the pregnancy categories as presently designated by the FDA. A majority of antidepressant medications fall under category C ("DCF psychotropic medication," 2012). It is essential to consider the benefits and risks of each medication as well as its indication for use before deciding on an appropriate treatment choice (Misri & Lusskin, 2013). Table 2 summarizes this information.
When selecting a psychopharmaceutical, it is also necessary to take into consideration if the patient wishes to breastfeed. If she does it is beneficial to choose an antidepressant that is most compatible with lactation and breastfeeding, as changing antidepressants in the post-partum period is rarely recommended (Misri & Lusskin, 2013). It is important to consider the amount of medication excreted in breast milk will be much less than the amount the fetus received during pregnancy (Toohey, 2012). At this time, sertraline is often recommended for mothers who plan to nurse. It is the safest known choice for breastfeeding as there is the least amount of medication excreted during lactation as compared to other antidepressants (Hübner-Liebermann, Hausner, & Wittmann, 2012).

Other considerations include if a woman is already on medications for depression when the pregnancy occurs. Discontinuing that medication prior to becoming pregnant, or upon finding out she is pregnant is a multi-faceted decision. It is very likely that prematurely discontinuing an antidepressant will result in a depression relapse (Misri & Lusskin, 2013). Several items to be taken in consideration include the patient’s previous success or failure with non-pharmacological treatments, the current severity of her depression symptoms as well as the previous severity of symptoms (Yonkers et al., 2011). Generally, with all factors taken into consideration, recommendations have been made against discontinuing antidepressant medication unless it is a known teratogen, as a depression relapse is very likely (Hübner-Liebermann, et al., 2012).

**Selective serotonin reuptake inhibitors.** Since the early 2000’s, Selective Serotonin Reuptake Inhibitor’s (SSRI’s) have been the most commonly used antidepressant in pregnancy. They are easy to manage and have decreased toxicity in the case of an overdose as compared to other options (Grzeskowiak, Gilbert, & Morrison, 2011). Most SSRI’s has been classified as a
FDA category C. The exception to this is paroxetine, which has been categorized a FDA category D due to several studies indicating the potential risk of cardiac malformations, primarily ventricular septal defects (Hayes, 2010; Toohey, 2012). However, some larger cohort studies have contradicted this information and have shown no association between paroxetine and birth defects (Toohey, 2012; Yonkers et al., 2011). In general most studies are inconclusive in correlating congenital anomalies with SSRI use early in pregnancy. It is thought that some malformations seen in infants born to mothers taking SSRI’s may be related to concurrent drug use or lifestyle changes seen in those who are depressed (Toohey, 2012; Yonkers et al., 2011). An association has also been shown between SSRI use in pregnancy and low birth weight as well as premature birth (Yonkers et al., 2011). Because these conditions are also related to depression in pregnancy, it is difficult to tell which is responsible.

Recent studies have raised the concern that fetal exposure to SSRI’s in the third trimester increases the neonate’s risk of several abnormalities upon birth. These include arrhythmias and persistent pulmonary hypertension of the newborn (PPHN), which can lead to right sided heart failure. (Hayes, 2010; Yonkers et al., 2011). The risk for PPHN is slightly elevated, 3-6 per 1000 births exposed to SSRI’s, as opposed to a 1 in 1,000 risk for the general population (Toohey, 2012; Yonkers et al., 2011). Neonatal withdrawal syndrome is also of concern, and symptoms that may be present in the newborn include irritability, weak cry, hypoglycemia and seizures. Due to some of these concerns, many providers feel the need to discontinue SSRI antidepressants in the third trimester. Because post-partum is often a high-risk time for those with a previous diagnosis of depression, the argument can be made against discontinuing antidepressants near the end of pregnancy (Toohey, 2012).
**Tricyclics.** Tricyclic antidepressants have demonstrated a very low risk of malformation during fetal development. Risks include low birth weight and premature birth, as with SSRI’s (Yonkers et al., 2011). There have been no studies that have shown birth defects to be more prevalent when the mother is on a TCA during her pregnancy (Yonkers et al., 2011). Increased irritability, hypotonicity, lethargy have been noted in infants born to mothers who have been on tricyclic antidepressants during the end of their pregnancy (Barrio & Burt, 2000; Yonkers et al., 2011). It is important to note that TCA’s in general can be difficult to manage for several reasons. These medications generally produce undesirable side effects such as dry mouth, constipation, and elevated heart rate (Marraccini et al., 1999; National Institute of Mental Health, 2013). They also have high toxicity with increased rates of associated morbidity and mortality in the case of an overdose (Hübner-Liebermann, et al., 2012). This is of particular concern when prescribing these drugs to depressed, potentially suicidal patients and must be carefully considered.

**Alternative antidepressants.** Other antidepressants such Serotonin Norepinephrine Reuptake Inhibitors (SNRI’s) including venlafaxine and duloxetine, as well as alternative antidepressants such as bupropion, and mirtazapine have been less studied than the SSRI’s and TCA’s. However, in one study, it was found that mothers who took SNRI’s had more incidence of preterm birth than those who were not on those medications. The risk for congenital defects was the same as women who did not take these medications. Long-term effects on the child have not been reported (Yonkers et al., 2011).

**Conclusion**
Perinatal depression must be diagnosed and treated to prevent adverse outcomes for the mother, fetus, neonate and family system. Potential unfavorable consequences of depression to a mother include: placental dysfunction; premature delivery; pregnancy induced hypertension; preeclampsia; spontaneous abortion; increased substance abuse; and death. Harmful fetal/infant effects include: increased cortisol level; EEG changes; prematurity; decreased fetal development; SGA; delayed growth and development in infancy and childhood; and death.

In order to properly diagnose and track perinatal depression throughout pregnancy, the use of an objective screening tool is crucial. The use of an objective assessment method can help identify pregnant patients suffering from depression and ensure proper, timely diagnosis and treatment. The Edinburgh postnatal depression scale is a commonly used reference tool that has been validated and proven to be effective, sensitive, and specific in screening for perinatal depression and therefore is recommended for sequential screening of pregnant patients. If a patient scores positive for severe depression, or demonstrates suicidal ideation, then referral to a psychiatric specialty provider should be considered. It is critical to stay in contact with the patient’s obstetric provider so that follow up can continue.

In considering treatment choices, the risk and benefits must be carefully considered and include the mother and family in the decision making process. For mild to moderate depression, psychotherapy with either CBT or IP is a first line treatment. Exercise, acupuncture, massage and bright light therapy may be considered for treating mild to moderate depression as well, although more studies are needed. If a patient’s depression is severe, causing risk to the fetus or the mother, then psychotherapeutic medications should be considered adjunctively with psychotherapy and/or an exercise program or alternative treatment options such as acupuncture,
massage therapy, or light therapy. At this time, selective serotonin reuptake inhibitors have the greatest amount of available research. They are generally the medication of choice for perinatal depression due to their low side effect profile and decreased toxicity when compared to other agents, such as tricyclic antidepressants.

It is clear that additional research is needed around this complex subject. Much of the current literature on this topic is outdated, and information and statistics have likely changed. This is especially true regarding treatment modalities. However, due to ethical concerns in studying pregnant women, research will continue to be limited. The most promising options for further studies include retrospective, observational studies regarding the maternal, fetal, and neonatal effects of antidepressant medication.

References

DEPRESSION IN PREGNANCY


DEPRESSION IN PREGNANCY


Hayes, B. (2010). From 'postnatal depression' to 'perinatal anxiety and depression': key points of the National Perinatal Depression Plan for nurses and midwives in Australian primary health care settings. Contemporary Nurse: A Journal For The Australian Nursing


Marraccini, R., Reynolds III, C., Houck, P., Miller, M., Frank, E., Perel, J., Cornes, C.,


Yonkers, K., Wisner, K., Stewart, D., Oberlander, T., Dell, D., Stotland, D., Ramin, S., &
Tables

Table 1

*FDA Pregnancy Category Rating*

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category A</td>
<td>Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester, and no evidence of risk in later trimesters.</td>
</tr>
<tr>
<td>Category B</td>
<td>Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.</td>
</tr>
<tr>
<td>Category C</td>
<td>Animal reproductive studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.</td>
</tr>
<tr>
<td>Category D</td>
<td>There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.</td>
</tr>
<tr>
<td>Category X</td>
<td>Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.</td>
</tr>
</tbody>
</table>

*Note.* FDA pregnancy category rating. Adapted from “FDA Pregnancy Categories” by US Department of Health and Human Services, 2011.
Table 2

**FDA Category and Effects of Antidepressant Medication**

<table>
<thead>
<tr>
<th>FDA Category</th>
<th>Fetal/Neonatal/Child affects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- No increased risk of miscarriage</td>
<td>- Risk benefit analysis should be done before discontinuing medication in 3rd trimester as relapse of depression may occur</td>
</tr>
<tr>
<td></td>
<td>- No known increased risk of still birth or infant mortality.</td>
<td>- Discontinuing SSRI in 3rd trimester has not been shown to decrease incidence of PPHN. No long term effects on child development noted.</td>
</tr>
<tr>
<td></td>
<td>- No increase rates of prematurity or low birth weight.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Possible small risk of omphalocele, anencephaly, craniosynostosis from one study, multiple other studies showed no increased risk.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Neonatal withdrawal symptoms noted with third trimester use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Greater risk for PPHN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- No long term effects on child development noted.</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>C</td>
<td>- No increase in congenital malformations.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Not associated with septal defects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Medication may accumulate in breastfeeding infant due to long half-life</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Increased risk of PPHN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Most studied drug in pregnancy and lactation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Average dose is 20 mg.</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>C</td>
<td>- No increased risk of birth defects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Possible small association with omphalocele</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Possible association with septal defects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Increased risk of PPHN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- First line choice for pregnant women who plan to breastfeed despite conflicts regarding birth defects.</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>D</td>
<td>- Possible association with ventricular septal defects and right ventricular outflow defects (4% vs. 2%).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Risk of PPHN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Not recommended as first line choice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Not recommended or necessary to switch antidepressants if a woman becomes pregnant while on paroxetine</td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>C</td>
<td>- Small possible association with septal defects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Possible association with anencephaly, omphalocele, and craniosynostosis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Risk of PPHN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Not recommended or necessary to switch antidepressants if a woman becomes pregnant while on citalopram.</td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>C</td>
<td>- No studies have been done, data from studies of citalopram thought to be applicable to Escitalopram</td>
</tr>
<tr>
<td>Fluvoxamine (Luvox)</td>
<td>C</td>
<td>- No increased risk of birth defects</td>
</tr>
<tr>
<td>TCA’s</td>
<td></td>
<td>- Most studies show no increased risk for</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Long-term studies show</td>
</tr>
</tbody>
</table>
**DEPRESSION IN PREGNANCY**

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>FDA Category</th>
<th>Effect on Fetus</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine (Norpramin)</td>
<td>Undetermined</td>
<td>-Preferred, less side effects to fetus.&lt;br&gt;-Risk of neonatal withdrawal after birth.</td>
<td>no negative impact on growth and development of child after fetal exposure to TCA</td>
</tr>
<tr>
<td>Nortriptyline (Aventyl)</td>
<td>D</td>
<td>-Preferred, less side effects to fetus.</td>
<td></td>
</tr>
<tr>
<td>Imipramine (Tofranil)</td>
<td>C</td>
<td>-Potential for sedative, gastrointestinal, and cardiac side effects to fetus</td>
<td>-May be useful if insomnia is a key characteristic of depression.</td>
</tr>
<tr>
<td>Amitriptyline (Elavil)</td>
<td>D</td>
<td>-Potential for sedative, gastrointestinal, and cardiac side effects to fetus</td>
<td>-May be useful if insomnia is a key characteristic of depression.</td>
</tr>
<tr>
<td>Clomipramine (Anafranil)</td>
<td>C</td>
<td>-Potential for sedative, gastrointestinal, and cardiac side effects to fetus&lt;br&gt;-Possible increased risk of neonatal heart disease, neonatal withdrawal syndrome</td>
<td>-Useful for OCD/depression</td>
</tr>
<tr>
<td><strong>SNRI's</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>C</td>
<td>- No increased risk of congenital defects</td>
<td>- One available study</td>
</tr>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>C (Micromedx)</td>
<td>- No reports of congenital defects</td>
<td>- Eight available studies</td>
</tr>
<tr>
<td><strong>ATYPICAL</strong></td>
<td>FDA Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion (Wellbutrin)</td>
<td>C</td>
<td>-Conflicting study data&lt;br&gt;-Possibility for cardiac defects, spontaneous abortion</td>
<td>-Indicated for depression and smoking cessation.&lt;br&gt;-Not a first line choice, but may be considered with co-existing attention deficit disorder or if the patient unresponsive to other medications.</td>
</tr>
<tr>
<td>Mirtazapine (Remeron)</td>
<td>C</td>
<td>-Possible association with spontaneous miscarriage, premature birth.</td>
<td>-Limited data available</td>
</tr>
<tr>
<td>Trazodone</td>
<td>C</td>
<td>- No increased risk for congenital malformations</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td>C</td>
<td>-No increased risk for congenital malformations</td>
<td></td>
</tr>
<tr>
<td>Monoamine Oxidase Inhibitors (MAOI’s)</td>
<td>Most are C, some undetermined</td>
<td>Postpartum hypertension more likely in non breastfeeding mothers. Animal studies show fetal growth restriction</td>
<td>-Not recommended</td>
</tr>
</tbody>
</table>

**Note:** Antidepressant Medication Effects. Adapted from “Depression in Pregnant Women: Management,” by S. Misri and S. Lusskin, 2013. Up To Date.