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RESEARCH ARTICLE

DEPRESSION AND SUICIDAL IDEATION IN PREGNANCY

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ABSTRACT

Depression mostly remains underdiagnosed during pregnancy and results in adverse outcomes for both mother and the fetus. Primary care physicians (PCPs) should be vigilant in recognizing nonspecific somatic symptoms, which could be the manifestation of underlying depression. Universal screening for depression should be done at least once during prenatal period by the PCP, using either Edinburgh Postnatal Depression scale or the nine-item Patient Health Questionnaire. If depression is diagnosed, the PCP should initially assess the suicide risk and need for hospitalization. With regards to the pharmacotherapy, no drug is deemed completely safe as all psychotropic drugs cross the placenta. SSRIs are preferred, but paroxetine should not be considered a first line drug. Other options include psychotherapy, and in severe cases of depression, electroconvulsive therapy.

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INTRODUCTION

Depression is a multifactorial disorder where genetics, social situation, temperament, economics, and environment play a key role in its development. The heterogeneous nature of the disorder results in screening and diagnostic challenges [1]. Depression is an emerging pandemic, resulting in significant burden on the health care system and its resources. According to the World Health Organization (WHO), major depression carries the greatest burden of disability among all psychiatric disorders, contributing 3.7% of United States (US) disability adjusted life years (DALYs) and 8.3 % of US years lived with disability (YLDs) [2]. The 2013 National Survey on Drug Use and Health (NSDUH) reported that in the US 6.6% of adult population suffered from major depressive disorder (MDD), with 4.3% having consequential severe impairment [3]. Females, when compared to males, are more prone to develop depression with peak onset of symptoms occurring during their prime reproductive years (between the ages of 20-40) [4-7]. Although the reported prevalence may be dependent on the screening tool used, the American College of Obstetricians and Gynecologists (ACOG) postulate that 14-23% of pregnant females suffer from depressive symptoms [7]. Studies have shown that sub-syndromal and prenatal depression is frequently overlooked during pregnancy, resulting in harm to both the mother and the developing fetus [8]. This article will focus on the recognition, diagnosis, and management of prenatal depression.

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Depression-Definition and Classification

The term 'depression' is ambiguous, often referring to a spectrum of depressive (symptoms?) that encompass multiple specific psychiatric conditions. These include disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder [9]. The common features are sadness,

anhedoniaand/or irritability, accompanied by somatic and cognitive symptoms that undermine functioning capacity of the individual. What separates these conditions are duration, timing, and presumed etiology [9]. According to the guidelines in DSM-V, major depressive disorder is diagnosed if the patient experiences at least 1 depressive episode for a continuous duration of 2 or more weeks [9]. A depressive episode must consist of 5 or more of the following symptoms in a 2-week duration, with the compulsory presence of either depressed mood, or loss of interest or pleasure.

- Depressed mood most of the day, almost every day.
- Loss of interest or pleasure in all or most of the activities.
- Loss in weight (in the absence of dieting) or gain in weight, which is significant (i.e. a change of more than or equal to 5% of total body weight in a month); or increase or decrease in appetite.
- Insomnia or hypersomnia.
- Increased or decreased psychomotor activities.
- Excessive fatigue or loss of energy despite adequate rest.
- Feeling of worthlessness, or excessive or inappropriate guilt.
- Diminished ability to think or concentrate.
- Recurrent thoughts about death, suicidal ideation, or a previous suicide attempt.

A popular mnemonic for depressive symptoms is SIG E CAPS (focusing on changes in sleep, interest, guilt, energy, concentration, apetite, psychomotor, and suicidal ideation), although it falls short of adequately addressing the range of symptoms found in MDD such as worthlessness. Vegetative symptoms associated with depression, not included in the DSM-V diagnostic criteria include disordered salivation, sweating or lacrimation, cardiac arrhythmias, dyspnea, sexual dysfunction, dizziness, nausea/vomiting, dyesthesias and chronic nonspecific pain [10]. It is important to note that the presence of symptoms alone is not enough to label a patient with MDD. The symptoms must also result in significant social and/or occupational dysfunction [9]. Simultaneously, these symptoms must not be associated with any underlying medical condition or the use of certain medications (Figure 2). It is estimated that 10-15% of patients presenting with depressive symptoms are associated with an underlying organic condition [11].

Depression in Pregnancy

Pregnancy is associated with increased vulnerability to psychiatric conditions, with depression being one of the most frequently encountered psychiatric complications [15]. Unfortunately, while there is a plethora of research and provider education supporting the identification and treatment of postpartum depression (not covered in this article), depression *during* pregnancy is less commonly acknowledged. As a result, many clinicians fail to recognize, diagnose or treat depression during pregnancy. Prenatal depression is difficult to recognize, as many somatic and emotional symptoms overlap with normal maternal physiologic changes. For example, appetite changes may be due to nausea/vomiting resulting from increasing levels of β-hCG;fatigue is often due to dilutional anemia; lower back pain is commonly encountered as the lumbar curve exaggerates in response to the rapidly enlarging uterus; sleep disturbances are a frequent occurrence, especially hypersomnia in the first trimester and insomnia in the third trimester [9,33]. Due to the challenge of deciphering normal findings from pathologic processes, medical providers caring for pregnant patients should have a low threshold to carry out screening for depression in those presenting with vague somatic symptoms.

Epidemiology

The prevalence of depression during pregnancy is estimated to be 13%, with predisposition during the second and third trimesters [16]. Numerous risk factors for the development of prenatal depression have been identified (Figure 4). These psychosocial adjustments likely interact with both neuroendocrine changes and hormonal shifts, ultimately leading to depression.

Effects on Maternal Status

Depression during pregnancy has been linked to maternal smoking [17,18], substance abuse [19], hypertension [20,21], preeclampsia [22,23], and gestational diabetes [24,25]. Affected women also suffer more frequently from poor nutrition, weight gain nonadherence to prenatal care, ncreased anxiety, insomnia, and somatic complaints, such as pain, dyspnea, gastrointestinal symptoms, and dizziness [26,27]. In addition, there are higher rates of not breastfeeding, impaired maternal-infant bonding, and postpartum depression [28,29].

Effects on the Developing Fetus

Historically, research has focused on postpartum depression and its effects on the health of neonatal and child development. Recent studies have shown that prenatal maternal depression also govern adverse antepartum and neonatal outcomes [30,31]. This supports the 'fetal origin hypothesis' which suggests that environmental exposures in-utero can have sustained effects across the lifespan of offspring [32]. Regarding psychologic processes in pregnancy, negative birth outcomes are most frequently seen if maternal illness is present during the second or third trimesters [34]. Much research has shown associations between depression and adverse pregnancy outcomes, such as teratogenicity [39], preterm birth (PTB) [39-41], low birth weight (LBW) [42,43], and intrauterine growth retardation (IUGR) [39,44]. However, the results have been inconsistent and studies often have small sample sizes or confounders.In a study comparing women with major depression (n > 3,000) and pregnant controls (n > 432,000), perinatal depression was significantly associated with congenital anomalies (OR 1.4, 95% CI 1.2-1.6), IUGR (OR 1.2, 95% CI 1.1-1.4), and PTB (OR 1.9, 95% CI 1.7-2.1) [39]. Although the analysis controlled for several potential confounders, it did not control for use of psychotropic drugs.In a meta-analysis of 29 studies (n > 48,000 pregnant women), the authors concluded that depression during pregnancy was significantly associated with PTB (RR 1.13, 95% CI 1.06-1.21), and LBW (RR 1.18, 95% CI 1.07-1.30), however IUGR did not show a significant relation (RR 1.03, 95% CI 0.99-1.08) [45]. Of note, the study did not control for multiple potential confounders including medications, comorbidities, prenatal care, or demographics [45].In a meta-analysis (stylistic opinion: last 3 studies all start with 'In a – study') of 15 studies, the authors reported that the probability of PTB was significantly greater in pregnant women who were depressed

compared to nondepressed pregnant women (OR 1.37, 95% CI 1.04-1.81) [29].

Another study examined trimester fetal growth via serial ultrasounds in depressed women not being treated with antidepressants (n = 570) and controls (n = 7,027). They concluded that compared with the control group, weight gain in fetuses of depressed mothers was reduced by more than 4g per week [46]. Despite the above study, a joint report published by the American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG) agreed there was insufficient data to warrant a cause-and-effect relationship between perinatal depression and adverse pregnancy outcomes. While both genetics and environmental influences likely play a role in these adverse outcomes, given the enormous potential harm to the fetus and the cost burden associated with such adverse outcomes, these findings highlight the importance of screening for depression during pregnancy to minimize potential fetal morbidity.

Screening for Depression in Pregnancy

Despite a lack of clear evidence supporting universal screening of perinatal depression, ACOG and the US Preventive Services Task Force (USPSTF) both recommen clinicians screen patients at least once during the perinatal period [53,54]. The initial prenatal visit is an ideal time to perform such screening, whereby a thorough history can be obtained to identify any risk factors. Positive identification of any risk factors would warrant further assessment, particularly close monitoring [53]. Women with multiple risk factors may benefit from serial screening each trimester.Many screening tools have been developed for depression [55] (Table 1), and the Edinburgh Postnatal Depression Scale (EPDS) is most commonly used during pregnancy and postpartum [56,57]. The EPDS consists of a self-reported questionnaire (Figure 5) consisting of 10 questions. The survey takes about 5 minutes to complete, is suitable for patients with a low literacy level, and is easy to score. If the patient scores more than 15 points during pregnancy or 13 points postpartum, then further assessment is necessary to establish a diagnosis of depression [58]. O'Connor et al. reviewed 23 studies comparing the accuracy of EPDS with a diagnostic interview and found that the sensitivity, with a cutoff score of 13, ranged between 0.67 and 1.00 (95% CI, 0.18-1.00), while the specificity for detecting MDD was at least 0.90 [59]. Another screening tool, the 9-item Patient Health Questionnaire (PHQ-9) (Figure 6) has been evaluated and validated in primary-care clinics and obstetrical-gynecological setting as well [60,61].

Regardless of which screening tool is used, duration of symptoms, degree of impairment, or presence of any co-morbid psychiatric disorders are not addressed [62]. Therefore, all patients who screen positive for depression by any of the methods listed should be further evaluated by a diagnostic interview to establish the diagnosis based on DSM-V guidelines.

Any pregnant woman diagnosed with depression should be ruled out for an organic disorder with baseline labs (complete blood count, thyroid, renal, and liver function tests, and urine toxicology screen) and be thoroughly evaluated for use of herbal medications and over-the-counter products which may precipitate or exacerbate depression.

Management of Depression in Pregnancy

Mild to moderate prenatal depression can generally be treated on an outpatient basis with interpersonal psychotherapy or cognitive behavioral therapy (CBT) [63,64], where as Those with severe prenatal depression (characterized by suicidal or homicidal ideation, aggressive behavior, psychotic features, poor judgement with imminent risk of harm, and/or grossly impaired function [9]) are typically hospitalized and treated with antidepressants and psychotherapy combined [63,65]. While primary care physicians and obstetricians often manage depression in pregnancy, those with severe illness or psychiatric comorbidities (anxiety disorders, eating disorders, bipolar disorders, or substance abuse disorders) should receive multidisciplinary care with consultation from a psychiatrist [63,64].There are no standardized guidelines for treating depression during pregnancy, partly because carrying out randomized control trials during gestation has ethical concerns. Additionally, research to date have not been able to clarify whether the adverse outcome were attributable to pharmacotherapy or effects of the psychiatric illness itself. Thus, clinicians are in a dilemma of how to balance maternal need for medication with the possible risk on the developing fetus [66].

Non-Pharmacologic Treatment Modalities

Interpersonal psychotherapy (IPT) and CBT have proven to be effective in treating perinatal depression [67]. In studies, IPT has been shown to reduce depressive symptoms and improve social adjustment, while CBT aims to modify negative thinking and correct problematic behaviors which occur in response [68,69]. Web and computer-based CBT are available in situations where accessibility to a behavioral therapist is limited. For pregnant patients with mild to moderate depressive disorders that stem from marital problems and poor family functioning, family therapy may be considered as a primary or adjunctive treatment.Light therapy can also be beneficial during pregnancy. One study compared high wattage fluorescent bright white lights with low wattage dim red lights in pregnant women with depression. Remission occurred more frequently in patients who received bright light therapy (11/16, 69%) compared to low light placebo (4/11, 36%) [70].Exercise is a safe alternative or adjuvant treatment for prenatal depression. Supportive evidence includes a meta-analysis of five randomized trials of depressed pregnant women comparing non-aerobic exercise (yoga) to controls. There was a moderate clinical benefit seen in the exercise group [71].

Pharmacotherapy

Initial Approach

Pregnant women with depression are often treated with medication. Studies estimate that 8% of pregnant American women are prescribed antidepressants during pregnancy [72-74]. The decision to medicate pregnant patients must be based on the severity of current symptoms, frequency of prior depressive episodes, response to prior pharmacotherapy, and plans to breastfeed. The is weighed against fetal exposure where untreated depression can lead to missed obstetrical appointments, poor nutrition, and suicidal ideation. Among the SSRIs, sertraline and citalopram are usually first line, as both are associated with little to no risk of teratogenicity and are reasonable choices during breastfeeding [75]. While fluoxetine

is also safe, the drug has a very long half-life which can accumulate in the neonate and breastmilk. [75]. Escitalopram and fluvoxamine have been studied less in pregnancy and thus are not typically prescribed. Paroxetine is regarded as a contraindication in pregnancy given the findings from multiple studies on associations with congenital cardiac defects [37,64]. Further research concluded that these risks occurred only with first trimester exposure above 25mg/day [76]. If a woman conceives while on paroxetine, switching to sertraline may be considered, however, switching carries the risk of relapse. If the patient is euthymic and on a dose below 25mg/day, or if she previously failed to respond to other SSRIs, continuing paroxetine is a reasonable approach with limited fetal risk.

Resistant Patients

Pregnant patients who do not respond to SSRIs should undergo a trial of either venlafaxine or bupropion [63,77] as the teratogenic risk is low and they are safe during breastfeeding. If a woman becomes pregnant while taking venlafaxine or bupropion, it is reasonable to continue the regimen.

Refractory Patients

For severely depressed pregnant patients who fail sequential trials of SSRIs, venlafaxine, and bupropion, tricyclic antidepressants (TCAs) or electroconvulsive therapy (ECT) may be used [63,78]. Most studies have not found any association between birth defects and TCAs, and only small concentrations are found in breastmilk. These are reserved for refractory patients, due to their poor side effect profile and lethality in overdose [63]. If a woman becomes pregnant while taking a TCA, it is reasonable to continue the regimen if she is euthymic. If TCAs are not tolerated, unsuccessful or declined, ECT is a safe and effective alternative [63,78] and is considered the best option for severe or refractory depression [79]. One study evaluating response to ECT in pregnant patients reported remission in 84% of participants [80].

Risk of Antidepressant Use in Pregnancy

Data is traditionally of low to moderate qualityin observational studies regarding medication use in pregnancy. Most studies compare depressed women on medications with healthy controls, so it is often difficult to ascertain if adverse pregnancy outcomes are actually attributable to the use of antidepressants or merely a confounder due to exposure to maternal psychiatric illness. Furthermore, surveillance bias may exist as women taking antidepressants are often screened more frequently with ultrasounds, fetal echocardiograms, and post-delivery examinations, thus yielding an apparent increased incidence of congenital anomalies. Nonetheless, the data available on adverse fetal outcomes associated with the use of antidepressants during pregnancy are summarized below. These outcomes depend upon several factors including gestational age, duration of exposure, and associated comorbidities.

Spontaneous Abortion

Multiple earlier studies reported an increased risk of spontaneous abortions with the use of various antidepressants during pregnancy [84-90], but these studies failed to control for numerous potential confounders such as substance abuse, maternal age, and the psychiatric illness itself. Newer data which did control for these and other factors concluded that SSRIs and other antidepressants are not associated with an increased risk of spontaneous abortion (13% in treatment groups versus 14% in controls) [91,92].

Teratogenicity

Most studies fail to demonstrate any relationship between use of TCAs during pregnancy and structural anomalies in the fetus [93,94]. Similarly, studies indicate that first trimester exposure to SSRIs is not associated with major congenital malformations [75,77, 95-102] and (excluding paroxetine) is not associated with cardiac anomalies [77, 99-101,103]. Multiple studies have demonstrated the potential for a small, but absolute increase risk in congenital cardiac defects with paroxetine use [102, 104-106]. One meta-analysis comparing more than 2.3 million controls with more than 4,000 neonates born to mothers who used paroxetine during pregnancy reported significantly more cardiovascular malformations in the exposed group (OR 1.5, 95% CI 1.1-1.9) [107]. Another meta-analysis of more than 1.6 million unexposed and 18,000 exposed neonates reported similar results with an increased risk of cardiac defects in the exposed group (RR 1.4, 95% CI 1.1-1.9) [108]. A third study evaluated children born to depressed women untreated in pregnancy (n > 23,000) and children exposed to paroxetine in utero (n > 1,200). After adjusting for maternal age and tobacco use, there was an increased incidence of cardiac defects in the exposed group (OR 1.17, 95% CI 1.0-2.8) [103]. In these studies, the absolute risk was low with only 1-3 additional cases of cardiac defects in the exposed group per 1,000 births. In 2005, GlaxoSmithKline reported that pregnant women who were taking paroxetine during their first trimester had a 1.5 to 2-fold increase in the risk of congenital heart defects (CHDs), in particular atrial and ventricular septal defects [109]. While the absolute risk is small and many of these are insignificant septal defects which close spontaneously during childhood, paroxetine has been classified as a 'category D' in pregnancy. Some recent evidence also suggests that fluoxetine may be associated with a small increased risk of major congenital malformations and cardiac anomalies [101]. One study reported an absolute risk increase of 7 per 1000 for any defects, and 4 per 1000 specifically for cardiac defects [107].

Low Birth Weight

It is not clear if the use of SSRIs during pregnancy is associated with LBW as studies report conflicting findings [110,111]. Some studies have shown that SSRI use in pregnancy results in LBW [84,93,112,113], while other studies contradict this finding [87,89,114,115]. Källén et al. analyzed the records of 997 births from the Swedish birth registry, and found that both SSRIs and TCAs resulted in LBW neonates, however, these neonates were not small for gestational age (SGA), suggesting that the LBW was due to preterm births [116].

Preterm Birth (< 37 Weeks Gestational Age)

While earlier research showed evidence for [84,93,114,116,117] and against [89,95,115] the maternal use of antidepressants, both SSRIs and TCAs, are associated with preterm birth [118].

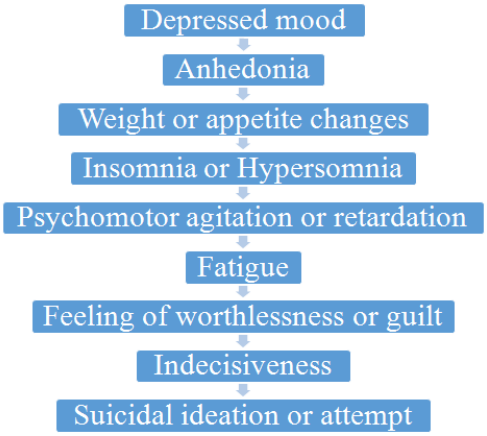


Figure Legend 1: Diagnostic Criteria for Major Depressive Disorder [9]

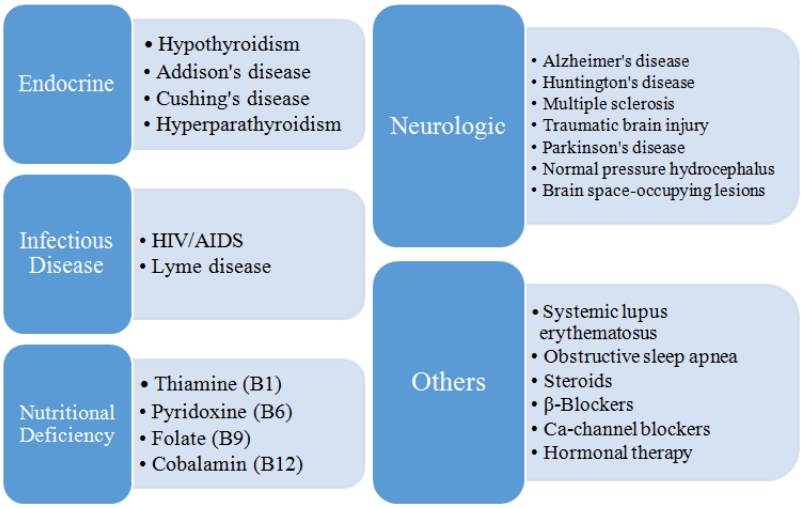


Figure Legend 2: Medical Conditions and Drugs Associated with Depression [11]

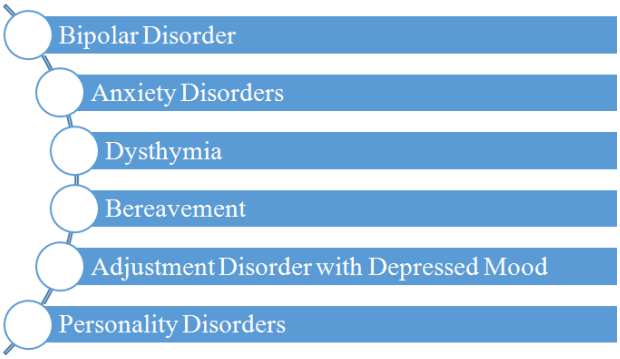


Figure Legend 3: Differential Diagnosis of Depression [9]

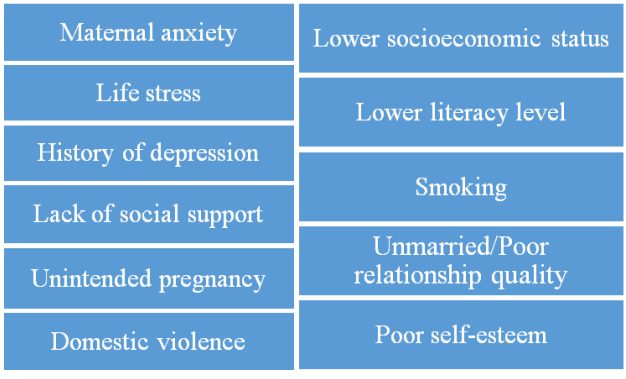
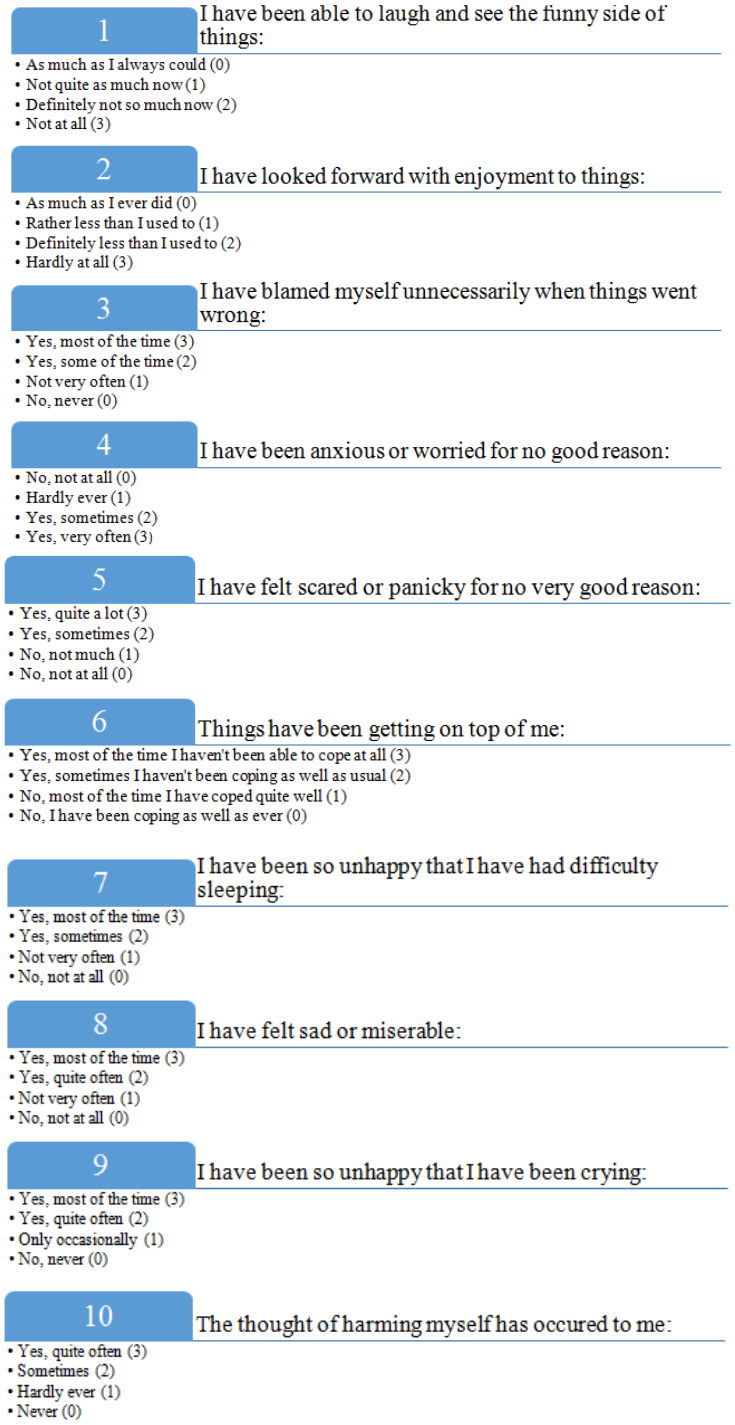


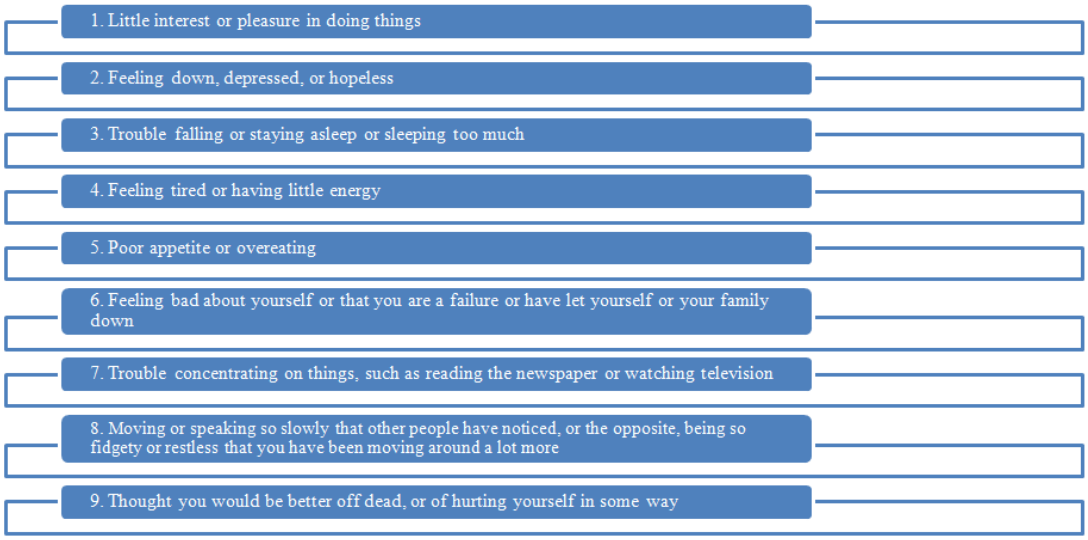
Figure Legend 4: Risk Factors for Depression During Pregnancy [53,54]



Range of EPDS Scores
0-9: Scores in this range *may* indicate the presence of some symptoms of distress that may be short-lived and are less likely to interfere with the ability to function day-to-day at home or at work. However, if these symptoms have persisted more than a week or two, further inquiry is warranted.
10-12: Scores within this range indicate presence of symptoms of distress that may be discomforting. Repeat the EPDS in 2 weeks and continue monitoring progress regularly. If the scores increase to greater than 12, further assessment is warranted.
13 +: Scores above this threshold indicate a high probability of depression and further assessment and referral to a psychiatrist/psychologist may be necessary.
For Item 10: Any woman who scores 1, 2, or 3 requires further evaluation prior to leaving the office to ensure her own safety and that of her baby.

Figure Legend 5: Edinburgh Postnatal Depression Scale [57]

"Over the past 2 weeks, have you had the following problems?"
"Not at all" (0 points)
"Several days"(1 point)
"More than half the days" (2 points)
"Nearly every day" (3 points)



Total Score
1-4: minimal depression
5-9: mild depression
10-14: moderate depression
15-19: moderately severe depression
20-27: severe depression

Figure Legend 6: Patient Health Questionnaire-9 [11]

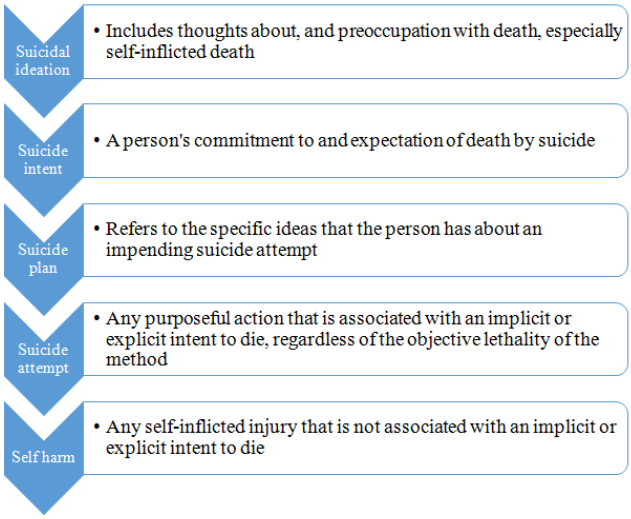


Figure Legend 7: Levels of Suicidal Acts [135]

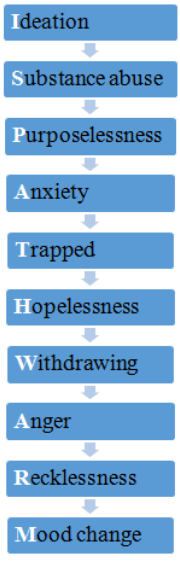


Figure Legend 8: 'IS PATH WARM' mnemonic

Table 1. Screening tools for maternal depression

Screening tool	# of items	Time to complete (mins)	Validation	Description
Beck Depression Inventory (BDI) Beck Depression Inventory-II (BDI-II)	21 21	5-10 5-10	Sensitivity 47.6-82% Specificity 85.9-89% Sensitivity 56-57% Specificity 97-100%	Used to detect depressive symptoms. Completed by patient.
Edinburgh Postnatal Depression Scale (EPDS)	10	< 5	Sensitivity 59-100% Specificity 49-100%	Assesses symptoms of both depression and anxiety. Completed by patient.
Postpartum Depression Screening Scale (PDSS)	35	5-10	Sensitivity 91-94% Specificity 72-98%	Used to identify women at high risk for postpartum depression. Completed by patient.
Patient Health Questionnaire 9 (PHQ-9)	9	< 5	Sensitivity 75% Specificity 90%	Screens for depression and can be used to monitor symptom severity during treatment. Completed by patient.
Patient Health Questionnaire 2 (PHQ-2)	2	< 1	Sensitivity 61-86% Specificity 78-92%	Simple 2-question inquiry about mood. Positive scores should be followed up with a more comprehensive tool. Endorsed by ACOG and USPSTF.
Center for Epidemiologic Studies Depression Scale (CES-D)	20	5-10	Sensitivity 60% Specificity 92%	Measures depressive feelings and behaviors over the past week. Completed by patient.
Zung Self-rating Depression Scale	20	5-10	Sensitivity 45-89% Specificity 77-88%	Completed by patient.
Hamilton Rating Scale for Depression (HAM-D)	21	15-20	Sensitivity 93% Specificity 98%	Determines patient's level of depression before, during and after treatment. Administered by clinician.
Montgomery-Asberg Depression Rating Scale (MADRS)	10	15	Sensitivity 75% Specificity 84.3%	Used in patients with MDD to measure the degree of severity of depressive symptoms and the change in symptom severity during treatment. Administered by clinician.

This association is probably related to the timing of exposure. This association is probably related to the timing of exposure withone study demonstrating that the third trimester is most highly associated with pre-term deliveries (PTD) (OR 2.0, 95% CI 1.6-2.4) [119]. It is noteworthy to mention preterm delivery by onlyone week or less [87,93,115].

Neonatal Neurobehavioral Outcomes – Kallen [116]and Altshuler et al. [94] both reported that maternal use of TCAs increases the risk of neonatal jitteriness, irritability, and rarely convulsions. Similar withdrawal symptoms commonly designated 'poor neonatal adaptation', have been reported during the first few neonatal days in infants exposed to SSRIs in utero [120]. The constellation of symptoms include irritability, tachypnea, hypoglycemia, temperature instability, weak or absent cry, and convulsions [84,117]. Studies show that these symptoms occur in approximately 15-30% of the infants born to mothers on SSRIs during the last trimester [84,117,121]. However, these symptoms are transient and usually resolve within 2 weeks of birth.

Persistent Pulmonary Hypertension of the Newborn – Neonates exposed to SSRIs for a prolonged duration in utero, or during the late third trimester, are shown to have an increased risk of persistent pulmonary hypertension. This condition can lead to neonatal respiratory distress, and in severe cases, cor pulmonale [120,122].

Postpartum Hemorrhage – Multiple observational studies suggest that SSRIs are associated with bleeding risks including postpartum hemorrhage (PPH), even when controlling for potential confounders such as coagulopathies, maternal age, and the use of other medications [123].One study comparing pregnant women who delivered vaginally reported that PPH occurred in more women who used SSRIs during pregnancy (n = 500) compared with women who did not (n > 39,000) (18% versus 9%) [90]. Another study included SSRIs and venlafaxine in their evaluation and found similar results when compared to controls (16% versus 11%) [124].

Pregnancy-Induced Hypertension (PIH) – There are conflicting findings regarding a potential association of SSRIs with PIH. A case-control study of more than 1,200 patients with PIH and >12,000 controls evaluated the use of antidepressants in pregnancy. Use of antidepressants was found in 3.7% of PIH patients versus 2.5% of controls. Exposure to antidepressants during pregnancy was significantly associated with PIH (OR 1.53, 95% CI 1.01-2.33). When stratified by class of antidepressants, SSRIs were associated with a higher risk (OR 1.60, 95% CI 1.00-2.55) and paroxetine was highest (OR 1.81, 95% CI 1.02-3.23) [125]. Another study, demonstrated comparable rates of pre-eclampsia among depressed pregnant women treated with paroxetine and those who did not receive treatment [126].

Preconception and Perinatal Considerations

Ideally the best time to counsel a patient regarding the potential effects of depression and medication in pregnancy is preconception. This section will review pre-existing depression, both prior to conception and after conception.

Preconception – For women who are currently depressed and not treated with medication, pregnancy should be deferred until treatment is initiated and symptoms have remitted over a stable period, such as 6 months [63]. For depressed women on medications, the same guidelines should apply. Following a period of improvement and stability, the decision needs to be made whether to continue treatment during pregnancy. *(See below).*

Perinatal – Once conception has occurred, clinicians may be faced with two distinct situations. Either the patient is currently depressed and treatment needs to be initiated, or the patient is on maintenance pharmacotherapy for a prior episode of depression and is contemplating discontinuation.

Management of Unmedicated Pregnant Patients

It may happen that previously untreated depression is diagnosed during pregnancy, or patients with a prior history of depression relapse during pregnancy. Yonkers et al. in a joint report from ACOG and APA proposed guidelines for the management of a pregnant patient with depressed symptoms not receiving medication [63]. First, the clinician should identify the severity of the depressive symptoms and if any suicidal ideation is present. If suicidal, a psychiatrist should be consulted emergently to optimize pharmacotherapy on an inpatient basis. If the symptoms are not severe and/or the patient is not considering medications, then psychotherapy is a good option. If the patient does not readily have access to a behavioral therapist, a psychiatrist should be consulted to determine the best management option available for the patient [63].Ideal treatment for a patient depends on many factors including severity of the symptoms, gestational age, drug safety, side effect profile, the patient's history, and therapeutic preferences. If the patient has symptoms of agitation along with depression, she may benefit more from a TCA. If pregnant females have depression and abuse tobacco, bupropion is a good choice, permitting that a history of seizures or bulimia has been ruled out [63].

Management of Medicated Pregnant Patients

Many patients who are already taking antidepressant medications inquire whether they should continue medications during pregnancy. Again, one needs to discern the severity of symptoms and if suicidal ideation is present, a psychiatric evaluation and inpatient setting is warranted. For euthymic women on maintenance therapy, clinicians should counsel patients that depression is often recurrent and discontinuing medication may increase the risk of relapse [127,128]. One study found that relapse occurred more frequently in pregnant patients who discontinued rather than maintained treatment (68% versus 26%) [63]. In another prospective study of pregnant women with severe recurrent depression, patients who discontinued medication during pregnancy experienced a 6-fold increase in the rate of relapse compared to those who continued medication throughout pregnancy [129]. For patients who wish to remain on medication, consideration may be given to switching to either sertraline or citalopram if they are on a less favorable antidepressant. However, switching also carries the risk of relapse. It is often advisable for patients to continue their current regimen after weighing the risk of recurrent depression [63]. For patients who do wish to discontinue their antidepressant, a slow taper under close monitoring is preferred to abrupt discontinuation [63]. For example, the drug may be tapered 25% every one to two weeks over a period of several weeks [130]. This approach can diminish the risk of withdrawal symptoms and the likelihood of inciting a relapse.

Suicide and Suicidal Ideation

All patients presenting with depressive symptoms must initially be screened for suicide risk. Suicide is defined as 'death caused by self-directed injurious behavior with an intent to die [131]. Suicide is the 10th leading cause of death among Americans of all ages [132]. Furthermore, suicide attempts are a source of high morbidity in patients suffering from MDD. Riihimaki et al. performed a 5-year prospective study and concluded that one-tenth of patients with depressive disorders attempted suicide in over a 5-year span [133]. There are few studies that focus on risk factors for suicide specifically during pregnancy. In one such study, Khalifeh et al. reviewed data from 1997 to 2012, from the UK National Confidential Inquiry into Suicides and Homicides by People with Mental Illness, and found that the women who died by suicide in the perinatal period were more likely to have a depressive disorder, and were less likely to be receiving any active treatment at the time of suicide [134].Suicidal behavior has been referred with various terms in the literature, which includes suicidal ideation, suicidal intent, suicide plan, suicide attempt, and self-harm [135]. An understanding of this terminology is crucial for PCPs to correctly label the behavior of the patient to avoid any subsequent misconceptions (Figure 7).

Suicide Risk Assessment

Despite a lack of standardization, the spectrum of suicide risk may be viewed across a timeline as imminent, near-term, or long-term [11]. The most important role a clinician has is to assess for imminent suicide risk. In 1983, Patterson and colleagues [136] proposed the SAD PERSONS scale (SPS) which was later revised in 1988 by Hockberger and Rothstein [137] to form the modified SAD PERSONS scale (MSPS). Both were used as suicide risk factors, with the latter focusing on the need for hospitalization. Even though both the scales consisted of an easy scoring system for assessing important risk factors for suicide, studies showed that they fell short for predicting suicidal behavior [11, 138-141]. In 2006, the American Association of Suicidology, proposed another mnemonic template 'IS PATH WARM' as a suicide assessment tool (Figure 8). Although its effectiveness has not been thoroughly tested in various clinical settings and the evidence for predicting suicide is mixed, it has the potential to identify high risk individuals [142,143]. It consists of the risk factors identified in people who have died by suicide:

- ***I****deation* – Are there any indications that the patient is contemplating suicide either in thought, writing, or in communication to others? Has the patient taken any steps to set a suicidal intention into motion?
- ***S****ubstance abuse* – Is the patient involved in alcohol or other drug abuse?
- ***P****urposelessness* – Has the patient lost or is lacking a sense of purpose in life? Are there any signs that the patient no longer wants to continue with life?
- ***A****nxiety* – Are there any indications that the patient is anxious, agitated, or unable to relax/sleep? Does the patient report sleeping more than usual?
- ***T****rapped* – Does the patient feel trapped in her current situation, seeing death as the only way to escape the pain in her life?
- ***H****opelessness* – Does the patient have a negative sense of self, others, or future?
- ***W****ithdrawing* – Does the patient give any indication that to withdraw from her significant others, family, friends, society, or already begun withdrawing?
- ***A****nger* – Does the patient expresses feelings of rage or uncontrolled anger? Is there any indication of intent to take revenge from others?

- ***R**ecklessness* – Does the patient continually engage in reckless activities with little or no concern for the potential consequences?
- ***M**ood change* – Does the patient exhibit or report dramatic mood swings?

The presence of the aforementioned risk factors are warning signs and should warrant a full mental health evaluation.

Management of Suicidal Ideation

Management of suicidal ideation and severe depression are identical. The clinician should weigh the risk factors of each case to decide if the patient is at imminentrisk for suicide. This would determine if the patient needs emergent psychiatric consultation with hospitalization. Following the algorithms provided above, and utilizing a multidisciplinary team approach when appropriate, will offer patients and fetuses the best possible care while minimizing adverse pregnancy outcomes. Gaining admission into a psychiatric ward, while pregnant with a mental health exacerbation, can be potentially problematic. Each psychiatric hospital dictates its own criteria for admission, and certain hospitals automatically exclude pregnant clients. Others deny admission to those < 20 weeks, > 32 weeks, or to patients who are considered high risk pregnancies. Of the 15 commonly accepting psychiatric facilities from a county hospital, two-thirds list pregnancy as an exclusion criterion. Vital signs can also present as an entry barrier because the heart rate can increase, and systolic and diastolic blood pressure can decrease while pregnant [33]. Other physiological changes in pregnancy, such as increased white cell count, mild thrombocytopenia, and hypercoagulability may also present as subjective barriers for admission [33].Clinicians should familiarize themselves with the basic psychiatric admission criteria, particularly as they apply to pregnant patients requiring transfer to a psychiatric hospital for concerns of self-harm. Consulting with a psychiatrist is the easiest way to seek guidance on how to admit a patient, but for those without a psychiatric ED or a psychiatric consult/liaison service, the clinician can locate the exclusionary criteria online for specific psychiatric hospitals to better inform themselves of the requirements before recommending their patients to visit the ED.

Conclusion

Research has shown that pregnancy is a period of great physical and psychological stress, with females already at a higher risk for developing depressive disorders. The neurochemical and hormonal changes which accompany pregnancy are an obvious trigger for women predisposed to mental health disorders. Given the enormous potential for adverse pregnancy outcomes, clinicians have a responsibility to meticulously screen for depressive symptoms and decipher them from normal physiologic changes in pregnancy. With improvement in providing universal screening for depression in pregnancy, the underdiagnosis of depression in pregnant females can be resolved. Pregnant females with depression must be identified and timely managed with psychotherapy, pharmacotherapy, and/or electroconvulsive therapy, to prevent any untoward effects on the health of the mother and the developing fetus. While suicide is an infrequent occurrence in the perinatal period, screening is critical to identify patients at risk.

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