DERLEME / *REVIEW*

Underrated Diagnosis: Prenatal Depression

Göz Ardı Edilen Tanı: Prenatal Depresyon

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ABSTRACT

Mental health disorders characterized by emotional lability, difficulty in concentrating, hopelessness, low energy level, irritability, food intake disorder, and changes in sleep patterns are called depression. To be diagnosed with depression according to the DSM-5, the following five or more symptoms must be present for at least 2 weeks, and at least one of the symptoms must be depressed mood or loss of interest or pleasure. Others include weight loss without dieting, decreased physical activity, fatigue or loss of energy, feelings of worthlessness, decreased ability to think or concentrate, and recurrent thoughts of death. The detection of antenatal depression may have many clinical implications because; it was associated with poor obstetric, neonatal outcomes, postpartum depression, preterm birth and low birth weight, small for gestational age, suicidal attempts, higher incidence of cesarean section, prolonged labor, more painful labor, operative delivery and it was also associated with a low APGAR score. While Covid 19 treatment is certain for pregnant women, we think it is useful to remember the treatment of anxiety and depression, which is more important and has increased prevalence during Covid 19 pandemics. The treatment options are Psychotherapy, Acupuncture, Bright light therapy, Exercise/yoga, Massage therapy, Family/couples therapy, Folic acid, Omega-3 fatty acids, S-adenosyl methionine, and medical Antidepressant treatment. In this review, current treatment methods used in the treatment of pregnant depression are summarized in detail.

Keywords: *pregnancy; depression; Covid 19; pandemic; SSRI*

ÖZET

Duygusal değişkenlik, konsantrasyon güçlüğü, umutsuzluk, düşük enerji seviyesi, sinirlilik, besin alım bozukluğu ve uyku düzenindeki değişiklikler ile karakterize ruh sağlığı bozukluklarına depresyon denir. DSM-5'e göre depresyon tanısı koymak için en az iki haftalık süre ile aşağıdaki beş veya daha fazla semptom olmalı ve semptomlardan en az biri depresif duygudurum veya ilgi kaybı veya zevk kaybı olmalıdır. Diğerleri ise diyet yapmadan kilo kaybı, fiziksel harekette azalma, yorgunluk veya enerji kaybı, değersizlik hissi, düşünme veya konsantre olma yeteneğinde azalma ve tekrarlayan ölüm düşünceleridir. Doğum öncesi depresyonun tespitinin birçok klinik anlamı olabilir çünkü; kötü obstetrik sonuçlar ve kötü neonatal sonuçlar, doğum sonrası depresyon, erken doğum ve düşük doğum ağırlığı, gebelik yaşına göre küçük fetüs, intihar girişimleri, daha yüksek sezaryen insidansı, uzamış doğum, daha ağrılı doğum, operatif doğum ve ayrıca düşük APGAR skoru ile ilişkilidir. Gebeler için Covid 19 tedavisi standart olmakla birlikte, Covid 19 pandemileri sırasında daha önemli olan ve prevalansı artan anksiyete ve depresyonun tedavisini hatırlamakta fayda olduğunu düşünüyoruz. Tedavi seçenekleri Psikoterapi, Akupunktur, Parlak ışık tedavisi, Egzersiz/yoga, Masaj terapisi, Aile/çift terapisi, Folik asit, Omega-3 yağ asitleri, S-adenosil metiyonin ve tıbbi Antidepresan tedavisidir. Bu derlemede gebe depresyonunun tedavisinde kullanılan güncel tedavi yöntemleri detaylı olarak özetlenmiştir.

Anahtar Kelimeler: *gebelik; depresyon; Covid 19; pandemi; SSRI*

Introduction

Mental health disorders characterized by emotional lability, difficulty concentrating, hopelessness, low energy level, irritability, food intake disorder, and changes in sleep patterns are called depression[1]. However, it is expected that the detection frequency of mental disorders in studies has been reported differently. Moreover, with the new coronavirus (2019-nCoV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019, a new pandemic is observed globally, and public health is at risk every respect[2].

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Kafkas J Med Sci 2023; 13(1):100–108
doi: 10.5505/kjms.2023.21033

Generalized anxiety disorder (GAD) is characterized by a hard-to-control, distressing, constant anxiety that lasts less than six months. Other features include physical anxiety symptoms, such as increased fatigue and muscle tension. Unipolar major depression (major depressive disorder) is at least one major depressive episode without a history of mania or hypomania[3]. According to DSM 5 (The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition), an episode of unipolar major depression lasts at least two weeks, with five or more of the following nine symptoms: loss of interest or pleasure in most or all activities, depressed mood, changes in appetite or weight, insomnia or hypersomnia, psychomotor retardation, or agitation, poor concentration, low energy, guilt or thoughts of worthlessness, and recurrent thoughts about death or suicide. In one study, it has been reported that in 10% of developed countries and 25% of developing countries, women suffer from mental health problems during pregnancy and after childbirth[4]. A meta-analysis reported that the average prevalence of prenatal mental disorders in low and middle-income countries was 15.6%[5]. In many studies, the prevalence of depression has been reported at different rates, and the incidence varies greatly from study to study. In studies, depression was reported between 11.7%–39%[6–8], while anxiety was reported between 54.2%–55.7%[8,9].

In a study, it was found that the rate of depression decreases as the gestational week increases. In this study, the depression was 11% in the first trimester and 8.5% in the second and third trimesters[10]. Pregnancy is a condition that increases the risk of depressive attacks, and more than 10% of women experience depressive episodes during pregnancy[11] and in adolescence, rising to 17%[12]. In addition, it was reported that depression, anxiety, and stress symptoms changed during pregnancy, and anxiety and stress increased in advanced gestational weeks when depression was observed in early pregnancy[13]. The prevalence of perinatal depression has been between 2 and 21% in international studies[14,15].

The detection of such high rates of antenatal depression may have many clinical implications because; it was associated with poor obstetric, neonatal outcomes[16], postpartum depression[17], preterm birth and low birth weight[18,19], small for gestational age[20], suicidal attempts[11,21,22], higher incidence of cesarean section, prolonged labour[23,24], more painful labour, perative delivery[25] and it was also associated with a low APGAR score in one study[26]. In another study, women anxious during pregnancy may feel more pain during labour, thus requesting more for analgesia[27].

Prenatal distress affects child development[28,29]. A review shows that pregnancy distress is related to mental health in the offspring later in life.

From a neurobiological viewpoint, anxiety and depression are thought to be effective on maternal-placental-fetal neuroendocrine mechanisms. Anxiety increases catecholamine release. The high catecholamine concentration has been associated with poor uterine contractility and prolonged labour. For all these reasons, the need for oxytocin increases[26]. Along with the serotonin system, corticotropin-releasing hormone (CRH) can affect prenatal stress and anxiety, fetal development, and infant and child development[30,31]. From a psychological view, depressive symptoms are associated with cognitive function that plays a significant role in pain control. If the cognitive function is labile, pain is viewed as intolerable and uncontrollable, and as a result, pain anticipation and attention to pain increases, and women experience childbirth more painful[32].

Many studies report that Covid 19 pandemics increased depression and anxiety among healthcare professionals. Some studies offer strategies to improve mental health that should be provided to healthcare professionals. Social isolation due to Covid 19 pandemic causes a feeling of loneliness and increases the risk of mental disorders (depressive and anxiety disorders) and even substance use disorder[33]. Studies have shown that anxiety, depression, fear, stress, and sleep problems are more common during the COVID-19 outbreak.

In a study, generalized anxiety disorder (GAD) was as high as 35.1% during a pandemic. It is also reported that younger people have a significantly higher prevalence of depressive and GAD symptoms than older people. In another study, females' anxiety risk was found to be approximately 3 times higher compared to males. For people younger than 40; the anxiety risk was 2.5 times higher than for those above 40 years old. In a study in Türkiye, it is shown that 23.6% of the population scored above depression, and 45.1% scored above the cut-off point for anxiety in the Hospital Anxiety and Depression Scale (HADS). In the same study, risk factors for anxiety were female gender, living in urban areas, and previous psychiatric illness[34]. Pregnant and non-pregnant women reproductive-aged have comparable clinical courses and outcomes when infected with

SARS-CoV-2. Vertical transmission of COVID-19 in the third trimester is not shown yet[35].

Measures to prevent Covid 19 transmission are the same for pregnant and non-pregnant people. These measures are to maintain social distance, use masks in public areas, pay attention to hand hygiene and disinfect surfaces. In a meta-analysis that examined 33 studies and 356 pregnant women, the most common symptoms in pregnant women infected with Covid 19 were fever (67%) and cough (66%)[36].

In many studies reporting a few cases, it has been reported that pregnancy and birth do not increase the risk of getting SARS-CoV-2 infection and do not worsen the clinical course of Covid-19 compared to non-pregnant individuals of the same age[37–41].

In a study examining 51 pregnant patients with Covid-19, it was reported that 39 percent of pregnant gave birth before the 37th gestational week and 96 percent delivered by cesarean section[42]. In another study in which 252 pregnant Covid-19 patients were examined, 15% of pregnant women were delivered before 37 weeks, and the cesarean rate was 70% in the same group of patients[36]. Guidelines published by the Society for Maternal-Fetal Medicine and The American College of Obstetricians and Gynecologists (ACOG) are available for treating pregnant women infected with Covid 19[43,44].

While Covid 19 treatment is specific for pregnant women, we think it is helpful to remember the treatment of anxiety and depression, which is more important and has increased prevalence during Covid 19 pandemics. Although, as mentioned above, many studies are showing that the prevalence of anxiety and depression increased during the COVID pandemic, we could not find a study on pregnant women in this regard in the literature[44].

It would not be wrong to say that anxiety and depression may increase in pregnant women during the Covid pandemic. For this reason, we wanted to contribute to this current issue by giving current treatment information on anxiety and depression in pregnant women. With these treatments, we think that some of the results of anxiety and depression can be prevented, maybe some of the preterm birth.

Pathophysiology of Perinatal Depression

Impact of Depression During Pregnancy

The pathophysiology of depression is not well known, and it has a complex etiology. Biological, social, and psychological factors may contribute to depression[45,46].

Because of studies conducted on animals and humans, the causes of mood disorders in the perinatal period are due to hormonal disorders, abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, and genetic and epigenetic factors. The main female reproductive steroid hormones, estrogen, and progesterone have some reproductive functions; they also affect nonreproductive behaviors, including mood and cognition[47]. Brain sensitivity to steroids increases after adolescence, and evidence suggests steroids have long-term effects on the brain[47,48]. The brain affected by these steroids may be more vulnerable to depression.

High estrogen and progesterone levels stimulate the HPA axis in the third trimester, and plasma cortisol levels increase accordingly[49]. Immediately after birth, estrogen and progesterone levels decrease rapidly, and the hypothalamic corticotropin-releasing hormone (CRH) is suppressed and gradually returns to standard[50]. Corticotropin-releasing hormone is secreted from the paraventricular nucleus of the hypothalamus; this hormone stimulates the secretion of the adrenocorticotropic hormone (ACTH) from the anterior pituitary and triggers the stimulation of cortisol from the adrenal cortex. This hormonal system is regulated by negative feedback with cortisol receptors and CRH autoreceptors. Maternal depressed infants are exposed to higher cortisol concentrations than infants of mothers who are not depressed in intrauterine life[51].

The regulation of the HPA axis is impaired in patients with depression. The same deterioration in pregnancy also explains the tendency to depression[52]. Interestingly, the HPA axis also affects other endocrine systems. One study reported that with lower total and free thyroxine concentrations in euthyroid patients, the risk of developing postpartum depressive symptoms might be higher even if the patient is euthyroid[53]. The field of epigenetics investigates heritable phenotypic variations without a change in the DNA sequence[54]. Most involve changes that affect gene activity and expression. Studies have shown that epigenetic changes effectively affect maternal behaviour in animal models. Although

there are not enough human data, they are likely to be effective[55–57].

Choosing Treatment

Psychotherapy

When choosing the treatment method, it is always necessary to decide according to the patient's previous history, the condition of the patient, and the severity of the disease. Structured psychotherapy can be tried as an initial treatment, such as cognitive-behavioural therapy (CBT) or interpersonal psychotherapy. If the patient was previously treated with psychotherapy and provided treatment, the same method can be tried while pregnant. If the patient has previously benefited from pharmacotherapy, the same drug can be used.

Many authorities primarily recommended psychotherapy. However, there are no well-designed randomized controlled studies on this subject. The reasons for the difficulties are it is difficult to diagnose, decide the severity of the disease, and evaluate the treatment's effectiveness.

Starting treatment with antidepressant drugs is an acceptable option in some cases[58,59].

- If the patient does not accept psychotherapy
- If the patient prefers pharmacotherapy
- If patients have a history of severe depression

In a prospective study, 41 women at 16 weeks of gestation without clinical depression but at risk of depression were randomized. Cognitive-behavioral was the intervention group. In follow-up, the depression rate was 14% in the intervention group, while 25% was in the control group[60].

Non pharmacological methods can be used alone or in combination in the treatment of depression. By adjunctive treatment, fetal exposure to medications may be minimized. Pregnant women may also prefer psychotherapy as the first-line treatment[61]. In a meta-analysis, psychotherapy methods were moderately effective in pregnant women and the postpartum period[62]. Cognitive-behaviour therapy (CBT) was reported to be effective in the same meta-analysis[62]. Exercise may also be effective[63].

Other Options

Some of the adjunctive interventions can be added to the primary treatment:

- Acupuncture
- Bright light therapy
- Exercise/yoga
- Massage therapy
- Family/couples therapy
- Folic acid
- Omega-3 fatty acids
- S-adenosyl methionine

Acupuncture: Evidence is insufficient to use acupuncture for depressed patients. Randomized studies have reported that acupuncture can effectively treat antenatal depression treatment[64].

Bright light therapy: Bright light therapy may be helpful in depression[65].

Yoga and massage: Maybe a treatment option[66,67].

Family/couples therapy: Family therapy may be an option for primary or adjunctive treatment.

Folic Acid: Folic acid is recommended for all pregnant women to prevent neural tube defects and many anomalies such as cardiac. Additionally, some studies show that folic acid can also help to treat depression[68].

Omega-3 Fatty Acids: The use of omega-3 fatty acids is recommended for all populations. It is the same in pregnant women. In randomized studies, it has been shown that omega-3 fatty acids can be effective as an add-on therapy for depression[69].

S-adenosyl methionine: S-adenosyl methionine may be helpful in the treatment of depression[70].

Antidepressant Treatment of Anxiety and Depression During Pregnancy

Approximately 7% of pregnant women in the United States use selective serotonin reuptake inhibitors (SSRIs)[71]. Another study reported that about 13 % of women used antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), during pregnancy[72]. If it is thought that psychiatric diagnoses are made less than it is, on the other hand, the actual number is more remarkable. Because there is an underestimation and underreporting of psychiatric disorders.

Table 1. *Relative Risks of Commonly Used SSRI*

	Spontaneous abortion	Hypertensive disorders of pregnancy	Postpartum hemorrhage
Paroxetine	No Risk	Unclear	RR:1.4
Fluoxetine	No Risk	No Risk	RR:1.5
Sertraline	No Risk	No Risk	RR:1.4
Fluvoxamine	No Data	No Risk	No Data
Citalopram	No Risk	No Risk	RR:1.5
Escitalopram	No Risk	No Risk	RR:1.6

RR: relative risk.

It is a difficult decision to prescribe medication for anxiety and depression during pregnancy, and it is necessary to consider the potential risks and benefits for the baby and mother. However, the most prescribed drug group in pregnancy is selective serotonin reuptake inhibitors (SSRI)[73]. Commonly used SSRI relative risksiz are Shown in Table 1

Studies have shown that stopping antidepressant treatment with a previous history of depression leads to a relapse of symptoms in as many as 60% to 70% of pregnant women[74,75].

Antidepressants cross the placenta and cross the fetal blood-brain barrier. Therefore, prenatal exposure to antidepressants involves risks of teratogenesis, low birth weight, preterm birth and pregnancy complications (e.g., postpartum haemorrhage and spontaneous abortion), and postnatal effects (e.g., persistent pulmonary hypertension).

However, maternal antidepressant usage during pregnancy has been associated with persistent pulmonary hypertension of the newborn (PPHN) and neonatal withdrawal/toxicity syndrome. Persistent pulmonary hypertension of the newborn is a rare condition, and it is prevalence in seen 1–2 infants out of 1000 normal populations and is affected by many conditions such as diabetes, meconium aspiration, cesarean section, and sepsis[76].

If SSRI is thought to increase the risk of PPHN 6–12 times, the probability of not having PPHN in the fetus of a pregnant woman using SSRI is 99%[77].

Prenatal Exposure to Antidepressants

Prenatal exposure to SSRIs may affect the serotonin system by reducing the calcium-binding protein specific to astroglia cells or by altering genes encoding the serotonin transporter protein[30,78]. Serotonin may also influence the HPA axis[78]. A recent study reported a 12% rate of spontaneous abortion when exposed to antidepressants, the relative risk 1.14 (95% CI 1.10–1.18. Selective serotonin reuptake inhibitor treatment during pregnancy significantly increases the risk of premature birth by 1.55–1.96[79–82]. However, studies have reported that preterm birth was just 3–5 days before, and its effect is minimal[83].

Although studies have shown a slightly increased risk of major congenital malformations with SSRI exposure, this may not be clinically important[84,85]. Therefore, SSRIs are not accepted as major teratogens[83,86].

Tricyclic Antidepressants (TCAs) During Pregnancy

Major congenital anomaly risk is not associated with TCA[87,88]. However, TCAs are associated with an increased risk of low birth weight and Preterm birth[87]. Nortriptyline and desipramine are the first-line TCAs in pregnancy due to low toxicity and low withdrawal risk[88].

Long-Term Effects of Antidepressants During Pregnancy

There are inconsistencies in the long-term outcomes of prenatal exposure to antidepressants in studies[89]. Although there are negative effects associated with the use of antidepressants, they improve over time and it is difficult to distinguish these effects from other factors such as asfiksia[89,90]. A study reported that untreated depression exposure in prenatal periods increases the risk of behavioural or emotional problems at 4–5 years of age compared to prenatal antidepressant use[91]. It was shown that children exposed to SSRIs and non-treated control group children have similar full-scale IQ, and depressed mothers' children may be at risk of future psychopathology[92].

Studies have claimed a relationship between SSRI exposure during pregnancy and autism spectrum disorder[93,94], as well as studies claiming the opposite[95,96].

It is possible to say the same for neonatal mortality. Studies have reported that it increases[97,98], and studies claiming that it has no effect[99,100].

Selective Serotonin Reuptake Inhibitors (SSRIs)

Research questions in perinatal psychiatry have been focused mainly on risks of medication exposure instead of risks of disease exposure for the mother and fetus.

Conclusions

The screening of psychiatric disorders and their identification is critical at prenatal visits and needs improvement. The diagnosis of depression is difficult for many reasons, and if the patient is pregnant multidisciplinary approach is necessary to optimize care. The treatment option decision is difficult for pregnant women. Untreated anxiety and depression and exposure to the fetus may have short-term and long-term adverse effects. Antidepressant treatment during pregnancy may increase the risk of miscarriage, probably a slight increase in the risk of congenital cardiac malformations, PTB, PPHN, and transient neonatal symptoms.

There may be a risk of delayed motor development. However, current medical data is unclear about the benefits or harms of antidepressant medications for infants and mothers. In decision making, the symptom severity is the primary determining factor. Nonpharmacological strategies can be helpful to women with mild or moderate depression. However, women with severe depression or recurrent depressive attacks should consider maintaining antidepressant treatment during pregnancy. Treatment modalities must be individualized. A multidisciplinary approach should be done, and decisions should be made with the clinicians, the patient, and her partner. During Covid 19 pandemic, this issue gained more importance.

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