International Journal of Basic & Clinical Pharmacology
Cristina D. Int J Basic Clin Pharmacol. 2023 Mar;12(2):284-289
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20230403

Review Article

Woman and pregnancy: focus on depression and psychopharmacological therapy

Davide Cristina*

Mental Health Dipartiment-Maria Paterno' Arezzo Hospital ASP of Ragusa, Italy

Received: 15 December 2022
Revised: 05 January 2023
Accepted: 06 January 2023

***Correspondence:**
Dr. Davide Cristina,
Email: ararat87@yahoo.com

ABSTRACT

Perinatal depression is one of the most common complications of pregnancy: it affects about 10-15% of women; the object of clinical attentionis postpartum depression (PPD) because it involves a impairment of the social and personal functioning of affected women and can have repercussions on the partner on the quality of life, on mother-infant interaction and neurodevelopment of the product of conception. Selective serotonin reuptake inhibitors (SSRI) are generally consideredas first-line antidepressant treatment in pregnancy, as they are generally safe and effective. Studies concerning the adverse effects of exposure to SSRIs during pregnancy on the developing foetushaveindicated an increased risk of various congenital malformations and un toward effects such as poor neonatal adaptation syndrome or persistent pulmonary hypertension, but here still remain inconsistencies between various study results. PPD can be a preventable disorder, there fore it be comes important that integrated actions between different medical sectors (interdisciplinary), diagnosis and any interventions are effective.

Keywords: PPD, Maternal stress during pregnancy, SSRI, Teratogenety

INTRODUCTION

Perinatal depression is one of the most common complications of pregnancy, affecting about 10-15% of women. PPD frequently lasts 3-6 months; in 25-30% of cases, it persists 1 year after onset. The prognosis for an acute episode is generally good: most women make a good recovery and return to previous levels of functioning. However, the risk of further relapse episodes in different life periods is high. History of major depression increases risk of PPD by 25% Previous history of PPD increases the risk of recurrence by 50%.[1-2]

Perinatal mental illnesses are not listed separately in DSM-5 (American psychiatric association 2013) or ICD-10 (World health organization 2010). The terms "perinatal depression" and "postpartum psychosis" have been preserved (with the advantage of providing prognostic information relating to risk in future pregnancies. Specifically, DSM-5 (but also DSM-IV and III) does not recognize PPD as a separate diagnosis from a major depressive disorder.To diagnose PPD, the defined criteria for the major depressive episode and the criteria for the perinatal onset specifier must be met.[1] The diagnosis of major depression DSMV are summarized in Table 1.[3]

ETIOLOGY OF MOOD DISORDERS AND RISK FACTORS IN PREGNANT WOMEN

The general male and female populations have the same risk of developing a psychiatric pathology over the course of their lives. However, there are gender differences in the prevalence and course of some psychopathologies, originating from biological and social differences between the two sexes (hormones, brain structure, social, and psychological factors). The phases related to reproductive life and risk factors for developing a mood disorder in women are also different (menstrual cycle, use of

hormonal contraceptives, pregnancy, abortion, birth, postpartum, menopause, and divorce). Women have an increased incidence and vulnerability of depressive onset/relapse in puberty (increase in estrogen), postpartum (rapid fall in estrogen levels and in the perimenopausal period (reduction in estrogen levels).[4]

The etiology of perinatal mood disorders can be traced back during pregnancy and postpartum to alterations in steroid hormone levels and some peptides which lead to deregulation of the hypothalamus pituitary adrenal (HPA) and hypothalamus-pituitary gonadal (HPG) axes which are related to the onset of mood disorders. The female HPA axis undergoes changes during pregnancy in relation to the increasing production of corticotrophin hormone produced by the placenta (CRH). The sudden drop in placental CRH concentrations in the postpartum leads to a hormonal homeostasis of the HPA axis in the following days, a process that is the basis of mood disorders corticotrophin.[1]

Table 1: DSM V diagnostic criteria for major depression.[3]

Diagnostic criteria	Symptoms
Five or more symptoms have been present simultaneously for a period of 2 weeks, most days, with a change from previous functioning. At least one of symptoms is	Depressed mood
	Loss of interest/pleasure
	Significant weight loss
	Insomnia/hyperinsomnia
	Agitation/psychomotor slowing
	Lack of energy
	Feelings of guilt or self-depreciation
	Reduced ability to concentrate or think
	Recurring thoughts of death Symptoms cause significant impairment or discomfort, symptoms are not caused by substance use or other medical condition or other mental illness (except bipolar/smood disorder).
Specifiers: with anxiety, mixed characteristics, melancholic, atific, psychotic, with catatonia, onset in the peripartum, seasonal trend	

POSSIBLE CONSEQUENCES OF MATERNAL STRESS DURING GESTATION

Maternal stress in perinatal periods can create an increase in maternal cortisol and a down-regulation of placental 11-beta-hydroxy-steroid-hydrogenase, an isoenzyme that transforms cortisol into metabolically inactive cortisone, with an increase in maternal cortisol levels in the amniotic fluid with consequent cerebral overexposure of the fetus and possible alterations on neurodevelopment.[5] A mood disturbance in the perinatal period can in fact not only activate the maternal HPA axis but can also increase the release of CRH from the placenta leading to interference on the birth itself inducing it prematurely, the excretion of vasoactive hormones with vasoconstrictive effects on the circulation placenta may lead to an increased risk of obstetric complications (spontaneous abortions, early labor low birth weight, and low Apgar index) and alterations in fetal and neonatal development (growth retardation, neurological alterations including hypotonia and neuropsychological and behavioral).[6] PPD is the subject of clinical attention because it involves a series of impairments in the social and personal functioning of affected women as well as repercussions on the partner (Roberts et al) and on mother-child interaction (Mc Mahon et al., 2006). It is in fact associated with a decline in the quality of family life (Da Costa et al), emotional (Goodman et al), intellectual (Sharp et al) and cognitive development of the child, Grace et al.

CLINICAL PRESENTATION AND TYPES OF PSYCHOPATHOLOGY

Mental disorders in the perinatal period can be classified into:

Baby blues: The 50-80% of women in the ten days following childbirth may present a very common transient psychopathological state characterized by humoral lability, emotional hypersensitivity, mood tone deflection, and feelings of anger. It resolves spontaneously in the second week. 20% of cases can lead to PPD.

PPD: 12-13% of cases present onset of major depressive disorder located during pregnancy/ 4 weeks after delivery with obsessive symptoms, panic attacks, and insomnia (even when the child does not have to be looked after). It can manifest as a unipolar/ bipolar depressive form and psychosis may also be present. PPD enters differential diagnosis with postpartum delirium, characterized by reduced level of consciousness and attention.

Postpartum psychosis: 1-2 cases out of 1000 present early onset (within 2-3 days), protracted insomnia with psychosis (high risk of infanticide).[2] Summary in Table 2.

The psychopathological condition of PPD presents itself as a subtle disease, with manifestations that are not always classifiable as a mood disorder. The deflected mood is not necessarily the first or the most important symptom manifested by these patients, but it is often preceded by anxiety, emotional lability, sleep disturbances, asthenia, and irritability. There is frequently a symptomatic procession characterized by low self-esteem, low confidence in one's parenting skills, and a sense of guilt and shame for the depressive experience in herself during pregnancy.[7] Kammerer et al in a scientific study identified different symptom profiles for prenatal and postnatal

depression by relating the different structures of the HPA axis in the two periods.Thus depression in pregnancy presents the typical symptoms of melancholic depression (insomnia, hypoxia, low reactivity of mood) related to an elevation in cortisol levels with a lack of cortisol suppression in dexamethasone test. DPP, on other hand, has characteristics of atypical depression (hypersonic, hyperphagia, emotional lability), follows a sharp reduction in cortisol levels that is observed in the postpartum period, and is related to an intense suppression of cortisol in dexamethasone test. [8] Most used evaluation/diagnostic tools are the EPDS (Edinburgh postnatal depression scale) by Cox, Holden and Sagovsky (1987) and the PDSS (Postpartum depression screening scale) by Beck and Gable (2010), BPDS (Bromley postnatal depression scale) by Stein and Van den Akker, 1992 self-completed questionnaires specifically designed for PPD screening.

Table 2: Psychiatric disorders in pregnancy.

Psycho-patology	Incidence	Clinic condition	Clinical course
Baby blues	50-80% of cases in the 10 days following delivery	transient condition: mood lability, emotional hypersensitivity, deflected mood, anger	Spontaneous resolution within 2nd week. 20% of cases may result in DDP
DDP	12-13% of cases during pregnancy or in the 4th wk. postpartum	DDM during pregnancy/4 weeks postpartum, obsessive-compulsive symptoms, panic attacks, insomnia (even when the baby is not being cared for).	3-6 months and in 25-30% of cases it persists 1 year after onset.
Post partum psychosis	1-2 cases /10000	Early onset (within 2-3 days), protracted insomnia and psychosis (high risk of infanticide).	

TREATMENTS

The treatment and cure of postpartum and perinatal disorders in general must be placed in a multidisciplinary context, i.e. with a team made up of a psychologist, gynecologist, psychiatrist, family doctor as well as the collaboration of the patient and informed partner. The medical history (previous psychopathologies) and the evaluation of the most appropriate treatment path such as psychotherapy, non-pharmacological treatments (phototherapy for depression), individual/couple psychotherapy, and cognitive behavioral therapy (CBT) for stress reduction are essential and psychopharmacological treatments. Psychopharmacological treatments during pregnancy and lactation should be considered only if absolutely necessary, especially in the first trimester of pregnancy (organogenesis) at the minimum effective doses and for the shortest times possible considering the risk/benefit ratio for the safety of the fetus and of the child (teratogenic risk, acute and developmental adverse pharmacological effects, neonatal toxicity).[9]

As regards the use of psychoactive drugs in pregnancy, the effect of drugs on the fetus can be transient or lasting. The classification of psychoactive drugs in pregnancy and breastfeeding according to the food and drug administration (FDA) is divided into categorization of the drug in based on the toxicity experienced with Band A from controlled studies there appear to be no fetal risks, band B does not appear to be any risk to the fetus despite possible risks for animals, band C the risks cannot be determined from human studies, the drugs can be given if the benefit is greater than the potential risk, band D evidence of risks for the human fetus: drugs can be given if any pharmacological benefits may be greater than the potential risks, band X contraindicated in pregnancy, and band Indeterminate not cataloged by the FDA.[10] The risks of pharmacological exposure in the perinatal period are considered as acute adverse effects or on the or development (Table 3).

Table 3: Types of adverse effects pharmacological acute and in the time.[9]

Variables	Acute	In the time
During pregnancy	Neonatal tissues	Somatic teratogenesis
	Neonatale abstinence	Teratogenesis
	Drug interaction	Neuro-behavioral
During lactation	Child toxicity	Teratogenesi
	Drug interection	Neuro-behavioral

Somatic teratogenesis refers to major or minor malformations, while neurobehavioral teratogenesis refers to alterations in cerebral development.[9]

SSRIs are generally regarded as first-line antidepressant treatment in pregnancy, as they are generally safe and effective. Studies investigating the adverse effects of SSRI exposure during pregnancy on the developing fetus have indicated an increased risk of various congenital malformations and side effects such as neonatal poor

adjustment syndrome or persistent pulmonary hypertension, but inconsistencies still remain between various study results.[11-12]

Therefore, in general, if the depression during pregnancy is mild or moderate, the following are valid treatments of the first choice: individual or group psychotherapy, anti-stress therapy, CBT. If, on the other hand, the depression is severe or resistant to treatments (suicidal ideation, psychosis or thoughts of abortion, no weight gain) the use of psychotropic drugs and/or integrated therapy (psychopharmaceuticals and psychotherapy) becomes necessary, which can last up to 6 months of pregnancy and electroconvulsive therapy (ECT).

ANTIDEPRESSANTS

The use of antidepressants (ADs) during pregnancy is common; in the Netherlands, up to 2% of women are prescribed ADs during the first trimester and in the US, about 10% of women are prescribed ADs during pregnancy, and this rate is increasing. Most prescriptions are for SSRIs.[13] Relapse rates are higher in those with a history of depression who discontinue medication than in those who continue. One study found that 68% of women who were well on antidepressant treatment and stopped it during pregnancy relapsed, compared with 26% who continued ADs. SSRIs do not appear to increase the risk of neonatal mortality. The neonate may experience withdrawal symptoms, which are usually mild, such as agitation and irritability, or rarely respiratory distress and seizures (with SSRIs). The risk is thought to be particularly high with drugs with a short half-life such as paroxetine and venlafaxine.

SSRIs may be associated with a higher risk of neonatal poor adjustment syndrome than serotonin-norepinephrine reuptake inhibitors (SNRIs). Increased levels of childhood anxiety symptoms have been reported in the exposed. SSRIs are generally considered as first-line AD treatment in pregnancy, as they are generally safe and effective. All SSRIs, SNRIs and other categories are not recommended in pregnancy, especially in the first trimester of pregnancy, however, treatment may be required. continuously during pregnancy and has not been shown to cause harm to the foetus. Patients who are already taking ADs and are at high risk of relapse are best kept on the same AD during and after pregnancy. If an AD is started during pregnancy or for a woman considering pregnancy, prior response to treatment should be considered.[13]

When weighing the risks and benefits of TCAs, SSRIs, or SNRIs for a woman considering breastfeeding, consider: the benefits of breastfeeding for the woman and her child, the uncertainty on the safety of these drugs for the breastfed baby the risks associated with switching or stopping a previously effective drug.[14]

Some data suggest that antidepressants may increase the risk of miscarriage, preterm delivery, low tneonatal special care unit. an association between SSRIs and an increased risk of postpartum bleeding but no notable bleeding has been reported in clinical practice.[13] A recent study showed that drug treatment is associatted with a reduced caesarean section rate without other complications for both the mother and the unborn child.[15]

Table 4: Antidepressiants.

Drugs SSRI	Band
Citalopram	C
Fluoxetine many studies highlight teratogenic safety.[13]	C
Paroxetine can increase the risk of malformations, risk of pulmonary hypertension, respiratory distress if used in the 1st quarter.[12]	D
Sertraline for previously untreated patients, sertraline may be considered. Little risk teratogenic, mainly used in lactation. [13-16]	C
Another drugs	
Venlafaxine appears to be associated with heart defects.[13-14]	C
Drug TCAs do not seem to increase the teratogenic risk for major malformations (except cloimipramine for cardiac malformations), during pregnancy especially in the 2nd and 3rd trimester to maintain plasma concentrations it is necessary to increase the dosages of TCAs.[16]	
Duloxetine is associated with an increased risk of postpartum hemorrhage and incrasing for risk of cardiac malformation.[17]	C

Sertraline is one of the safest antidepressants while breastfeeding. In most cases, women already taking sertraline should be advised to breastfeed and continue treatment. It is recommended to start with low doses and slowly increase the dose, with close monitoring of the infant for adverse effects (irritability, poor feeding or restless sleep, especially if the infant was born prematurely or had a low birth weight.[18] Sertraline use during the first trimester of pregnancy was associated with an icreased risk of atrial/ventricular defects.[19] A recent observational study suggest an association between in utero exposure to SSRIs and ventricular size in infants. Increasing use of SSRIs during pregnance and the importance of early life programming on future cardiovascular health.[20]

For some ADs, dose adjustments of 50% or even more in the 3rd trimester are necessary, especially TCAs but also fluvoxamine.[21]

Even if treated pharmacologically not in the right times, prenatal depression an health consequences not only for the patient but also for the children, and can contribute to the onset of emotional, behavioral, and emotional problems later in the child's life, cognitive and relational.[22-25]

CONCLUSIONS

Perinatal depression is one of the most common complications of pregnancy, and episodes of PPD often begin during pregnancy and present subclinical, including psychotic episodes apparently arising after delivery. It is essential to frame perinatal depression in an interdisciplinary context, early identifying the various treatments. SSRIs continue to be the safest and most used in pregnancy, trying to avoid their administration, if possible, in the first trimester. Pregnancy related physiological changes exert a crucial impact on the pharmacokinetics of several ADs. For some ADs, dose adjustments of 50% or even more in the 3rd trimester are necessary, especially TCAs but also fluvoxamine. Also for other ADs the changes are pronounced which may configure the high risk of drug exposure for the child. The use of ADs in pregnancy must have a follow-up and therapeutic monitoring of psychiatric drugs. Untreated prenatal depression can lead to a poor prognosis, not only for the mother but also for the child during pregnancy, and can contribute to the onset of emotional, behavioral, and emotional problems later in the child's life, cognitive and relational.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Cristina D. Woman and pregnancy: focus on depression and psychopharmacological therapy. Int J Basic Clin Pharmacol 2023;12:284-9.