Perinatal Depression

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Marta Serati and Greta Carnevali

Abstract

Perinatal mood disorders are one of the most common complications observed during pregnancy and postpartum, impairing maternal caregiving skills and, in most severe cases, especially in the presence of psychotic symptoms, can lead to suicide and infanticide. In the postpartum period, it is important to detect the possible risk of diagnostic conversion from unipolar to bipolar disorder, with the onset of subtle signs of hypomania or mixed symptoms, till full mania presentation.

In this chapter we present a 42-year-old woman that came to our attention for the onset of a major depressive episode during pregnancy; she previously received a diagnosis of major depressive disorder, when she was 36 years old. Her psychiatric family history was positive for depression and suicide. Four months after delivery, she experienced a recurrence of depressive episode with psychotic symptoms and mixed features. We discuss changes in pharmacological therapy to prevent relapses during pregnancy and breastfeeding. Therapy was modified due to the diagnostic conversion to bipolar II disorder, adding a second generation antipsychotic to SSRI to reach mood stabilization. Furthermore, the patient performed neurocognitive evaluation, brain magnetic resonance imaging, and fluorodeoxyglucose positron emission tomography: results are discussed with respect to the available literature. Finally, we mentioned the main biological markers associated with perinatal depression diagnosis.

In conclusion, it is necessary to screen for perinatal mood disorders during pregnancy and over the first year postpartum, especially to rule out suggestive signs for bipolar disorder onset, with assertive follow-up, to address suicide/infanticide risk.

M. Serati (✉) · G. Carnevali
Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

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9.1 Introduction

Perinatal depression is one of the most common complications observed during pregnancy and postpartum, differing from baby blues syndrome, a frequent condition observed in up to 50% of women, with symptoms disappearing spontaneously within few days after delivery [1]. The DSM-5 [2] introduced a specifier for major depressive episode (MDE), "with peripartum onset," considering both the onset during pregnancy and in the 4 weeks following delivery, differently from the previous DSM version. Risk factors predisposing to perinatal depression are a past history of anxiety or depression, psychiatric positive familiar history, single marital status, and inadequate social support [1]. The risk of developing perinatal depression is about 2–5% without a previous history of mood disorder, whereas a history of major depressive disorder in life-span not linked to the peripartum is associated with a 25% risk for a postpartum mood disorder [3, 4]. It is important to underline that most severe perinatal episodes occur within the first month postpartum, with mania or psychosis having an earlier onset than depression; moreover, mood episodes in the postpartum period are significantly more common in bipolar I disorder and recurrent major depression [5]. If depressive symptomatology is untreated, the risk of relapse in a subsequent pregnancy rises to 50%. Moreover, depressed women delay care, and less than 50% attend prenatal clinics; in addition, substance, alcohol, and cigarette use are highly correlated with psychiatric disorders, thus increasing medical risk for both mothers and newborns [4].

From a clinical point of view, it is important to consider the rate of diagnostic conversion (from unipolar to bipolar) in the postpartum period, called "hidden bipolar disorder" by Sharma et al. [6], reporting 11- to 18-fold higher conversion rates, particularly in the first 6 months postpartum [7, 8]. Higher bipolar II disorder diagnosis has been previously reported in patients with depressive symptoms developed in perinatal period by Mandelli et al. [9] and Çelik et al. [10]. Furthermore, we found that a longer duration of untreated illness (DUI) (>1 year) can be associated with a family history of bipolar disorder; hypomanic episodes come to medical attention later with respect to patients with major depressive episodes and suicidal attempts [11].

Beyond genetic loading, perinatal period is at risk for sleep deprivation due to baby care, so women with a risk for mood disorder, in particular BD-I subtype, need to monitor their sleep in order to reduce the possible trigger of mood episodes, as recently reported by Lewis et al. [12] and by Munk-Olsen et al. [13] for patients with previous psychiatric episodes outside postpartum period. In the most severe cases, perinatal depression could lead to suicide (near to 20% of all postpartum deaths) [4]. According to the Australian Department of Health, 73% of suicides by women

within 1 year of delivery were conducted by violent means (jumping from a high place, lying in front of moving objects, gunshot, strangulation, and suffocation), compared to suicide in nonpregnant women, and at a higher rate among women with a previous or current mental illness [14]. Another important risk to consider is infanticide, committed to relieve the baby from malignancies or alterations in some body parts, seen by the mother as having psychotic symptoms [4, 15]. We actually know that perinatal depression impairs maternal caregiving skills, with subsequent difficulties in mother-infant relationship, due to lack of maternal emotional and behavioral sensitivity to the infant, leading to reduced breastfeeding, altered neurodevelopment, and future emotional and behavioral problems for children [16, 17]. To evaluate depressive symptomatology in perinatal depression, beyond other diagnostic and evaluation tools, the Edinburgh Postnatal Depression Scale (EPDS) [18] is one of the most well-known and validated instruments across age, languages, and cultural dimensions [19, 20]. It consists of 10 self-report items rated on a 4-point scale; a score of 10 or more (maximum 30) is considered a positive screen. However, some studies have used cutoff scores of 12–13 [18]. Moreover, Clark et al. [21] recently reported that Mood Disorder Questionnaire (MDQ) added to EPDS can improve the distinction of unipolar depression from bipolar depression in a sample of postpartum women. The use of both evaluations is supported also by Merrill et al. [22].

Box 9.1 Differential Diagnosis of Depression in the Peripartum Period

- Baby blues: less than 10 days of duration; onset within 2–3 days postpartum; prevalence up to 50% of women; mild dysfunction; suicidal ideation is usually not present.
- Organic disease: e.g., iron deficiency, thyroid dysfunction, brain tumor, etc.
- Perinatal depression: more than 2 weeks of duration; onset is often within the first month postpartum, but it may occur up to the first year; moderate to severe dysfunction; suicidal ideation may be present.
- Bipolar disorder: subtle signs of emerging hypomania or mixed symptoms, up to full mania presentation.
- Postpartum psychosis: onset is often from the first 48 h to 2 weeks postpartum, but it may occur up to 3 months postpartum; incidence of 1/1000 women; severe dysfunction; high risk for suicide and infanticide ideation.

9.2 Case Presentation

A 42-year-old pregnant woman came to the Department of Psychiatry, University of Milan, in October 2013, sent by the obstetric-gynecological outpatient clinic of our hospital. She was at the 13th week of gestation; the baby's birth was expected at the beginning of April 2014 (last menses July 10, 2013). The patient reported a voluntary interruption of pregnancy when she was 16 years old. With regard to her

psychiatric family history, her mother was 61 years old; she suffered from chronic depression (never treated) and hypothyroidism. Her father was 66 years old, described as healthy. Her paternal grandmother died by suicide; her diagnosis is unknown. The patient used to smoke; she reduced her cigarette consumption to one cigarette per day after the beginning of her pregnancy; she didn't consume alcoholic drinks during pregnancy and denied current/previous substance abuse. With regard to medical comorbidity, she suffered from polycystic ovary syndrome, and she had a retroverted uterus.

With regard to patient psychiatric history, psychopathological onset was in April 2007, when she was 36 years old: she experienced difficulties in the workplace (she worked in the State Scientific Police), with quarrels with her colleagues due to persecution ideation. She thought to be unable to cover her working position; she didn't feel to be up to that. At the same time, her mood worsened when she separated from her husband because of his extramarital relationship; she had death thoughts and anti-conservative ideation. She received a diagnosis of MDE, and she was treated by a neurologist with pharmacological treatments (drugs prescribed unknown) and started in association psychotherapeutic sessions, with clinical recovery. The last depressive episode dated back to February 2012, with dissatisfaction in the workplace and persecution ideation, feelings of worthlessness, and difficulties in covering a role of authority in the workplace. Moreover, she described anxiety, psychomotor agitation, feelings of inability, and interpretativity as prodromic symptoms of her psychopathological episodes. At that time she received fluoxetine and olanzapine, taken for 1 year with benefit; she completely reacquired her high work functioning.

At the first psychiatric visit to our clinic, at 13 weeks of gestation, the patient was taking fluoxetine 20 mg for another depressive episode started about 6 months before, with a good psychopathological compensation. There were no ideation alterations, and the mood was stable; she reported mild sensations of anxiety and tension during the interview. Sometimes she experienced guilt feelings and weakness and weariness in starting working activity, with difficulty in paying attention to her tasks. She described a slightly reduced interest in her activities and hobbies. There was no anti-conservative ideation. The sleep-wake rhythm was regular. We reduced fluoxetine till stopping it and introduced sertraline up to 50 mg and started psychotherapeutic supportive sessions.

The patient came to the second appointment at 23 weeks of gestation; she was euthymic, guilt feelings toward herself and her family were reduced, and she experienced a greater willpower in the workplace. She continued psychotherapeutic sessions and maintained the pharmacological treatment; 4 weeks before delivery, the administration of sertraline was gradually reduced to 25 mg. The patient gave birth to her daughter, with a natural delivery with epidural anesthesia, on March 22, 2014. At birth, the baby weighed 2.990 kg and her length was 46 cm. The Apgar score is 10. During hospitalization in the puerperium, the patient decided to breastfeed the baby. Sertraline 50 mg was divided in two separate doses taken just before breastfeeding. Because of the patient's and her family's psychiatric history, to prevent relapses, she was monitored almost once a month during postpartum by a

psychiatrist, and twice a month she had psychological supportive sessions with a trained psychologist specialized in the perinatal field [23].

At the first postpartum examination, the patient showed an expressive mimic; sometimes she smiled. There were no ideation alterations with regard to form and content and the mood was good. She was breastfeeding and often went to the counseling center. During the weekdays her mother helped her with the housework and to look after the baby, whereas during the weekend she stayed with her partner. In July 2014 she experienced feelings of worthlessness and incapacity ideas, moreover with guilt feelings, causing difficulties in carrying out daily activities. In addition, she reported increasing anxiety and tension, with thoughts going faster in her head. In the hypothesis of a depressive episode with "mixed features" diagnosis, a dose of olanzapine from 5 mg to 10 mg/day was added to reach mood stabilization. In September 2014 she described a worsening of inadequacy feelings and insecurity; she was critical toward herself, especially with regard to her skills in a mother's role. She experienced these feelings as reflected in the baby's eyes: "my daughter yawns because she gets bored with me, she never yawns with her father." The patient often received disapproving comments from her partner and her mother-in-law, which highlighted her lack of enthusiasm in the couple relationship. We thus augmented sertraline up to 100 mg/day, maintaining olanzapine 10 mg/day. In December 2014 she reported subjective improvement of her symptoms; the therapy was confirmed without changes.

The patient underwent a Structured Clinical Interview for Axis I Disorders (SCID 1) and a Structured Clinical Interview for Axis II Disorders (SCID 2) in postpartum, receiving a diagnosis of severe depressive episode with psychotic features and specifiers: with peripartum onset and with mixed features in patient with bipolar II disorder. No personality disorder was found.

During postpartum, the patient underwent a neurocognitive evaluation, the Brief Assessment of Cognition in Schizophrenia (BACS), showing a deficit in executive functions (frontal efficiency and motor proficiency), as shown in Table 9.1.

Moreover, brain magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET) were performed in the postpartum. The MRI resulted in normal ventricular system amplitude and peripheral liquor spaces for the patient's age, except for a minimal extension of the design of the cerebellar

Table 9.1 Neurocognitive evaluation assessed by BACS subtest

Test	Normal score	Score	Comment
Language			
Verbal fluency	v.n. $\geq$ 31.68	48,25	Normal
Memory			
Verbal memory	v.n. $\geq$ 33.01	61	Normal
Motor proficiency			
Token task	v.n. $\geq$ 68.77	57.50	Deficit
Symbol-coding task	v.n. $\geq$ 40.49	48,25	Normal
Frontal efficiency			
Working memory	v.n. $\geq$ 14.93	24,25	Normal
Tower of London	v.n. $\geq$ 12.37	12	Deficit

folia (Fig. 9.1). MRI studies have shown both volume and cortical thickness reduction in gray matter in bipolar disorder, also in the cerebellum [24]. For more information, see paragraph 3.2 (Neuroimaging and Neurocognitive Impairment). The PET did not evidence any significant modification in the normal and symmetric brain metabolism (Fig. 9.2). Moreover psychopathological rating scale have been completed during treatment (Fig. 9.3).

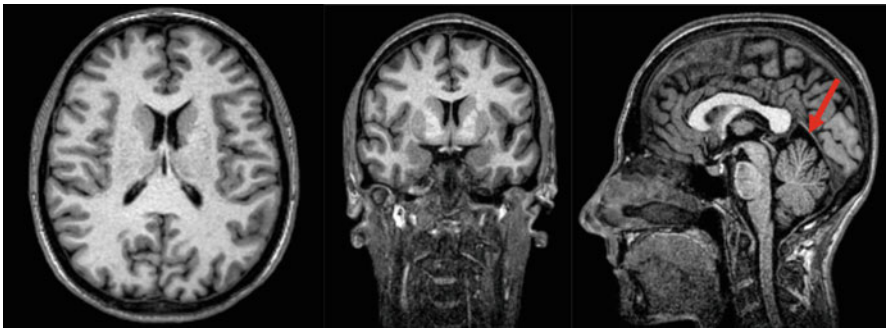

Fig. 9.1 T1-weighted cross, coronal, and sagittal images, showing a normal amplitude of the ventricular system and of the peripheral liquor spaces, except for a minimal extension of the design of the cerebellar folia (red arrow)

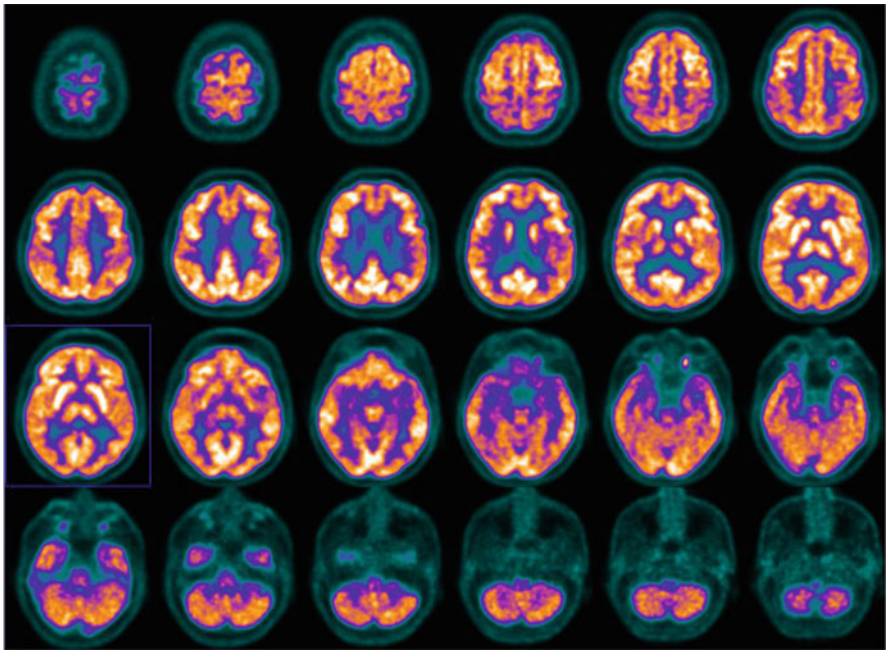

Fig. 9.2 FDG-PET shows no significant alterations of the normal symmetric glucose metabolism of the brain

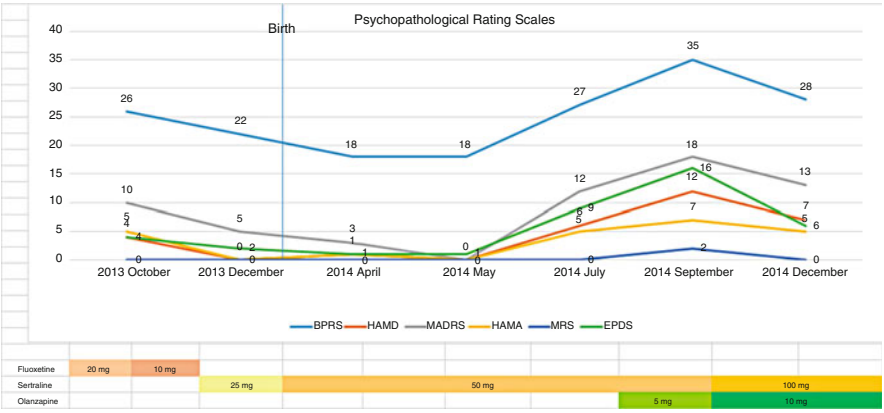

Fig. 9.3 Psychopathological Rating Scale time course. *BPRS* Brief Psychiatric Rating Scale, *HAM-D* Hamilton Depression Rating Scale, *MADRS* Montgomery-Asberg Depression Rating Scale, *HAM-A* Hamilton Anxiety Scale, *MRS* Mania Rating Scale, *EPDS* Edinburgh Postnatal Depression Scale

9.3 Literature Review

9.3.1 Biological Biomarkers

Recently, biomarkers for early perinatal depression detection have been investigated, having for this condition, as for other psychiatric disorders, a genetic loading [25, 26]. Over and above others, BDNF [27, 28], oxytocin system [29, 30], and proinflammatory immune system activation (IL-1, IL-6, and TNF-α) are involved [31, 32]. Such biological alterations probably interfere with nutrient, oxygen, and growth factor transfer to the fetus, thus compromising neurodevelopment [33, 34]. We actually know that prolonged prenatal maternal stress, due to a psychiatric disorder, may alter glucocorticoid feedback, creating a vulnerability to addictive and mood disorders in offspring and contributing to alterations in fetal neurodevelopment [3, 35–37].

9.3.2 Neuroimaging and Neurocognitive Impairment

Neuroimaging studies in bipolar patients have shown an enlargement of the third and lateral ventricles and a reduction in orbital and medial prefrontal cortex gray matter volumes, ventral striatum, and mesotemporal cortex (Severino [38]). Moreover, MRI studies have shown both volume and cortical thickness reduction in gray matter in bipolar disorder, also in the cerebellum [24]. The cerebellum is involved in cognition and affect, beyond motor functioning, with a role in modulating cortical-limbic interconnections: it receives motor and cognitive information through its

connections with afferent (cortico-ponto-cerebellar) and efferent (cerebello-thalamo-cortical) pathways and takes part in neural circuitries responsible for superior cognitive functions, usually disrupted in bipolar patients [39]. We actually don't know if cerebellum alterations are due to bipolar disorder itself or to maternal diseases during gestation altering mood regulation pathways and influencing normal brain development, the so-called early neurodevelopmental model [40].

Some data suggest that even normal pregnancy is associated with structural changes in the maternal brain. Using voxel-based morphometry (VBM), Kim et al. [41] reported gray matter volume increases during postpartum period in the superior, middle, and inferior prefrontal cortex, precentral and postcentral gyrus, superior and inferior parietal lobe, insula, and thalamus. These volume changes concern areas involved in maternal behavior and maternal-infant interactions. However, no imaging studies to date have examined structural MRI differences between euthymic peripartum women and those with peripartum mood disorders [42].

Neurodegeneration in mood disorders is the result of several factors, such as inflammation; oxidative stress, increasing with repeated mood episodes; duration of untreated illness; and aging [43–45]. Thus, bipolar patients often present a significant cognitive impairment, during both the acute phase of illness and remission, worsening with cumulative episodes. The main cognitive impairment generally affects executive functions and verbal memory, due to prefrontal and medial temporal cortex impairment, respectively (Severino [38]).

Our patient showed normal ventricular system amplitude and peripheral liquor spaces for age, except for a minimal extension of the design of the cerebellar folia, probably due to atrophy. Her neurocognitive evaluation revealed a deficit in the executive functions (frontal efficiency and motor proficiency; see Table 9.1), without verbal memory impairment.

9.3.3 Treatment Strategies

9.3.3.1 Pregnancy

Ford et al. [46] recently observed that counseling by general practitioners and referrals to specialists were common in the postnatal period, less in pregnancy, with antidepressants as first line of treatment and various SSRIs considered safe and well tolerated [46–49]. No substantial evidence supports the use of one SSRI over another [50]; however, if the patient has a history of response to a particular SSRI, it is reasonable to use that medication initially [51]. Moreover, the use of antidepressants seems to be more favorable compared to exposing the mother and child to untreated depressive illness [52]. An analysis conducted by Langan and colleagues showed that with paroxetine and fluoxetine exposure during pregnancy, there was a small increase in specific birth defects, while the use of sertraline, citalopram, and escitalopram was not associated with severe birth defects [53]. Fluoxetine, with a long half-life and active parent compound and metabolite, is thus associated with neonatal syndrome. Elevated infant fluoxetine levels at birth could result in serotonergic toxicity, so, the high rates of neonatal syndrome (31%) with

third trimester exposure, compared to 9% with early gestational exposure, may be explained [54, 55]. Hendrick et al. determined the maternal and umbilical cord blood antidepressant and metabolite concentrations in 38 mother/baby pairs. The lowest ratios of cord to maternal serum concentrations were for the antidepressants sertraline and paroxetine; the highest ratios were for citalopram and fluoxetine. These data suggest that some drugs produce less fetal exposure than others [56]. The recent Council on Patient Safety in Women's Health Care focused on the management of perinatal depression and anxiety [4], with a treatment cascade model, suggesting multiple opportunities to improve perinatal depression management [57].

The administration of drugs during pregnancy calls for special attention due to possible effects on the fetus, since infants exposed to SRI during the third trimester have a threefold increased risk for neonatal behavioral syndrome [58], which consists in respiratory distress, feeding problems, jitteriness, altered muscle tone, agitation, and irritability [54]. Whether the observed adverse fetal effects are related to the mother's medication or her underlying maternal illness remains difficult to determine; weighing the risks of treatment against the risk of untreated depression for both woman and child is warranted. In women in contact with UK psychiatric services, suicides in the perinatal period were more likely to occur in those with a depression diagnosis and no active treatment at the time of death. Assertive follow-up and treatment of perinatal women in contact with psychiatric services are needed to address suicide risk in this group [59]. Moreover, although causality has not been established, SSRI use during pregnancy is associated with increased risk of persistent pulmonary hypertension of the newborn, lower Apgar scores, attention-deficit/hyperactivity disorder, and speech delay [53]. Guidelines recommend that pregnant women exposed to any SSRI in early pregnancy be offered options for prenatal diagnosis through ultrasound examinations and fetal echocardiography to detect the presence of birth defects. Stopping or switching to other therapy in early pregnancy, if appropriate for the individual, may also be considered on a case-by-case basis [60].

With regard to mood stabilizers, women with chronic bipolar illness should continue treatment with lithium during pregnancy, in order to avoid relapses, or starting again at the second or third trimester to prevent postpartum recurrences [61], whereas valproate is banned during pregnancy [62]. Recent studies show promise for second generation antipsychotics in the treatment of bipolar depression with mixed features, due to their mood-stabilizing effects [8, 63]. Antidepressant monotherapy should be avoided, as it may worsen manic symptoms [64]. Electroconvulsive therapy (ECT) is an efficacious alternative choice for treatment-resistant cases or patients requiring emergent treatment who may not tolerate pharmacological therapy.

With regard to antipsychotics, placental transfer varies; typical antipsychotics have been widely used for approximately 50 years, with minimal associated risks during pregnancy. Generally, no increase in the rate of major anomalies or neurodevelopmental problems has been reported with atypical antipsychotics [63].

For a complete and updated drugs used in pregnancy, see http://www.farmaciegravidanza.gov.it.

9.3.3.2 Breastfeeding

If the patient is breastfeeding, the relative transfer of a medication into breast milk should be considered as the main parameter determining the degree of drug penetration into breast milk plasma protein binding: the higher the percentage of protein binding, the less the drug is found in maternal milk. Moreover, drugs with a large volume of distribution are poorly excreted into breast milk, while lipid-soluble drugs readily diffuse across cell membranes by dissolving in the lipid bilayer, compared with water-soluble drugs [61]. In a recent paper, Langan and collaborators observed that fluvoxamine, paroxetine, and sertraline are preferred in breastfeeding women, leading to the lowest serum medication levels in infants [53].

With regard to mood stabilizers, lithium during lactation is generally contraindicated, because of the high variability of the transfer into breast milk; lactation can be permitted through an individualized approach to breastfeeding in women receiving lithium. Valproate is theoretically safe during lactation, due to limited passage into breast milk.

From the available studies, treatment with most antipsychotics does not preclude breastfeeding, as only minimal concentrations of the active components have been found in breast milk. In particular, quetiapine and olanzapine are safe and should be the first-line treatment options when an antipsychotic is indicated, with low infant olanzapine plasma concentrations and low relative infant doses; generally, no adverse events were reported in infants exposed to olanzapine [61].

For updated and complete data on breastfeeding in pregnancy, see https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm.

9.3.3.3 Other Treatments

Recently, Dama et al. [65] outlined the importance of treating perinatal depression by considering in a new onset episode medical comorbidities above all, performing a full laboratory analysis to exclude, e.g., iron deficiency and thyroid dysfunction. Nutritional medicine could in the future be an important strategy to improve treatment effectiveness, women with perinatal depression having lower levels of total $n-3$ PUFAs and docosahexaenoic acid and significantly increased $n-6/n-3$ ratios [66]. Bright light therapy (BLT) is a well-tested and safe treatment, effective in both depression and circadian/sleep disorders [67]. If the depression is severe, resistant, and with psychotic features and requires rapid treatment, when the risk of complication is lower than the possible benefit, electroconvulsive therapy (ECT) is an excellent option in the peripartum patient [68].

A 10-week Internet-delivered cognitive behavior therapy (ICBT) has been reported to be effective in antenatal depression in a randomized controlled trial [69]. A 9-week CBT in perinatal depression group showed a clinically significant improvement in depressive symptoms [70]. The use of technology is common among perinatal women, and apps aiming to disseminate prevention programs for perinatal depression are under study [71–73].

In conclusion, women with psychiatric disorders, either already affected before pregnancy or with a new psychiatric onset in this period, pose a great challenge for treatment management [14]. Therefore, in several European countries (UK, France,

Holland), in the USA, and in Australia, mother-baby units are available to treat severe psychiatric episodes, to hospitalize both mother and child [74].

Prevention plans from earliest and prodromal depression signs and symptoms (medication prophylaxis, birth plan, and intervention strategies) are fundamental, in order to take care of women and neonatal well-being from pregnancy, including strategies for adequate sleep, maintenance of stable circadian rhythm, stress reduction, and familial support of maternal-newborn bonding [75].

Box 9.2 Treatment

- Second-generation antidepressants are considered to be relatively safe for use during pregnancy. Citalopram, escitalopram, and sertraline do not augment the risk for major malformations, while first trimester exposure to paroxetine, particularly at doses up to 25 mg/day, has been associated with a small increased risk of cardiac defects (see ToxMed for updated info). With regard to breastfeeding, antidepressants are differently excreted in breast milk [76, 77]; routine pediatric care is appropriate monitoring for breastfed infants of women taking SSRI (see LactMed for updated info).
- Lithium prophylaxis immediately postpartum has been shown to decrease relapse in high-risk women with bipolar disorder; however, it is not recommended when breastfeeding, unlike valproic acid which is allowed when breastfeeding and banned in pregnancy.
- No increase in congenital malformations with prenatal antipsychotic exposure has been reported by the National Pregnancy Registry for Antipsychotics [78]. Nevertheless, babies exposed to psychotropic drugs during pregnancy have less optimal neonatal outcome than unexposed and should be considered as a high-risk population [79].

Key Points

- Screen for perinatal depression during pregnancy and over the first year monitoring postpartum patients carefully, to rule out subtle signs of emerging hypomania and mixed symptoms, suggestive of bipolar disorder. Assertive follow-up and treatment of women to address suicide/infanticide risk are needed.
- Women at high risk for perinatal depression: previous history of mood disorders, history of postpartum depression, depressive symptoms in pregnancy, positive psychiatric family history, and poor social/family support.
- SSRI is the gold standard for perinatal depression and anxiety treatment, being considered safe and well tolerated: drug reduction before birth to minimize neonatal behavioral syndrome at birth.
- If the patient is breastfeeding, breast milk transfer should be considered: fluvoxamine, paroxetine, and sertraline lead to the lowest serum medication levels in infants.

- If depression is severe, resistant, and with psychotic features, it is recommended to add antipsychotics/mood stabilizers or consider electroconvulsive therapy (ECT) as an alternative treatment in the peripartum.

Self-Assessment Questionnaire

1. Which is the major assessment tool used to screen perinatal depression?
   (A) HAM-A
   (B) HAM-D
   (C) **EPDS**
   (D) MRS
2. Which biomarker could detect depressive states in pregnancy/postpartum?
   (A) IL-6
   (B) BDNF
   (C) Oxytocin levels
   (D) **All of the above**
3. Which drug has been reported to be unsafe during pregnancy?
   (A) Lamotrigine
   (B) **Valproic acid**
   (C) Quetiapine
   (D) Sertraline
4. Which factors have been reported to augment the risk for a severe perinatal depression?
   (A) Previous depressive episodes
   (B) Inadequate social support
   (C) Family psychiatric history
   (D) **All of the above**
5. Drug penetration into breast milk increases with:
   (A) Increasing plasma protein binding
   (B) **Increasing solubility in lipids**
   (C) Decreasing solubility in lipids
   (D) Increasing volume of distribution

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