Perinatal mood and anxiety disorders. Clinical assessment and management. A review of current literature

Disturbi dell'umore e disturbi d'ansia perinatali. Valutazione clinica e gestione del trattamento. Una revisione attuale della letteratura corrente

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Summary

This article reviews recent literature on mood and anxiety disorders during the perinatal period. We conducted a search of the PubMed databases. Key words included pregnancy, perinatal depression, risk factors, clinical presentation, drug treatment. Childbearing is one of the most complex periods of human experience; pregnant women and mothers who recently delivered are vulnerable to the entire spectrum of psychiatric disorders. The cumulative point-prevalence rates of major and minor depression range from 8.5% to 11% during pregnancy, and from 6.5% to 12.9% during the first year postpartum. Anxiety symptoms are frequently reported by pregnant women; in recent literature antenatal anxiety has received increased attention with regard to both its impact on infant outcomes and as a risk factor for postnatal depression. Gender-specific differences in the prevalence and clinical course of depression undoubtedly stem from a variety of factors, including biological differences between women and men. Several studies reveal the psychoactive effects of female hormones; low estrogen levels are associated with premenstrual syndrome, postpartum, and menopausal depression. Untreated perinatal mental disorders may have severe obstetrical and psychiatric short- and long-term consequences, not only for the woman but also for her family and mostly for the newborn baby, such as premature birth, cesarean section, instrumental vaginal deliveries, intrauterine growth retardation, low birth weight, and postnatal complications. Every woman is potentially at risk for developing postpartum depression, women who present specific risk factors have a significantly increased risk for becoming depressed after delivery. These risk factors are widely studied in literature; the strongest predictors of postpartum depression are the experience of depression or anxiety during pregnancy or a previous depressive illness; in addition to these predictors, life stress and lack of social support have a moderate-severe effect size. Psychological factors and marital problems have a moderate effect size, while obstetric factors and socioeconomic status have a small effect size. Pharmacological treatment of mood and anxiety disorders are based on clinical experience and management of disorders during pregnancy, postpartum and lactation requires a careful balancing of maternal and fetal risks and benefits. Antidepressants are relatively safe in pregnancy and during lactation; a greater attention should be given to the use of stabilizers and neuroleptics, but clinical dates are still contradictory.

Key words

Pregnancy • Perinatal depression • Risk factor • Clinical presentation • Pharmacological treatment

Introduction

Mental illness during the perinatal period is socially unacceptable, due to the common belief that women "bloom" during pregnancy and that they "must be happy" for the imminent motherhood [1-5]. Nevertheless, childbearing is one of the most complex events in human experience;

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pregnant women and mothers who delivered recently are vulnerable to the entire spectrum of psychiatric disorders [6]. Even though Marcé had long ago shown [7] the importance of mental disorders during pregnancy, research has been mainly focused on postpartum mental disorders. Consequently, little is known about mood and anxiety disorders during pregnancy, despite a growing body of evidence underlines their epidemiological and clinical relevance [8]. Recent literature suggests that perinatal mood and anxiety disorders are not culturally bound: they affect women in every society and from every socioeconomic background [9]. The prevalence rates of clinical depression in the perinatal period are comparable to those seen in non-childbearing groups [10]; however, rates of subclinical symptoms of depression reported at this time are higher than expected [11]. A recent meta-analysis sponsored by the Agency for Healthcare Research and Quality (AHQR) [8] highlighted that the point prevalence of major and minor depression ranges from 8.5% to 11.0% during pregnancy and from 6.5% to 12.9% during the first year postpartum. Moreover, Andersson et al. [12] suggested that anxiety and depressive disorders are at least as common during pregnancy as otherwise. They reported that in an unselected clinical sample of women at the second trimester of pregnancy, 14.1% met criteria for at least 1 psychiatric disorder; of these women, 11.6% had a mood disorder and 6.6% an anxiety disorder. A recent Italian study [13] conducted in an unselected non-clinical sample of women at the third month of pregnancy found a point prevalence of current DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edn.) mood and anxiety disorders, of 8.8% and 21.7%, respectively. Among anxiety disorders, panic disorder (PD) needs to be carefully noted, because, despite variability in assessment times and procedures, relatively consistent prevalence rates ranging from 1.3% to 2.0%, have been reported for this disorder during the perinatal period [14-16].

Gender-specific neural correlates of depression and anxiety

Gender-specific differences in the prevalence and clinical course of depression undoubtedly stem from a variety of factors, including biological differences between women and men. Probably due in part to genetically primed alterations in mood response to changing hormones during reproductive transitions, women are at increased risk for mood instability at puberty, during the premenstruum, the postpartum, perimenopause, following miscarriage, and during pregnancy [17-19]. Animal studies reveal the psychoactive effects of female hormones; for example, in a study of ovariectomized rats which received estradiol replacement there was an increase in neuronal dendritic spine's density compared with rats that were not treated with estrogen. The same study showed that progesterone augmented the effect of estradiol within hours [20]. In human studies, low estrogen levels are associated with postpartum and menopausal depression, as well as cyclic estrogenic fluctuations may explain the symptomatology of pre-menstrual syndrome [21] [22]. The presence of receptors for gonadal hormones and glucocorticoids in different areas of the central nervous system (CNS) is well established [23]; in particular, estrogen receptors were localized in pre-optical area, amygdala [24] and hypothalamus [25]. Steroid hormones appear to modulate neuronal transmission through different mechanisms [26-29]. Estrogens seem to have an agonist action towards serotonin, cholinergic and noradrenergic receptors, and finally seems to modulate the dopamine D_2 receptors.

These hormonal changes are particularly evident during pregnancy and immediate postpartum period, and can explain the symptomatology of well-known baby-blues. The concentration of progesterone and estrogens increases rapidly and remains constant until a few days before the birth, when there is a sharp decline in placentar steroids: the concentration of estrogen and progesterone is over 200 times lower at the end of the first week after birth compared to the level of the final stage of pregnancy. More recently, the attention of researchers moved to the hypothalamic pituitary adrenal (HPA) axis mediators involved in stress-responses. During pregnancy there is a very large increase in plasma corticotrophin releasing hormone (CRH), produced by not only the hypothalamus but even by the placenta (pCRH) [30]. Also in this period, peptidergic systems directly involved in the mechanism of reproduction (gonadotropin releasing hormone – GnRH –, prolactin, oxytocin) and others involved in a more marginal way (thyroid hormones, endogenous opioid and CRF-atch) undergo significant fluctuations.

Gender-specific psychosocial correlates of depression and anxiety

For some women, the risk for depression is increased by major negative life events. Traumatic experiences play a significant role and increase risk for major depression in women as compared to men. Thus, early traumas, such as parental loss, as well as more proximal events such as divorce, separation, marital discord, severe illness, assault, loss of a job, or the death or serious illness of a close relative all appear to contribute to the preponderance of depression in women [31]. As noted, females are much more vulnerable to a lack of social support than their male twin siblings [32]. It is not surprising that increased child-bearing responsibilities and little social support are among the factors that increase the risk for postpartum depression. Clinically, this can be seen in young mothers who have little support when pregnant and in the postpartum, leaving them to shoulder the burden of child-bearing responsibilities [33 34].

The impact of untreated perinatal depression and anxiety

Although untreated perinatal mental disorders may have severe obstetrical and psychiatric short- and long-term consequences, not only for the woman (i.e., suicide, reduced self-care, substance abuse) [35] but also for her family and mostly for the newborn baby, only 5% of mentally ill pregnant women receive any kind of treatment, including psychological support [36]. These data have been more recently confirmed by Flynn et al. [37] who found, in high-risk pregnant women, that only a minority of women with a prenatal diagnosis of major depressive disorder (MDD) were being treated and that current MDD was not predictive of treatment use, suggesting the need for improved detection of depression. Recent attention has been posed on the consequences of untreated anxiety disorders on the well-being of mothers; anxiety during pregnancy has been linked to negative expectations about motherhood [38], difficulties adjusting to the demands of the maternal role [39], and the development of other forms of distress, particularly postnatal depression [14 40-43]. Several prospective studies have shown that a prenatal anxiety disorder is one of the strongest risk factors for developing postnatal depression [14 44 45]. In a recent Italian study performed in the framework of the Perinatal Depression-Research & Screening Unit (PNDReScU), DSM-IV personal or family history of panic disorder proved to be an independent risk factor for postpartum depression, i.e., women with panic disorder during the early phase of pregnancy were 4.2 times more likely to have post-partum depression than those without panic disorder [46]. Moreover, women with lifetime diagnosis or family history of panic disorder were 2.5 and 2.1 times more likely to develop postpartum depression [46], respectively. In addition to the many negative effects of untreated depressive and anxiety illness during pregnancy on maternal well-being, the risk for adverse neonatal outcomes include an increased incidence of premature birth, cesarean section, instrumental vaginal deliveries, intrauterine growth retardation, low birth weight, postnatal complications, increased levels of neonatal stress hormones cortisol and catecholamines, and neonatal inconsolability [47]. Fetal exposure to elevated levels of hormones (particularly cortisol) may contribute to premature labor and delivery [48 49]. Maternal exposure to stress and anxiety may precipitate the release of catecholamines that can result in maternal vasoconstriction and ultimately a limitation of oxygen and vital nutrients to the fetus [50]. The exposure of the fetus to maternal stress and increased levels of adrenal hormones therefore has possible consequences for fetal central nervous system development and specifically glucocorticoid brain receptor development [49-51]. Neonates of depressed mothers have poorer orienting skills, decreased motor tone, lower activity levels, lower vagal tone, right EEG asymmetry, poorer orientation, reflex, excitability, and withdrawal clusters on the Brazelton Scale [52-54]. Other negative child outcomes include increased depression, anxiety, aggressiveness, withdrawal, hyperactivity, and delay in development at one year [55-58]. Of even greater concern, prenatal maternal anxiety has been linked to persisting neurobehavioral problems, including poorer performance on tests of neurodevelopment, increased fearfulness [59], and with the development of difficult infant temperament [60-62]. The profound impact of maternal depression on the health and well-being of children aged 7-17 years was recently documented in a multi-site study of children of mothers who were treated with medication as part of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D). Those children who were free of any psychiatric symptoms at

study entry and whose mothers' depression remitted with treatment remained well, while 17% of initially well children whose mothers did not remit acquired a psychiatric disorder (depressive, anxiety, or disruptive behavior disorders). Successful treatment to remission of maternal depression was associated with an 11% decrease in rates of diagnosis for their children, whereas failure to remit resulted in an 8% increase in psychiatric diagnoses in their children [63]. As a corollary of this data, a twenty-year follow-up study of adult offspring of depressed parents revealed that they had higher rates of depression, anxiety, substance dependence, work dysfunction, family dysfunction, and physical illness (especially cardiovascular disease) than age-matched offspring of non-depressed parents [64].

Clinical features of perinatal depression and anxiety

Postpartum affective disorders are typically divided into three categories: postpartum blues, postpartum depression, and puerperal (postpartum) psychosis. The "baby blues" is the most common observed puerperal mood disturbance, with a prevalence ranging from 30% to 75% [65]. Symptoms are mild and include mood lability, irritability, tearfulness, generalized anxiety, sleep and appetite disturbances. The onset is typically four to five days after delivery and it resolves by two weeks. Treatment is not required [66 67].
Postpartum depression is the most common complication of childbearing, occurring in approximately 10-15% of women [9], up to 26% [68] in teenage mothers. Postpartum depression usually begins within the first 6 weeks after delivery: in some cases baby blues simply endures and become more severe, otherwise a period of well-being after delivery is followed by a gradual onset of depression. Postpartum depression is characterized by tearfulness, despondency, emotional lability, guilt feelings, loss of appetite, suicidal ideation, and sleep disturbances as well as feelings of inadequacy and inability to cope with the infant, poor concentration and memory, fatigue, and irritability [69]. Some women worry excessively about the baby's health or feeding habits and see themselves as "bad," inadequate, or unloving mothers [69]. The majority of postnatal depressions are self-limiting, resolving within months of onset [70 71]. After one postpartum episode the risk of recurrence for major depression is 25% [72]. The mainstay of treatment has been antidepressant therapy, alone or in combination with psychotherapy.
Postpartum psychosis is the most severe of postnatal affective illness, with a prevalence ranging from 0.1-0.2%. The clinical onset is rapid, with symptoms presenting within the first 48-72 hours after delivery, in any case no later than 2 weeks postpartum. The presenting symptoms are typically expansive or irritable mood which can fluctuate rapidly, disorganized behavior, mood lability, insomnia, delusions and hallucinations that often involve the infant [2]. Postpartum psychosis is a medical emergency and it often requires hospitalization. Evidence from clinical, genetic, and follow-up studies indicates that most cases of puerperal psychosis meet criteria for bipolar disorder [2 73-77]. Although the prognosis is generally favorable and women fully recover, they are at risk of developing further puerperal and non puerperal episodes of bipolar affective disorder [78].
Recent evidence from epidemiological and clinical studies suggests that symptoms of perinatal depression are essentially the same in women who are pregnant and women who are not [79]. Depressed pregnant women and depressed non pregnant women have similar severity of depressive symptoms. However, depressed pregnant women show fewer intense feelings of suicide [80] and guilt, suggesting that pregnancy may be a protective factor for this important symptom; moreover, depressed pregnant women have significantly less difficulty falling asleep, but are more likely to show psychomotor retardation. Somatic symptoms such as poor appetite and difficulty falling asleep are common complaints of women near term, so it can be difficult for clinicians to distinguish between depressive symptoms and the supposed "normal" sequelae of childbirth, such as weight loss, sleep disturbances, loss of energy [81]. Postpartum, these symptoms generally improve, and as a result, scores on these items are more likely to be indicative of depression [82]. Anxiety symptoms are a key component of postpartum depression and may distinguish it from typical major depressive episodes: the greater anxiety associated with postpartum depression may result in part from the stress of looking after a newborn and from sleep deprivation [83].

Anxiety features

Anxiety symptoms are frequently reported by pregnant women and are often considered as part of

the normal psychic experiences of pregnancy, especially if they are focused on the baby's health or on maternal competencies, thus leading to underestimate their real prevalence. The clinical features of anxiety disorders in pregnancy are similar to those in nonpregnant women. However, concerns over the pregnancy and fetus may present as the predominant feature [84]. For example, in panic disorder, women may interpret panic attacks as something being wrong with the fetus [85-87]. Perinatal obsessive compulsive disorder (OCD) is classically described as involving obsessive concerns of harming the child together with checking and cleaning compulsions [88]. It is important to differentiate this from homicidal impulses toward the child (e.g., as part of a psychotic disorder). In OCD, these thoughts are intrusive, egodystonic, and the mother has no wish to harm her child. It has been postulated that these features may be an exacerbation of the normal vigilance toward the child that is characteristic of the pregnancy and the postpartum period [89]. Women with anxiety disorders also commonly present with physical complaints. Studies of health in pregnancy in women with psychiatric disorders showed an increased frequency of nausea and vomiting, disability days, and physician visits in women with anxiety or mood disorders [44]. Frequent physical complaints with no discernible physical cause should prompt the clinician to screen for an anxiety disorder [84]. Among all anxiety disorders, panic disorder (PD) needs to be carefully noted. PD is associated with high rates of psychiatric comorbidity especially with major depression (i.e. approximately 50% of women with PD [90] and, notably, PD patients with comorbid depression usually display greater symptom severity [91-94], more suicidal ideation [95 96] and poorer response to both psychotherapeutic [92 97 98] and pharmacological treatments [92-94 98], compared to PD patients without comorbidity. Finally, it has to be acknowledged that PD represents an independent risk for suicidal behaviors [96 100-103]. Although symptoms of panic during the perinatal period are similar to symptoms in the general population, they are often interpreted in the context of the perinatal state. In a qualitative, phenomenological study of 6 postpartum women with panic disorder, women reported feeling unable to leave their homes, to take their children to groups and activities, and worried about the long-term impact of their panic disorder and the resulting isolation on their children [103]. Although no literature has reported risk factors for or predictors of perinatal panic disorder, there is some evidence from retrospective studies of a relationship between lactation/weaning and panic symptoms. Controlled, prospective studies are needed to determine whether breastfeeding reduces, and/or weaning increases, risk for panic disorder [5]. Although there are conflicting findings, a general pattern of improvement in panic symptoms during pregnancy, followed by worsening during the postpartum period, has been reported in retrospective studies and case reports [86 104 105]. However, other evidence [106-109] suggests that the most common effect of perinatal status on panic disorder may be no change in symptom severity. The best predictor of symptom change may be symptom severity anterior to pregnancy, with greater severity predicting a worse course [106].

Risk factors

Although every woman is potentially at risk of developing PPD, women who present specific risk factors have a significantly increased risk of becoming depressed after delivery. These risk factors are widely studied in literature [110-112] and meta-analyses that incorporated results from over 70 studies, and 12,000 research subjects [9 110 113] were carried out to estimate the effect size of each of them. Currently, the known risk factors have been classified, according to their effect size, into three categories: strong-moderate, moderate and small.

Strong-moderate risk factors

The strongest predictors of PPD are the experience of depression or anxiety during pregnancy or a previous depressive illness [112]. A previous history of anxiety disorder [114 115] and anxiety during pregnancy [8 114 116-119] have been identified as important determinants of postnatal depression. In one study [8], a diagnosis of anxiety disorder during pregnancy was associated with a 3-fold increase in postnatal depression at 6 weeks. Although mental disorders during pregnancy represent a risk factor for depressive episodes during the postpartum period [120 121], they often go unrecognized and undiagnosed largely because many depressive symptoms are similar to those that commonly occur during pregnancy, including sleep and appetite disturbances, diminished libido, and low energy [9 78].

Women who have recently experienced a stressful life event are also at high risk of illness, as well as those who perceive they have low levels of social support, even though this may not be true.

Past history of psychiatric illness

Similarly, there is little question that a past history of psychiatric illness puts women at risk for depression in the postpartum period. The average effect size is one of the largest for the risk factors of postpartum depression. Studies consistently show that having previously experienced depressive symptoms at any time, not just related to childbirth [9 113 122 123], leads to a significantly increased risk for postpartum depression.

The current evidence from large-scale studies suggests that having a positive family history of any psychiatric illness confers risk of postpartum depression, although the effect size is small [123]. One of the difficulties in establishing family history of mental illness is that the patient needs to be aware of relatives with psychiatric problems and be willing to disclose that information. The results from studies that have been able to report completed clinical interviews with women suffering from postpartum depression and members of their family have also shown a highly significant relationship between family history of depressive or psychiatric illness and postpartum depression [124 125]. In addition to these predictors, life stress and lack of social support have a moderate-severe effect size; psychological factors and marital problems have a moderate effect size, while obstetric factors and socioeconomic status have a small effect size [112]. All of these predictors should be assessed during routine pregnancy care [110 126], in fact, early identification, preventative interventions and treatment could alleviate months of suffering for a new mother and decrease the potentially harmful impact on her infant [110 127].

Life events

The relationship between life events and the onset of depression is well established [128]. Experiences such as the death of a loved one, relationship breakdown or divorce, losing a job, or moving home are known to cause stress and can trigger depressive episodes in individuals with no previous history of affective disturbance. Pregnancy and birth are often regarded as stressful life events in their own right, and the stressfulness of these events may lead to depression [129]. However, some researchers have studied the effects of additional stressful life events that women experience during pregnancy and the puerperium. One of the difficulties of assessing a possible relationship between life events and the onset of depression postpartum is the study design. Retrospective collection of data may lead to over reporting of life events as subjects (perhaps subconsciously) try to link a stressful event as a possible cause of the illness. The prospective collection of data eliminates this source of bias, as the outcome of postpartum depression is not known a priori. In their meta-analyses, O'Hara and Swain [9] took values from 15 studies, comprising data on over 1000 subjects, that had prospectively recorded data on life events. They found a strong–moderate relationship between experiencing a life event and developing postpartum depression. However, there was heterogeneity between studies that related to where the study was conducted: studies undertaken in Britain and North America showed strong associations between postpartum depression and recent life events, while Asian studies showed a nonsignificant association [130]. It is not clear why this should occur.

Social support

Receiving social support through friends and relatives during stressful times is thought to be a protective factor against developing depression [131] and several earlier studies have evaluated the role of social support in reducing postpartum depression. Social support is a multidimensional concept. Sources of support can be a spouse, relatives, friends, or associates. There are also different types of social support, e.g., informational support (where advice and guidance is given), instrumental support (practical help in terms of material aid or assistance with tasks), and emotional support (expressions of caring and esteem). Studies have consistently shown a negative correlation between postpartum depression and emotional and instrumental support during pregnancy [9 132-135]. Two recent studies have found that perceived social isolation (or lack of social support) during pregnancy was a strong risk factor for depressive symptoms postpartum [135 136]. These findings suggest that women who do not receive good social support

during pregnancy are more likely to develop postpartum depression. This concept was confirmed in a recent study that argued that receiving informational support from a large number of social network members was protective against postpartum depression [135]. It should be noted that researchers have consistently found differences between depressed women's perceptions of social support, and the amount of support they objectively received [137]. These differences may be accounted for, in part, by the fact that depressed individuals tend to view everything more negatively, including the level of support they perceive.

Moderate risk factors

Psychological factors

Neuroticism. Maternal personality characteristics including neuroticism and cognitive attributional style have been measured as risk factors for postpartum depression. Neurotic disorders can be defined as psychological disorders that are usually distressing but allow one to think rationally and function socially. The neurotic disorders are usually viewed as ways of dealing with anxiety. The term neurotic is no longer used within psychiatric classification systems, although it is commonly included in personality questionnaires as a measure of psychological distress.

Neuroticism measured in women prenatally was found to be a weak-to-moderate predictor of postpartum depression [9 130]. Johnstone et al. [123] found that women who were defined as "being nervous", "shy, self-conscious," or a "worrier" through questionnaires were significantly more likely to develop postpartum depression. Similarly, women with negative cognitive attributional styles (e.g., pessimism, anger, ruminations), previously shown to be good indicators of depression [138], were more likely to develop postpartum depression [9].

Marital relationship. Closely linked with findings on social support, studies have reported an increased risk of postpartum depression in women who experienced marital problems during pregnancy [9 70 113]. This would be reflected in feelings of isolation and lack of support. The effects of parenthood on all aspects of the mother's psychosocial functioning should not be underestimated. Robinson and Stewart [69] discuss how in many cases, the family system must be reorganized, and many couples adopt more traditional roles. The mother usually tends to do the greater share of parenting tasks, and the parents must decide how their new roles will affect their previous work patterns and implement the necessary changes. With the added burden of childcare, the relationship between the partners often suffers, and there is less time for socializing. A supportive relationship with the father can help mitigate the stresses of being a new mother. These stresses should be borne in mind when evaluating the role of factors in the development of postpartum depression.

Small risk factors

Obstetric factors

Obstetric factors including pregnancy-related complications such as preeclampsia, hyperemesis, premature labor, as well as delivery-related complications, such as cesarean section, instrumental delivery, premature delivery, and excessive bleeding intrapartum have been examined as potential risk factors for postpartum depression. The results from 16 large-scale studies of 9500 women indicate that pregnancy-and delivery-related complications have a small but significant effect on the development of postpartum depression [9 123 136 139]. Although there is little evidence supporting an association between delivery by caesarean section and postpartum depression from large studies [123 136 139], it has been reported that women undergoing emergency caesarean sections were more likely to develop postpartum depression [140 141]. It is unclear, however, if delivery complications or long and painful labor leading to emergency procedures account for the association. Equivocal findings have been reported for associations between unplanned or unwanted pregnancies [132 139] and breastfeeding and postpartum depression [136 139 141]. In summary, the evidence suggests that obstetric factors make only a small but significant contribution to the development of postpartum depression. However, one must be very cautious when interpreting the results. Some of the variables measured may not be truly independent but rather are influenced by extraneous variables. For example, the decision to perform caesarean sections may differ between physicians and hospitals, and certainly internationally. Similarly, rates of breastfeeding or attitudes toward breastfeeding may differ within cultures and countries. It should also be noted that an unplanned pregnancy merely reflects the cir-

cumstances in which the pregnancy occurred, and is not a measure of the woman's feelings toward the fetus. Therefore, the results may be reflecting trends within the sample rather than an etiological relationship between postpartum depression and obstetric variables. Socioeconomic status Socioeconomic deprivation indicators such as unemployment, low income, and low education have been cited as risk factors in mental health disorders, and depression, in particular [142-144]. The evidence suggests that these factors play a small but significant role in the development of postpartum depression. Indicators such as low income, financial strain, mother's occupation, and lower social status have a small but significant predictive relationship to postpartum depression [9 113 130 135 139 143]. These results are consistent across different cultures and countries.

Factors not associated with postpartum depression

It is also worth establishing which factors have no relationship with postpartum depression. Here, nonsignificance is defined as the confidence interval containing 0. Two meta-analyses of over 10,000 subjects found the following factors were not associated with postpartum depression [9 113]: maternal age (in samples of women aged over 18 years, as previously stated the risk is much higher in teenage mothers), level of education, parity, and length of relationship with partner. Studies conducted within Western societies have found no association between the gender of the child and postpartum depression. However, recent studies provide evidence from India [145] and China [130], which suggest that spousal disappointment with the gender of the baby, specifically if the baby is a girl, is significantly associated with developing postpartum depression. Therefore, the parent's reaction to the gender of the baby may be a potential risk factor for postpartum depression within certain cultural groups.

Treatment during pregnancy and postpartum

In the past decades the interest for the best pharmacological treatment for psychiatric disorder occurring in pregnancy has increased. Nevertheless, the management and treatment choices for these diseases are primarily driven by clinical experience, without the support of literature and controlled studies. Up today, the Food and Drug Administration (FDA) has not approved the use of antidepressants during pregnancy, but has emphasized the importance of assessing the relationship between the risks of an untreated disease and the benefits of a treatment with antidepressants, taking into account the potential teratogenic effects.

When the psychiatric disorder is clinically relevant, a pharmacological treatment is indicated: clinicians have to use drugs with the best safety profile, in accordance with woman's whishes.

Given that depression during pregnancy affects 10-20% of women [146 147], only a minority of them (about 20%) receive some form of treatment, although in recent years the use of antidepressants in pregnancy and postpartum, especially with regard to the SSRI, appears to be significantly increased [148]. Recent studies emphasize that the rates of relapse of major depression during pregnancy vary from 43% to 68% in case of discontinuation of treatment [149] and that depression and anxiety during pregnancy are associated with an increased risk of adverse outcomes as prematurity of the unborn, fetal distress and behavioral changes [150]. In addition, discontinuing medication increases the risk for postpartum depression [151] and recurrence in subsequent periods [152]. Recent studies have emphasized the teratogenic effect of psychopharmacological treatments, their abortive risk, neonatal complications and their potential effect on the neuro-cognitive development of the child. The risk-benefit ratio must be carefully assessed, taking into account the well-being of mother and child. In case of mild depression, the first intervention should be represented by non-pharmacological treatments (Support Psychotherapy, Brief Interpersonal Psychotherapy or Cognitive Behavioral Therapy). In cases of moderate to severe depression, however, the use of antidepressants (AD) is recommended, and its choice should be made in accord with international guidelines, considering also the previous response to a specific drug. The probability of response to an AD that has been proved its efficacy in the past is superior to that of a poly-pharmacotherapy in case of inadequate response. Several antidepressants are currently available, with different pharmacological actions and side effects. The selective serotonin reuptake inhibitors and the secondary amine tricyclic anti-

depressants are preferred agents in pregnancy and appear safe even in the first trimester. As stated above, personal or family history of response to a given agent frequently guides the first choice. Additionally, many women prefer to avoid the side effects of the tricyclic agents. The selective serotonin reuptake inhibitor fluoxetine has been best studied in pregnancy. Preliminary studies on sertraline, paroxetine, and citalopram are similarly encouraging without evidence of teratogenicity. These should be considered for women who have previously had good outcomes. The tricyclic antidepressants nortriptyline and desipramine are good candidates for use in pregnancy because they tend to cause less orthostatic hypotension, dry mouth and constipation [153]. The data on teratogenicity are still limited and sometimes contradictory. For the treatment of women with depression during pregnancy the serotonin (SSRI) drugs are currently the most prescribed antidepressant worldwide and have been used up to now by millions of women. Their safety profile is still high. The rate of congenital malformations (2-3%) after SSRIs exposure [154 155] is similar to the rate of malformations found in children of non-exposed women. The SSRIs most commonly used up to now are fluoxetine, sertraline, citalopram, and paroxetine. In a recent retrospective study conducted on the paroxetine by its manufacturer, has been provided data on the possible cardiovascular malformations risk, but only for first trimester exposure. These data have been re-evaluated and are possibly related to a dose-response relationship [156 157]. Equally safe in terms of teratogenic effects are the tricyclic AD [158 159]. Even concerning about neonatal toxicity of both types of AD, there are contradictory evidences. While in a study of 2003 [160] the risk of abnormalities was calculated similar to that of the general population, two more recent studies have reported an increased risk of preterm birth, low birth weight, and other minor problems [159 161]. It was also suggested a possible association between exposure to SSRIs by the 20th week of gestation and persistent pulmonary hypertension at birth [162]. There are also evidences about withdrawal syndromes (especially with SSRIs): these are avoidable by reducing the dosage and suspending the drug a few weeks before the birth. Anyway these symptoms are reversible and manageable, by maintaining the administration of the drug through breastfeeding and reducing the intake gradually [161]. Up today, with regard to cognitive and behavioral abnormalities in the long term there are no sufficient evidences. All antidepressants are secreted into breast milk, and are passed on to the nursing infant in varying amounts [163 164]. Available information about the short-term risks associated with antidepressant use during breastfeeding is generally favorable; however, data are still limited and are derived mainly from case reports and case series. Little is currently known about the long-term developmental risks of these agents, although limited data on fluvoxamine and the tricyclic antidepressants (TCAs) are reassuring [163 165 166]. In general, antidepressants with the most evidence to support their safety are preferred for use during lactation [166]. SSRIs as a class have been used relatively frequently in breast-feeding women, and are recommended as first-line agents because of their favourable toxicity profiles [164]. Specifically, sertraline and paroxetine have been suggested as initial options based on a number of case series and case reports documenting minimal risk to nursing infants [163 164 166 167]. Fluoxetine is not generally recommended for early postpartum use due to reports of adverse effects in young infants [167 168] however, breast-feeding need not be discontinued if it is the only suitable agent, provided that infants are healthy and are monitored appropriately [166 169]. If fluoxetine has been used throughout pregnancy, switching to an alternative SSRI, immediately postpartum is an option [169]. Use of fluoxetine in infants > 4 months of age is not likely as hazardous, as metabolic and excretory functions are more developed by this age. Citalopram and fluvoxamine should be used with caution, as there is little information available regarding their use in breastfeeding women [163]. The TCAs may be useful in breastfeeding women when SSRIs are unsuitable [163]. Of the TCAs, nortriptyline has been studied most thoroughly [164]. Data regarding the use of other classes of antidepressants in breast-feeding women are limited, and the decision to use such agents should take this fact into consideration, bearing in mind the risks of untreated depression and the benefits of feeding [164]. Notwithstanding the above recommendations, any agent to which a woman has previously had a positive response should strongly be considered for therapy [164]. In general, the lowest effective doses of antidepressants should be used in breastfeeding women [164] and the medications are best taken as single daily doses, before the infant's longest pe-

riod of sleep [166]. Feeding should be timed, if possible, to the period when concentrations are likely to be lowest in breast milk [163], and breastfeeding immediately prior to a dose [166] and avoiding times of peak milk concentrations will often help minimizing infant exposure.

Treatment of bipolar disorder during pregnancy and postpartum period need a particular attention. There are no epidemiologic exposure data reported specifically for women with bipolar disorder who take anticonvulsants during pregnancy.

In the past, risk for Ebstein's anomaly in children with fetal exposure to lithium may be 20 times higher than the risk in unexposed children, although the absolute risk with lithium exposure remains low (1 in 1000 births) [170 171]. Valproate, its derivatives and carbamazepine are human teratogens. To date, no studies have examined the outcomes of children whose mothers took anticonvulsants for bipolar disorder during pregnancy, though the research concerning epileptic mothers is extensive. Data associate anticonvulsant exposure with a significantly greater risk for malformations than in the general population. Specifically, anticonvulsants may cause neural tube defects such as spina bifida, anencephaly in 2 to 5% of those exposed, as well as craniofacial anomalies, microcephaly, growth retardation, and heart defects. Maternal folate supplementation reduces the risk of neural tube defects. More minor malformations, such as rotated ears, depressed nasal bridge, short nose, elongated upper lip, and fingernail hypoplasia, have been reported in infants exposed to anticonvulsants *in utero*. Teratogenicity increases with the use of multiple anticonvulsants and possibly with higher maternal plasma levels and toxic metabolites [172-175]. The three most commonly used mood stabilizers are all teratogenic. The least risk may occur with lithium (0.1%) *vs.* valproate (2 to 5%) or carbamazepine (1 to 3%). These risks must be weighed against the up to 50% chance of relapse with medication discontinuation [176]. Lamotrigine does not negatively impact major reproductive outcomes, but the data are limited. On the contrary carbamazepine and valproate, but not lithium, have generally been considered compatible with breastfeeding [177]. Antipsychotic drugs are often used as monotherapy or adjunctive medications for patients with bipolar disorder. The largest body of evidence regarding safety for use in pregnancy exists for the older, first-generation antipsychotics [178]. First-generation antipsychotic medications may also be a choice for women with bipolar disorder who elect to discontinue medication during pregnancy but begin to experience a recurrence of symptoms while pregnant [179]. In a 2004 review of the management of bipolar disorder in pregnancy, Yonkers et al. [179] support the role of first-generation antipsychotic agents both in the treatment of acute mania during pregnancy, and as an alternative to selected mood stabilizers. Psychiatric clinicians may elect to switch a patient's medication from lithium or an anticonvulsant to a first-generation antipsychotic either for the entire pregnancy or for the first trimester. This strategy is particularly recommended for patients who have benefited from mood stabilization with antipsychotic medications in the past. While atypical antipsychotics are widely used by reproductive-aged women who suffer from bipolar disorder, sparse data exist regarding the safety of these agents during pregnancy, with postmarketing surveillance mostly limited to case reports and small series [158 180 181]. Other data suggest that atypical antipsychotics are not associated with an increased risk for major malformations; however, the limited numbers are inadequate to determine the risk of fetal exposure. Therefore the use of atypical antipsychotics during pregnancy and breastfeeding is generally not recommended based on current knowledge, although it is recognized that potential benefits of their use to both mother and child may outweigh potential risks.

Conclusion

The post-partum period, as well as pregnancy, is associated with a risk of anxiety and/or affective disorders [5]. Recent data suggest that an early screening could detect women at the highest risk to develop perinatal depression, for the presence of risk factors such as a personal or family history of depression, anxiety during pregnancy, lack of social support [110 127]. Today, only few standardized preventive interventions have been developed to reduce the impact of this pathology. Treatments found to be effective for depression and anxiety are also safe and efficacious in postpartum women, including those who are breastfeeding [148]. Antidepressant are relatively safe in pregnancy and during lactation [154-162]; a greater attention should be given to the use of stabilizers [170-177] and neuroleptics, but clinical data are still contradictory [179].

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