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Peripartum Psychological Distress Conditions and Disorders: Biopsychosocial View

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Abstract

The childbearing years including pregnancy and postpartum are periods of high susceptibility to mental conditions and disorders which include depression, anxiety, psychosis and obsessive compulsive and post-traumatic stress disorders. Peripartum depression and/or anxiety remain the commonest peripartum psychological distressing conditions. The prevalence of peripartum depression and anxiety has been estimated to be 20-40% and 20-60%, respectively or even higher in some countries. Advances in understanding the risks, predisposing and predicting factors and causes of peripartum mental illnesses have attributed the onset of peripartum mental problems to a complex integration between the psychosocial risks and protective factors in the context of a biological (hormonal and neurotransmitters changes) and immune system states in a genetically vulnerable women. There are socio-demographic, psychological and social variables correlated with peripartum mental illnesses. They include younger age, low level of education, low socioeconomic status, low self-esteem, low hope, poor social provision, high degrees of anxiety, some personality traits and past and family history of peripartum mental illness or mental illness not related to pregnancy. The importance of peripartum mental illnesses is not only because they affect women at a highly vulnerable time, but they also have deleterious effects on the development and behavior of the child. The United States task force recommends screening for peripartum depression due to its high prevalence rate. Strategies for prevention and treatment have to be undertaken including psychoeducation, psychotherapy and pharmacotherapy.

List of Abbreviations: *OCD: Obsessive compulsive disorder; PTSD: Post-traumatic stress disorder; ICD-10: The International Classification of Diseases, 10th Edition; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition; GABAAR: γ-aminobutyric acid (GABA) type A receptors; HPA: Hypothalamic-pituitary-adrenal; CRH: Corticotropin releasing hormone; ACTH: Adrenocorticotropic hormone; SSRIs: Selective serotonin reuptake inhibitors*

Keywords: *Peripartum; Psychological distress; Antepartum; Postpartum; Depression; Anxiety; Psychosis*

Introduction

The childbearing years including the peripartum periods [pregnancy and the first 6-12 months postpartum, particularly the first 4 weeks to 3 months] are periods characterized by biological [marked physiological], psychological and social changes [adaption to new roles and responsibilities of motherhood] making women highly vulnerable to a wide range of psychological distress conditions and disorders. They include antepartum and postpartum depression [1-4], antepartum and postpartum anxiety [3,5,6], insomnia [7,8], postpartum blues [9-11], psychosis [12-14], obsessive compulsive disorder (OCD) [15,16], post-traumatic stress disorder (PTSD) [17,18] and maternal suicide [19-21]. Studies concerned with mother mental health reported the followings in some women in the peripartum periods **(a)** different incidences of mental disorders throughout the three trimesters of pregnancy [1,22], **(b)** some mental disorders just begin or become worse in pregnancy [13], **(c)** high relapse rates of mood disorders [~70%] during peripartum periods particularly if previously untreated [~ 3 folds] or in women who discontinued their mood stabilizers earlier [~ 2 folds] [23], and **(d)** occurrence of more than one mental disorder in the same woman [24]. The importance of peripartum mental illnesses is not only because it affects women at a highly vulnerable time, but it also has deleterious effects on children and families [25-30].

In the last four decades, there was unclear classification for peripartum mental disorders being categorized by many within the context of mood spectrum disorders and by few as separate distinct conditions. While in the past 20 years with advances in systems for definitions and classifications, peripartum psychiatric disorders, The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) encoded them under the specific psychiatric disorder but using a special or a second code [31]; The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) uses the term "with postpartum onset specifier" under major depression or bipolar disorder if brief psychotic disorder, current or recent major depressive, manic, or mixed episode with psychotic features occur within 4 weeks postpartum [32]; while the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) uses "with peripartum onset specifier" instead of "with postpartum onset specifier" if mood symptoms occur at any time either during pregnancy (antepartum) or within the first four postpartum weeks (postpartum) [33].

The new definitions and classifications provide the following advantages: **(a)** optimize early diagnosis of maternal health problems which will reduce the adverse impacts on mother, infant and family, **(b)** A specialty known as "peripartum psychiatry" has been emerged to concern with the mother's mental health from conception till the end of the first year postpartum as well as the mother infant relationship, and **(c)** Enrich researches which aim for understanding the mechanisms of peripartum mental conditions and disorders.

Advances in understanding the risks, predisposing and predicting factors and causes of peripartum mental illnesses have attributed the onset of peripartum mental problems to a complex integration between the psychosocial risks and protective factors [3,9,34-37] in the context of a biological (hormonal and neurotransmitters changes) [9,38-45] and immune system states [46] in a genetically vulnerable women [47].

Due to high prevalence rates of some peripartum mental illnesses, screening has been recommended by the United States (U.S.) task force particularly for peripartum depression [48]. Strategies for prevention and treatment have to be undertaken including psychoeducation, psychotherapy and pharmacotherapy.

Peripartum Psychological Distress Conditions and Disorders

Postpartum Blues [Known Also as Maternity or Baby Blues]

Postpartum blues is a commonest transient phenomenon occurring in 40-85% of women in the immediate first 7-10 days after delivery. Symptoms include rapid mood shifts or lability, depressed mood, crying episodes, irritability, anxiety, insomnia, easy fatigability, anorexia and overwhelmed feeling of newborn care tasks. Some women may have confusion, marked agitation and even delirium and delusions [9-10]. Typically such manifestations occur in the 3rd day after delivery, peak in the 5th day and spontaneously recover by the 10th day and are commonly self-limited in 75% of women [i.e. spontaneously resolve without treatment (only reassurance) and without interference of social or occupational functions], however, 20-25% may develop full-blown postpartum depression or mood disorder [11] particularly if manifestations of blues persist for more than two weeks [49].

Peripartum major depression (antepartum and postpartum depression)

Despite decades of research aiming for identifying the risks, predisposition and causes of peripartum depression and developing effective methods of screening, prevention, and treatment, peripartum depression remains the commonest peripartum psychological distressing condition and one of the most important public health problems and its causes are complex. Several studies in developed countries estimated relatively high prevalence rates for **antepartum depression** similar to those in developing countries or even higher in developed compared to developing countries. These estimates varies from 10 to 58%, however, many including meta-analyses studies found that the commonest prevalence estimates of antepartum depression is 10-20% [2,4]. It has been estimated to be 10.4% in Egypt [50], 14.8% in Spain [51], 16.8% in Turkey [52], 18% in Bangladesh [36], 24.3% in Oman [53], 27% in Canada [54], 32.9% in Cote d'Ivoire [55], 33.8% in Tanzania [56], 44.2% in Riyadh City, Saudi Arabia [57] and 57.5% in Jeddah, Saudi Arabia [58]. The wide variation in prevalence rates among different studies could be explained by the followings: **(a)** Estimates may differ according to different trimesters. For example, Holcomb *et al*. [59] reported severe depressive during the first then third and second trimesters. Bennett *et al*. [60] reported a prevalence of 7.4% in the first, 12.8% in the second, and 79.8.0% in the third trimesters. Gavin *et al*. [1] reported a prevalence of 11.0% in the first trimester then drops to 8.5% in the second and third trimesters. **(b)** Estimates may differ according to periods of follow up after childbirth [2,4]. **(c)** Greater percentages of women may suffer from minimal to mild depression only and being ignored as clinically non-significant symptoms [2,4]. **(d)** Inclusion of other co-morbid conditions, for example, Abdelhai and Mosleh [50] reported that women who expressed simultaneous anxiety and depressive manifestations accounted for 63%, whereas 11.4% and 10.4% of them expressed only anxiety and only depression, respectively. **(e)** Differences in methodologies or study settings, for example

community or hospital-based or recruitment from primary Health Care Center or the use of different screening and psychometric tools.

Postpartum depression describes depression that persists or occurs after the tenth postpartum day and may extend to the first postpartum year [4]. Typically the onset of postpartum depression is within few days to a week postpartum but commonly within 2–4 months postpartum [61]. Postpartum depression is the commonest psychiatric disorder in the postpartum period with an estimated prevalence varies from 7 and 52% [62-64], however, commonest prevalence estimates of postpartum depression are 10 to 20% [1,3]. It had been estimated to be 15.8% in Arab countries [41], 16% in Zimbabwe [65], 34.7% in South African [66], 11.2% in China [67], 23% in Goa in India [68], 8-39% in United States [1,69], 20% and 28% in Brazil [70] and 7.14-51.8% in Egypt [63,64].

Symptoms of antepartum or postpartum depression although varies widely and ranged from minimal [misidentified by the treating obstetricians as just a somatic symptoms or manifestation of hormonal imbalance, e.g. sleep problems, eating problems, weight gain, irritability, fatigue, etc.] to severe major depressive episode with suicidal attempts, however, the usual symptoms of peripartum depression are similar to those in non-pregnant women. These symptoms include: depressed mood, sleep and appetite disturbance, low energy, impaired concentration, psychomotor disturbance, lethargy, feelings of worthlessness or guilt, anhedonia and suicidal ideation. However, some recognized prominent symptoms for antepartum or postpartum depression which differ from non-pregnant woman including agitation and lethargy, mood lability, anxiety, restlessness, panic attacks, impaired concentration and decision making, guilty feeling about new responsibilities of the motherhood and preoccupation with infant health and survival [4,49].

Antepartum and Postpartum Anxiety Disorder

Generalized Anxiety Disorder: Childbirth is a stressor and only a peripartum anxiety has been reported to be as common as peripartum depression with an estimated prevalence of 20-60% [3-5]. Some identified difference prevalence in relation to different trimesters for example; Reck *et al*. [22] reported a prevalence rate of anxiety to be 21.7% during the 3rd trimester of pregnancy and 11.1% during the first 3 postpartum months. However, depression is a common comorbid condition with anxiety in pregnant women in 4-66% [6,71,72]. In a large depression screening study of 10,000 women during the postpartum period Wisner *et al*. [73] reported that 66.1% of women with postpartum depression had a secondary anxiety and 96% of women with postpartum anxiety had a secondary depression. Mohamed *et al*. [74] reported postpartum psychiatric disorders in 20% of women and classified as follow: 68% with blues, 20% with depression; 8% with panic disorder and 4% with anxiety disorder. Symptoms of postpartum anxiety include: vigilance, sleep deprivation due to excessive worry and preoccupation about the health of the infant [maternity neurosis] [75,76].

Postpartum Obsessive Compulsive Disorder (OCD): Postpartum onset of OCD can occur during pregnancy or within the first 6 weeks postpartum. It is commonly comorbid with postpartum depression and manifested by repetitive, intrusive thoughts or images of harming the baby and associated with compulsive checking behavior [15,16].

Postpartum Posttraumatic Stress Disorder (PTSD): The incidence of postpartum PTSD has been estimated to be ~5.6% and can continue for some weeks or months, and may recur toward the end of the next pregnancy [77]. The most common comorbid conditions with postpartum PTSD are depression and substance/alcohol abuse/dependence and anxiety [18]. Symptoms of postpartum PTSD include: tension, nightmares, flashbacks, hyperarousal severe anxiety, hypervigilance, difficulty concentrating, sleep disturbances, re-experiencing trauma, avoidance of trauma-like situations and dissociative amnesia [17].

Postpartum Psychosis

Postpartum psychosis is defined as a sudden, acute or rapid onset of gross behavioral changes which usually occur within the first 2-4 weeks or even as early as 2-3 days postpartum, however, it can occur within 3 months postpartum [12,78]. Postpartum psychosis has an estimated prevalence of 0.1-0.2% [12,78]. Symptoms and course of postpartum psychosis vary widely and sometimes complex. Postpartum psychosis is considered by many as a first psychotic episode which may present later as mania or an exacerbation of mania in patients with previous manic episodes or bipolar disorder in the non-pregnancy period [13]. The usual manifestations of postpartum psychosis are mood swings or lability, excessive activity, transient or alternating episodes of delusions of guilt, persecution, paranoid, grandiose, or bizarre delusions and grossly disorganized behavior, auditory hallucinations, delirium-like symptoms, limited reality testing and cognitive impairment. Delusions related to the baby are common in postpartum psychosis including the infant being in harm or is dead [78]. Infanticide and suicide may occur in 4% and 5% of mothers with postpartum psychosis [79]. It has been suggested that it is unclear whether postpartum blues, postpartum depression and postpartum psychosis are actually three distinct entities or they all fall under the heading of postpartum mood disorder, in which symptoms range from minimal or no to severe disturbance [4].

Postpartum Insomnia

Insomnia is a common comorbid postpartum condition with postpartum depression, anxiety and chronic sleep deprivation in new mothers [7,8]. Manifestations of postpartum insomnia include: fragmented sleep which results in reduced psychomotor vigilance, increased levels of daytime fatigue and mood disturbance [80-81]. Hedman *et al*. [82] reported change in sleep patterns from the first trimester (increased deep sleep and poor sleep quality), through the second and third trimesters (progressively less total sleep).

Maternal Suicide

Suicide is one of the causes of peripartum maternal mortality [21]. Peripartum depression and severe maternal mental disorders are risk factors for maternal suicide accounting ~20% of postpartum deaths in depressed women [20]. Appleby *et al*. [19] reported an 80 fold increase in suicide in the first year postpartum in women with severe mental health conditions. The filicide rate is also high in depressive psychoses (4.5 %) [1].

The Biopsychosocial View of Peripartum Psychological Distress Conditions and Disorders

Many previous works conceptualized a biopsychosocial model of peripartum psychological distress conditions and disorders particularly peripartum depression, which are comprised of vulnerability, precipitating and maintaining factors. The complex interaction between hormonal fluctuations during peripartum period, alterations of central and peripheral neurotransmitters and other biological factors together with sensitivity of some brain system and influenced by genetic vulnerability [47], all contribute to pathogenesis of peripartum mental illnesses. In general, human, experimental and functional imaging studies confirmed that hormones play a major role in basic emotion processing, arousal, cognition and motivation [83,84]. Biological stressors theory of peripartum mental illnesses is supported by the fact that other reproductive events such as premenstrual dysphoric disorder, infertility, miscarriage, oral contraceptives, hormone replacement treatment and menopause have also been reported to cause depression, anxiety and PTSD in women [18,85,86]. The periods of pregnancy and postpartum are associated with gross hormonal fluctuations and changes including changes in reproductive (estrogen and progesterone), thyroid and lactogenic hormones, gonadotropins and gonadal steroids [9,34,38-45]. It has also been suggested that psychosocial stressors may sensitize the brain to subsequent metabolic or hormonal changes and vice versa [87] (Figure 1).

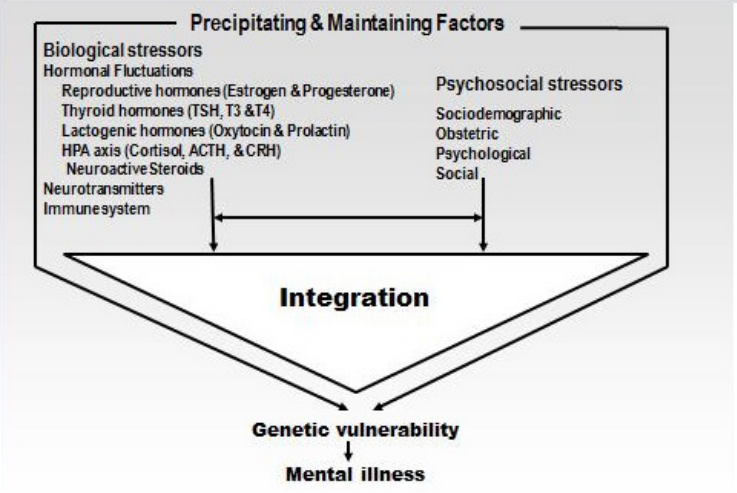

Figure 1: Biopsychosocial view of peripartum mental illnesses

Hormonal Theory of Peripartum Mental Illnesses

Reproductive Hormones (Estrogen and Progesterone): Several studies have investigated the relationship between estrogen (usually estradiol) and progesterone and peripartum depression and postpartum blues. During pregnancy, there are very high levels of estrogen and progesterone compared to the pre-pregnancy levels. In early postpartum period, a marked decrease in gonadal steroids occurs as follow [9,38]: **a)** a sudden drop in estrogen levels after expulsion of the estrogen-secreting placenta and rapidly reverse to their pre-pregnancy levels within a few days of parturition [50-fold lower than the pregnancy level], and **b)** a considerable decrease in the levels of progesterone between the first and second stages of labor and rapid reversal to the pre-pregnancy level within few levels of parturition [10-fold lower than the pregnancy level]. Some reported that progesterone deficiency may be causally related to postpartum mood disturbance. Other studies found that there was no difference in progesterone between depressed and non-depressed women postpartum [9]. Harris *et al*. [40] reported lower levels of progesterone among depressed breastfeeding women than non-

depressed breastfeeding about 8 weeks postpartum. Estrogen levels decrease markedly after childbirth. Lower levels of total estrogen were reported before delivery among women who experienced the blues in the first week postpartum [40]. Under normal physiological conditions, the function of estrogen is to keep in the peripheral and central monoamine centers in the brain in a stable condition. Furthermore, estrogen has an influence on adrenaline, norepinephrine, and serotonin receptors. It has been known that estrogen primarily affects the monoaminergic system, especially serotonin and dopamine; influencing affective symptoms and psychotic symptoms respectively [9,38].

Neuropeptides and neurotransmitters [e.g. serotonin or 5HT, adrenaline and noradrenaline] have various roles in the physiology and behavior of the central nervous system [88]. It has been suggested that the modification of estrogen and progesterone during peripartum period have an effect on neurotransmitters which are involved peripartum mood disorders [83-91]. Serotonergic system has a role in peripartum depression. Moses-Kolko *et al*. [92] observed reduction from 20 to 28% in 5-hydroxytryptamine 1A (5HT1A) serotonin receptor binding in the depressed mothers group in comparison with the control group.

Thyroid Hormones: The relation between thyroid function and depression has long been recognized [93]. Some studies reported that 9.6% of women who developed postpartum depression had relative hypothyroidism with lower total T4, free T4, total T3 relative to the amount of thyroid hormone binding capacity and higher T3 uptake during the late gestation and early postpartum periods [45]. It has been reported that diminished thyroid function in association with postpartum mood changes is through its association with diminished central 5-HT1A (serotonin) activity [39,45]. In contrast, others reported no link between postpartum thyroid dysfunction and postpartum depression [94,95]. Some reported a positive significant relation between thyroid antibody and postpartum depression. Harris *et al*. [96] found that positive thyroid antibody status was predictive of postpartum depression. The authors reported thyroid antibodies in up to 11.6% of postpartum women and attributed this to the immunosuppressant effect of high cortisol levels during pregnancy followed by a "rebound" immune phenomenon after delivery, producing a high incidence of postpartum thyroid antibodies. Surks and Ocampo [97] reported that 43% of the antibody- positive women had mild-to-moderate depressive symptoms at 6 weeks postpartum compared with 28% of the antibody-negative women.

Lactogenic Hormones [Oxytocin and Prolactin]: Studies reported that lower oxytocin levels during the third trimester are associated with increased depressive symptoms during pregnancy and the immediate postpartum period [44]. Stuebe *et al*. [98] observed that oxytocin secretion during breastfeeding was inversely associated with depression and anxiety symptoms at 8 weeks postpartum. However, it has been identified that depressed women has greater variability in peripheral oxytocin release in response to a stressful situation and the increase in oxytocin is related to enhanced attachment anxiety [100].

Some reported positive correlation between postpartum mood changes and daily basal levels of prolactin [101]. Others found that lower levels of prolactin were associated with higher levels of depression in breastfeeding women at 6-10 weeks postpartum [41,96]. In contrast, some studies have found no association between postpartum mood and prolactin levels [98,3].

Hypothalamic-pituitary-adrenal (HPA) axis, Cortisol and Corticotropin Releasing Hormone: During normal peripartum period, studies reported profound plasticity in the HPA axis with increased basal levels of plasma glucocorticoids cortisol in humans and corticosterone in rodents but limited alteration in the level of adrenocorticotropic hormone (ACTH) [102]. In pregnant women with depression, studies identified significant associations between corticotropin releasing hormone (CRH) and cortisol concentrations [103,104]. In women with postpartum depression, Pedersen *et al*. [39] reported a positive association between morning serum cortisol levels at 6 weeks postpartum and degree of dysphoria. Some reported increased basal concentrations of plasma cortisol with postpartum depression and the suppression of cortisol by dexamethasone is blunted which are similar to findings in non-pregnant women with depression [43]. Bloch *et al*. [105] reported that compared to controls, women with postpartum depression had higher cortisol response to ovine corticotrophin releasing hormone (CRH) administration when administered in higher (supraphysiological) doses and those women developed more labile mood after withdrawal of steroids. Authors suggested that during the postpartum period, the HPA axis works differently in women with susceptibility to depression through the suppression of CRH [106,107]. Szpunar and Parry [45] did a systematic review of cortisol, thyroid-stimulating hormone, and prolactin in peripartum women with major depression and reported reduced morning cortisol in association with major depression but not thyroid hormones or prolactin. Thus, it has been suggested that fluctuation in corticosteroid levels (i.e. overproduction and sudden withdrawal) has been suggested as a potential cause of postpartum mood disorder. In contrast, Harris *et al*. [40] reported association between lower levels of prenatal cortisol with elevated depression scores at about 6 week's postpartum. Meltzer-Brody *et al*. [108] reported that mood

fluctuation in women with postpartum depression does not associate with CRH suppression and the role of HPA axis in the pathophysiology of postpartum depression is doubtful.

Neuroactive Steroids and Peripartum Depression: Neuroactive steroids are the steroid hormones which act and modulate the function of the brain and other parts of the nervous system. Neuroactive steroids include: **(a)** the peripherally synthesized gonadal steroids (e.g. estradiol and progesterone) which cross the blood brain barrier, bind membrane steroid receptors and ion channels and locally metabolized to neurosteroids and **(b)** those which are synthesized de novo in the brain from cholesterol [109]. Progesterone is metabolized by 5α-reductase and 3α hydroxysteroid dehydrogenase (3α-HSD) enzymes into allopregananolone [which is also a neuroactive metabolite] in certain brain cells [the hippocampus, cortex, amygdala, thalamus, cerebellum and striatum] [110]. Although neuroactive steroids have either excitatory or inhibitory actions [111], they have potent modulatory action on γ-aminobutyric acid (GABA) type-A receptors (GABAAR) [112]. The principle target of allopregnanolone, is the GABAAR and thus its anxiolytic, anti-convulsant, sedative/anesthetic, and analgesic properties [113]. Due to fluctuations in neurosteroid levels under physiological conditions, the GABAARs, are extremely plastic to maintain an optimal level of inhibition and, thus, neuronal excitability. GABAAR [particularly GABAAR δ subunit] homeostatic plasticity is essential for maintaining network function at normal levels during periods characterized by elevated levels of neurosteroids, such as estrous cycle, during puberty, and throughout pregnancy [114]. Neuroactive steroids have a role in reproductive mood disorders. Alterations in neurosteroid levels results in δ subunit-containing GABAARs plasticity under conditions such as over the estrous cycle, during puberty, and throughout pregnancy and the postpartum period have been suggested to play a role in increase vulnerability to mood disorders, such as premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), and postpartum depression [115]. The highest physiological concentrations of neurosteroids [200-fold] are observed during pregnancy [116]. Experimental studies confirmed that mice lacking the GABAA-δ receptor subunit only display depressive-like behavior, in both the forced swim test and the sucrose preference test, and poor maternal care during the post-partum period [115].

The Controversies of Hormonal Theory of Peripartum Mental Illnesses: The controversial results of the hormonal theory of peripartum mental illnesses could be explained by the followings: **(1)** women may experience depression throughout different hormonal conditions (e.g., first trimester of pregnancy versus first week postpartum). **(2)** the use of different hormonal measurement methods, for example: some examined absolute hormone concentrations in those with and without the disorder, some have examined the change in hormone levels during pregnancy and the immediate postpartum period and some used hormones as a treatment for peripartum depression, which make it difficult to identify the precise role of hormonal changes in the pathogenesis of perinpartum depression [43,117]. **(3)** Large epidemiologic studies looking for the risk factors of peripartum depression reported that not only hormonal fluctuations during pregnancy and postpartum period but also there are number of psychological and social factors play a large role in the pathogenesis of peripartum depression as discussed below.

It has been suggested that although there is controversies about the role of hormones in peripartum depression, however, there is a general census that levels of hormones such as estrogens, progesterone, prolactin, thyroid hormones and cortisol are either too high or too low in the peripartum periods [118,119] and such changes occur too quickly or not quickly enough resulting in peripartum depression [38]. The most acceptable reproductive hormone theory as a cause of peripartum depression is that a hormone-sensitive postpartum depression phenotype (i.e. genetic vulnerability) in which reproductive hormone changes alone is sufficient to provoke mood dysregulation in otherwise euthymic women [47,120].

The Sociodemographic, Clinical and Psychosocial Correlates of Peripartum Mental Illnesses

Pregnant and postpartum women may experience more stressful events than non-pregnant women. Pregnancy is a stressor due to the novelty of the situation in primipara [transition to motherhood], adaptation to new demands, roles, responsibilities and concerns with the infant's future and the overload and demands of other children on subsequent pregnancies. In addition, physical changes, concerns about weight gain and body image may provide additional burden on some women. The lack of woman's psychological adjustment before and during the pregnancy is one of the most important risk factors of peripartum mental illness. Authors identified some socio-demographic, obstetric and psychosocial risk factors for peripartum mental illnesses particularly depression and anxiety.

Sociodemographic and Obstetric Risk Factors

Sociodemographic Factors: Studies indicated that there is a great overlap between risk factors for antepartum and postpartum depression. Many studies identified young age of marriage as risk factor of antepartum and postpartum

depression. Authors suggested that young maternal age may be associated with loss of identity, withdrawal of love, affection, and loss of independence, loss of social approval or family's negative attitude, loss of future education or career options, financial hardship, unwanted pregnancies, being unmarried and a lack of partner support, pessimism toward oneself, the world and the future and a rejection in accepting their own mother's role and trouble coping or adapting to their new role of motherhood, thus the psychopathology increases due to maladjustment of the copying mechanisms when the challenges of pregnancy are superimposed on the developmental challenges of adolescence. In addition, predisposition of new mothers to postpartum depression could be due to internal conflicts which enhances certain characteristics of personality [121-125]. Furthermore, the unrealistic expectation of childbirth and motherhood, a lack of a capability to cope with infant's demands and care may cause mothers anxious, controlling, perfectionist, and exhibit compulsive tendencies [122,125].

While in India, Prost *et al*. [37] identified high maternal age as a risk for stress and antepartum depression. In Oman, Islam *et al*. [126] reported that neither maternal age nor gravidity were significantly associated with antepartum depression. In addition, studies identified low education level as risk factor for peripartum depression. Several studies reported a significant correlation between low level of education and unemployment and antepartum depression [37,127,128]. For example, in Brazil, Melo *et al*. [127] found that low educational attainment was associated with 2.38-fold increased odds of antepartum depression. Lara *et al*. [128] found that low maternal educational attainment was associated with more than 5-fold increased odds of postpartum depression among Mexican women.

Furthermore, several studies reported a significant correlation between low socioeconomic state and increased number of antepartum and postpartum depression [35,63,64,74,129,130]; low income and financial stress and increased number of children [129]. A higher frequency of postpartum depression has been found in studies with participants from a low socioeconomic status (30-40%), while a prevalence rate of about 20% was found in population-based studies with probabilistic samples [131]. Faisal-Cury and Rossi Menezes [132] reported prevalence of anxiety, state and trait were 59.5% and 45.3% in Brazilian women in the antepartum period and anxiety trait were associated with lower women's educational level and lower women's income. Prost *et al*. [37] screened 5801 mothers [in rural Jharkhand and Orissa, eastern India, where over 40% of the population who live below the poverty line and access to reproductive and mental health services is low] in the 6th week postpartum using the Kessler-10 item scale. The author reported that 11.5% of mothers had symptoms of distress. It has been suggested that the low income and low education are associated with unemployment, a state of despair and reduce the individuals' capacity to cope with stressful situations like motherhood.

Obstetric Risk Factors: Previous studies reported significant obstetric risk factors and predictors of antepartum depression which include: primigravida; unmarried mother; cesarean sections or other perinatal or natal complications as a history of miscarriage and pregnancy termination [17,133]. Bunevicius et al. [34] reported the highest prevalence of depressive disorders in the first trimester and the lowest in mid-pregnancy. The authors indicated that unwanted and unplanned pregnancy, high neuroticism were independent predictors of antepartum depression throughout whole pregnancy, while low education, previous history of depression and the occurrence of psychosocial stressors at the end of pregnancy were trimester specific.

Psychosocial Factors: Several researches identified a significant relationship between psychological variables and peripartum depression which include: low self-esteem, poor trait hope, negative cognitive attribution style, low levels of social support [134-137], abandonment by the child's father or the ambivalence of the infant's father during the pregnancy, great financial difficulties [3,9], history of domestic violence or marital conflict or marital dysfunction, marital dissatisfaction [136], history of sexual abuse [137] and past and family history of mental disorder [137-139].

The risk for postpartum depression increases to 25% in presence of previous history of major depression or history of bipolar disorder or anxiety and depression in non-pregnancy periods [138] and to 50% in presence of past history of antepartum or postpartum depression or anxiety or psychosis [137,139] as well as a personal history of previous depressions related to reproductive events (such as premenstrual dysphoric disorder) [36,136-144]; personality traits [140] and family history of psychiatric illness, especially mother and sister having postpartum disorder (e.g., schizophrenia or bipolar disorder) [141].

In support, research conducted in the U.S. showed that 30-50% of postpartum depression cases begin early during pregnancy [antepartum depression] [137,139] and symptoms of depression and anxiety during pregnancy are more prevalent than during the postnatal period. Some studies reported a higher prevalence rate of 56% maternal depression at 28 weeks antepartum as compared to 34% at 6 weeks postpartum confirming that depression during pregnancy is as common as after delivery [140]. Evidence suggests that depression is linked to traits such as neuroticism/negative

emotionality, extraversion/positive emotionality, and conscientiousness. Personality may be an important and stable determinant of postpartum depression. Studies observed that the combination of high neuroticism and high introversion considerably improved the risk estimates for clinical depression across the first year postpartum [145-146]. In the meta-analysis done by Beck [147], the authors identified self-esteem, marital status, socioeconomic status, and unplanned/unwanted pregnancy as predictors of postpartum depression. Dennis and Ross [148] reported that women with depressive symptoms at 8-weeks postpartum (14.1%) had overall significantly lower perceptions of relationship-specific support at 4 weeks than non-depressed women. These women also had lower perceptions of support on all social provision subscales including: guidance, reliable alliance, reassurance of worth, attachment, social integration, and opportunity for nurturance. Leigh and Milgrom [2] reported the following as significant predictors of antepartum depression: low self-esteem, antenatal anxiety, low social support, negative cognitive style, major life events, low income and history of sexual abuse. In the big meta-analysis and systematic review done from 57 studies by Lancaster *et al*. [140] demonstrated several correlates that are consistently related to an increased risk of depressive symptoms during pregnancy which include maternal anxiety, life stress, history of depression, lack of social support, unintended pregnancy, Medicaid insurance, domestic violence, lower income, lower education, smoking, single status, and poor relationship quality. Karaçam and Ançel [149] evaluated 1,039 pregnant Turkish women, the authors identified that 27.9% of women experienced depression at a level requiring treatment. The authors reported the following as statistically significant factors influencing the experience of both depression and anxiety in a stepwise multiple linear regression analysis model: perceived social support; recent experience of marital or emotional problems during and before pregnancy; recent experience of life stress; having a negative self-perception; experience of physical violence; and experience of physical problems during pregnancy. The authors also reported that the statistically significant factors influencing depression were marital dissatisfaction, being a housewife, having an unwanted pregnancy and having a formal marriage. Veselska *et al*. [142] reported that in hierarchical linear regression, family affluence, personality dimensions of extroversion, emotional stability and openness to experience, as well as mental health subscales and social support from family and significant others to be associated with self-esteem. Di Florio *et al*. [150] observed that the incidence of puerperal psychosis rises 300-fold, i.e. from 0.1% to 30%, and rises more than 500-fold (to more than 50%) for those with a past episode of puerperal psychosis.

The Animal Models of Peripartum Depression

Some models are developed based on the biopsychosocial theories of peripartum depression. These models include: **(a)** The hormone withdrawal model [151], **(b)** the chronic corticosterone treatment model or hormonal stress model [152], **(c)** The social stress models during pregnancy or the postpartum period which include: (i) the gestational stress model, (ii) the repeated maternal separation model [153], (iii) the chronic social stress model [154], **(d)** the learned helplessness model [a known model of depression in the non-pregnancy period], and **(e)** the maternal immune activation (MIA) potentiated by repeated maternal separation stress model. **In the hormonal withdrawal model,** Galea *et al*. [151] used the ovariectomized female rats and injected them daily with 2.5 µg of estradiol benzoate and 4 mg of progesterone for 16 consecutive days, then increased the dose of estradiol to 50 µg/day for 17 to 23 to mimic the levels observed in pregnancy, then did withdrawal of the hormones and after 3 days tested the animals for evidence of depression using the forced swim test and for anxiety using the open field test. The authors observed that estradiol withdrawal was associated with increased immobility and decreased struggling and swimming behaviors in the forced swim test and continual treatment with high levels of estradiol was able to reverse the depression-like behaviors. Schiller *et al*. [155] implanted intra-cranial electrodes in the lateral hypothalamus in a group of ovariectomized rats withdrawn from estradiol treatment. It is well known that rats implanted chronically with electrodes in the posterior lateral hypothalamus can be trained to press levers in order to self-stimulate this brain region electrically [the brain's reward processing] while anhedonic animals tend to show a decrease in self-stimulation. The authors observed that hormonal withdrawal models had reduced responding for electrical stimulation and had significantly greater immobility and less swimming than controls in the forced swim test. **In the chronic corticosterone treatment model [CORT-based model] or hormonal stress model**, Brummelte and Galea [151] studied the effect of chronic administration of corticosterone (CORT) [in a dose of 40 mg/kg/day from the first day after parturition till day number 26 of lactation to maintain the high levels found in pregnancy] on the maternal behavior and scored from lactation day 2 to day 8 depressive-like behavior was assessed on lactation days 24–25 using the forced swim test and anxiety like behavior was assessed using the open-field test. Authors observed that dams on chronic CORT injection spent less time nursing their pups and had increased immobility in the forced swim test compared with control (sesame oil) mothers indicating depression. Workman *et al*. [156] reported reduced dendritic complexity and increased the density of mushroom spines of hippocampal CA3 arbours in CORT model. **The gestational stress models** are considered more relevant to the human condition than other non-social stress

paradigms (e.g. repeated restraint stress). In this model, the pregnant female rats were alternatively subjected to daily restraint stress and overcrowding (4 unfamiliar pregnant rats housed together for 24 h) from gestation days 4-16. Stressed females showed decreased body-weight gain and increased adrenal weight relative to their nonstressed controls [157]. **In the repeated maternal separation model,** Boccia *et al*. [153] did a separation of the mothers from their rat pups on postpartum days 3-14 for 3 h or 15 min per day. The authors observed that mothers showed immobility in the forced swim test and maternal behavior tests compared to the control rats. They found that mothers which were repeatedly separated from their pups for 3 hours daily from postnatal day 3-14 developed depression-like behaviors at postpartum week 3, immediately after weaning, with increased immobility in the forced swim test compared to non-separated and 15 min separated dams. **In the chronic social stress model,** Nephew and Bridges [154] did a chronic daily exposure of a novel male intruder which results in robust stress responses and depression in the lactating female resulting in decreased pup licking and nursing), and increase aggression which may causes a mother to kill her litter.

The Consequences of Maternal Antepartum Depression and Anxiety on the Mother, Infant and Family

The immediate and longer-term exposure to peripartum depression and anxiety is related to adverse maternal psychological and behavioral problems, poor infant-child outcomes and family malfunctioning. Depression in pregnancy may diminish the capacity for self-care, inadequate nutrition, poor follow up in the antenatal clinic [158], parenting stress [159] which range from withdrawal to rejecting, less sensitive [160] and harsh parenting [161]. Anxiety in pregnancy is associated of being negative and intrusive [160] and development of later depression [158]. Depressed and anxious mothers often have difficulties nursing and are more likely to stop nursing earlier [98], a behavior highly dependent on the oxytocin system. In the longitudinal study of Wolkind *et al*. [158], the authors reported that a high percentages of women (44% to 78%) who experienced postpartum depression also experienced later depressions at 14, 27, and 42 months after delivery. The authors also reported that women who had experienced a new episode of depression at 3 months postpartum continued to seek psychiatric assistance in the following 4 years. Peripartum psychological distress can adversely affect mother-infant interaction and attachment [162,163]. Mothers with PTSD have impaired mother-infant bonding [164] similar to mothers with postpartum depression.

It has been observed that higher levels of maternal cortisol, adrencorticotropic hormone (ACTH) lower dopamine and serotonin levels at the third trimester with antepartum depression are associated with the following adverse infants and children outcomes which include: a low birth weight [3,26], poor motor development and stunted growth [30,165], abnormal sleep pattern [29,166], less optimal orientation, poorer attention, poorer cognitive performance [167], mixed handedness, dyslexia, abnormal brain laterality abnormalities [168], lower autonomic stability, lower vagal tone [169], temperament difficulties, irritability and stressful behavior as excessive crying [29,166] and behavioral and emotional problems as poorer attention, hyperactivity and autistic spectrum disorders [26]. Higher oxytocin is associated with elevated anxiety in children with high functioning autism [170].

Prespectives

Screening for Peripartum Mental Illnesses

Literature mentioned that peripartum mental illness is under-diagnosed. Women are reluctant to seek help for perinatal distress. Only about half of women with depression and anxiety are identified; and even fewer receive adequate treatment [171]. Because antepartum depression is a common condition and a strong predictor of postpartum depression, thus the optimum time for diagnosis and treatment is before childbirth. The U.S. Preventive Services Task Force recommends screening pregnant and postpartum women for depression [48]. The unified consensus for the most commonly used screening tools for depression of women in the peripartum period includes the following three screening tools because many symptoms of major depressive disorder are not specific: (1) The 10-item Edinburgh Postnatal Depression Scale (EPDS) [172], (2) The Patient Health Questionnaire-9 [173]. (3) The 35-question Postpartum Depression Screening Scale [174]. The 10-item Edinburgh Postnatal Depression Scale has a sensitivity of 75% to 100% and a specificity of 76% to 97% in English-speaking populations [175]. By comparison, the Patient Health Questionnaire-9 has a sensitivity of 75% and a specificity of 90% and the 35-question Postpartum Depression Screening Scale has a sensitivity of 91% to 94% and a specificity of 72% to 98%. The Patient Health Questionnaire-9 and the Postpartum Depression Screening Scale can be used to classify the severity of peripartum depression. Many family physicians are familiar with two-step screening for major depressive disorder, which uses a shorter screening test initially, such as the Patient Health Questionnaire-2, followed by a more comprehensive screening test if either of the two questions is positive.

In doubtful cases, screening for thyroid function is necessary. The baby’s completely depends on the mother's supply of

thyroid hormone and iodine till around 12 weeks' gestation. For the first trimester for thyroid hormones and throughout pregnancy for iodine [which is essential in making thyroid hormones]. The new recommendations for thyroid stimulating hormone (TSH) levels during pregnancy are as follow: First trimester: less than 2.5mIU/L with a range of 0.1-2.5mIU/L, Second trimester: 0.2-3.0mIU/L, and Third trimester: 0.3-3.0mIU/L. If the TSH is greater than 2.5mIU/L at any time during pregnancy, T4 levels should be checked to determine whether the hypothyroidism is overt or subclinical. If TSH is high and the T4 is normal, the diagnosis is subclinical hypothyroidism. Subclinical hypothyroidism (SCH) is defined as a serum TSH between 2.5 and 10 mIU/L with a normal free T4 (FT4) concentration. Women with a TSH concentration above the trimester-specific reference interval with a decreased FT4, and all women with a TSH concentration more than 10.0 mIU/L, irrespective of the level of FT4, are considered having overt hypothyroidism. Treatment is necessary when TSH is 10mIU/L or more, regardless of the T4 level. In addition, TSH should be monitored every 4 weeks during the first 20 weeks of gestation and between 26 and 32 weeks [176]. The World Health Organization (WHO) recommends the pregnant women should consume 250 micrograms (μg) of iodine per day during pregnancy, which usually requires a supplement containing iodine [177].

The Management Strategies of Peripartum Mental Illnesses

Once diagnosed, a woman with depression, anxiety and insomnia has to receive standard care. The treatment choices depend on the type of disorder, the woman's preference, and the expertise of the clinician [178]. The treatment strategies of peripartum psychiatric distress and disorders include:

Reasurance, familial and Social Support, Psychoeducation and Psychotherapy

Mild to moderate depression should be treated with psychotherapy. Education and reassurance can manage maternity blues. Reassurance and emotional support toward the mother can improve the self-esteem and confidence. Individual psychotherapy to facilitate coping with transitions to the motherhood role is an integral part of treatment, especially for females with difficult adjusting to motherhood and/or apprehensions about the new responsibilities. Peer support and psychoeducation and emotional support for the partner and other family members are important. Interpersonal therapy may result in greater reduction in depressive symptoms and improvement in social adjustment. Group psychotherapy may also be helpful [123]. Antepartum interventions may include enhancing self-esteem, increasing satisfaction with social support and teaching couples appropriate ways to provide feedback and communicate expectations, especially those relating to companionship, infant care, household tasks and when to seek help.

Pharmacotherapy

The decision to use the psychotropic drugs to treat a mother during pregnancy is dependent on the risk–benefit analyses. Indications for pharmacotherapy with psychotropic drugs [antidepressants, antipsychotics and anxiolytics] include the risks of clinical deterioration as severe psychological distress, suicidal ideation, social and occupational dysfunction, financial hardship, and an inability to plan for and successfully cope with the impending life transitions. Cases of suicidality, incapacitating vegetative signs, or psychosis warrant hospitalization. Moderate to severe depression should be treated with a combination of psychotherapy and medication. When compared to the use of non-serotonergic tricyclic antidepressants, serotonergic agents or selective serotonin reuptake inhibitors (SSRIs) has been found to have a low risk of adverse effects on the mother and can reverse or improve vegetative signs and other manifestations accompanying moderate or severe depression episodes of antepartum depression and its neuroendocrine abnormalities which do not resolve with supportive intervention. The previous response to a specific antidepressant indicates the use of the same to treat the patient. Citalopram, escitalopram, and sertraline are the safest SSRIs during pregnancy, whereas sertraline, paroxetine nortriptyline and fluvoxamine are preferred in breastfeeding women because they lead to the lowest serum medication levels in breastfed infant [179]. Physicians who prescribe medications to breastfeeding mothers could limit infant drug exposure by choosing the lowest effective dose, avoiding polypharmacy, and dividing daily doses to reduce peak concentrations [180]. Most psychotropic drugs are metabolized in the liver. In full term infants till the first few months till the first 3 months, the hepatic drug metabolism is about 1/3-1/5 adults capacity, thus psychotropic drugs should be utilized with caution to reduce infantile hepatotoxicity. Peak concentrations in breast milk are attained 6-8 h after ingestion of medications. Therefore, breastfeeding can be restricted to times when the breast milk drug concentration is lowest, that is, just before or after taking medication [181].

For psychosis, monotherapy is preferable than polytherapy to reduce the adverse effects on the mother and babies. The use of high-potency dopamine blockers [e.g. haloperidol] has been proven to be effective in treating antepartum psychosis. For the newer atypical antipsychotics, olanzapine and quetiapine were considered the most acceptable for postpartum for psychosis and mania [182]. Lithium prophylaxis may be more useful in women who only have a past history of

postpartum psychosis than in women with bipolar disorder who have had mood episodes outside the postpartum period. However, the American Academy of Pediatrics (AAP) give a warn against the use of lithium but recommend the use of valproic acid or carbamazepine for postpartum psychosis in breastfed mothers because plasma levels in the infant may exceed 10% of the mother's plasma levels, resulting in toxicity particulate in infants with dehydration [183].

For the postpartum period, the selective serotonin reuptake inhibitor (SSRI) [e.g. fluoxetine, sertraline and venlafaxine are effective for treatment of postpartum depression [179]. Treatment with SSRI should be initiated at half the recommended starting dose (e.g., 25 mg of sertraline per day or 10 mg of paroxetine per day) for 4 days, and doses should be increased by small increments (e.g., 25 mg of sertraline per week or 10 mg of paroxetine per week) as tolerated until full remission is achieved because recently delivered mothers have been found to be sensitive to the side effects of medications [180]. In addition, as all antidepressants are excreted in breast milk, therefore, only the lowest effective dose of antidepressants should be administered in a nursing mother. Improvement with a specific antidepressant within the first 6-8 weeks is an indication for continuation on the same antidepressant for a minimum of 6 months after full remission to avoid relapse. Long-term treatment is indicated for women with three or more episodes of severe depression to avoid recurrence. Benzodiazepines may be needed for depression associated with anxiety and agitation [179,180].

Severe cases of postpartum depression or psychosis warrant hospitalization and electroconvulsive therapy (ECT) [184].

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