J Obstet Gynecol India Vol. 55, No. 3 : May/June 2005 Pg 218-227

REVIEW ARTICLE

The Journal of Obstetrics and Gynecology of India

Psychiatric disorders associated with pregnancy

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Key words : psychiatric disorders, pregnancy, stress, depression, mania, anxiety, psychosis, teratogenesis

Introduction

Mood and anxiety disorders are common in women during their childbearing years.[1-3] Pregnancy and the post –partum period are considered to be relatively high-risk times for women with pre-existing psychiatric illnesses, especially for depressive episodes in women [4]. The prevalence of depression has been reported to be between 10 and 16% during pregnancy [3,5,6]. Pregnancy and the post –partum period appear to confer an even greater risk for women with bipolar disorder. Rates of relapse are estimated at 30-50% during the post-partum period [7,8]. The course of panic disorder can be variable with some studies reporting an improvement of symptoms [9] and others reporting a worsening [10]. In obsessive-compulsive disorder (OCD), symptoms typically worsen during pregnancy [11]. Some reports suggest an initial onset of OCD symptoms during pregnancy [12]. Special considerations are needed when psychotic disorders present during pregnancy.

Stress and pregnancy

Pregnancy either induces or exacerbates pre-existing stress and in turn stress seems to have a negative effect on pregnancy, especially in the first trimester [2]. The period of greatest stress during pregnancy, the first trimester, is also the period of the highest rate of pregnancy loss [2].

In the earlier times, pregnant women were advised by Hippocrates to beware of unnecessary psychic stress [13] .That abortion occurred as a reaction to wrath, fear, grief, joy and, even disagreeable odors, was widely believed by the medical profession in the 17th and 18th centuries. In a Nova Scotia study, two types of women were especially abortion-prone: the immature, dependent, psychosexually retarded type with a stern father and an inadequate mother, and the independent, frustrated women with ambivalent feelings about their feminine role [14,15]. Mann [16] in a New York study of repetitive aborters also found dependency traits but a dominating mother and stressed paternal inadequacy. Simon et al [17] reported that with 20 out of 32 women with one or more abortions appeared to have a psychiatric diagnosis after one or more years. Grimm [18] used several psychological tests on 61 recent aborters and 35 controls. Ten tests showed significant psychopathology in the women who aborted compared to the control group.

It is known that the hypothalamic-pituitary-adrenal axis (HPA) reacts to sustained anxiety and depression. Stress factors may affect uterine circulation, in turn decreasing blood flow reaching the decidua, and thus affecting the implantation site [19]. Catecholamines play a role in the emotional centers of the brain as well as in steroidogenesis. A 90% success rate was obtained in treating 20 patients who had three or more abortions with cyproheptadine-HCL, an anti-serotonin drug [20]. All of these women had emotionally disturbed personalities with an increased excretion of 5-hydroxy-indole-acetic acid (5- HIAA) and serotonin [20]. Some women under stress use tranquilisers, drugs, alcohol and cigarettes. These in turn could have additional detrimental effects on placental function. The frequency of psychogenic abortions is reported to be as high as 15% [21]. Keeping all these factors in mind, it becomes even more important to recognize psychiatric disorders in pregnancy and to treat them effectively .

Major depression in pregnancy

Major depression is twice as common in women than in men and frequently clusters during the childbearing years. Although pregnancy has traditionally been considered a time of emotional well-being for women conferring protection against

Paper received on 20/03/2005 ; accepted on 21/04/2005

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psychiatric disorders, at least one prospective study describes rates of major and minor depression as approximating 10% [5,6]. Other studies also note clinically significant depressive symptoms during pregnancy, particularly in the setting of antidepressant discontinuation [22]. The risk increases with a past history of mood disorder [23-25]. However, it has also been observed that in about one third of depressed pregnant women, this represents the first episode of major depression [26]. Other risk factors for antenatal depression include marital discord or dissatisfaction, inadequate psychosocial supports, recent adverse life events, lower socio-economic status, and unwanted pregnancy [25-27].

Women with recurrent major depression who have been maintained on an antidepressant medication before conception appear to be at an especially high risk for relapse during pregnancy [28]. There have been cumulative data to support the relative safety of using certain antidepressants during pregnancy [22]. High rates of relapse occur after discontinuation of maintenance pharmacological treatment in non-gravid populations [29,30]. In women who have been diagnosed as recurrent depression prior to conception and in whom antidepressant medications have been discontinued, rates of relapse can approximate 75% and can be seen frequently during the first trimester [22,28]. Frequently, depression during pregnancy can be missed. Pregnant women may have many clinical signs and symptoms overlapping with those seen in major depression (e.g. sleep and appetite disturbance, diminished libido, and low energy). Some medical disorders commonly seen during pregnancy, such as anemia, gestational diabetes, and thyroid dysfunction, may be associated with depressive symptoms and may complicate the diagnosis of depression during pregnancy [1,31]. Clinical features that may support the diagnosis of major depression include anhedonia (loss of pleasure), feelings of guilt and hopelessness, and suicidal thoughts. Suicidal ideation is often reported; however risk of self-injurious or suicidal behavior appears to be low in the population of women who develop depression during pregnancy [32,33].

Risks of untreated depression in the mother

The risks of untreated depression in the mother include risk of self-injurious or suicidal behavior, inadequate self-care, and poor compliance with prenatal care [1]. Women with depression often present with decreased appetite and consequently lower than expected weight gain in pregnancy, factors that have been associated with negative pregnancy outcomes [1,34]. Women with depression are also more likely to smoke and to use either alcohol or illicit drugs, behaviors that further increase the risk to the fetus [34].

Some studies suggest that maternal depression itself may adversely affect the developing fetus [34,35]. Although it has been difficult to assess the impact of antenatal depression on fetal development and neonatal well-being in humans, several studies have found an association between maternal depression and factors that predict poor neonatal outcome, including preterm birth, lower birth weight, smaller head circumference, and lower apgar scores [34,35]. Increased maternal serum cortisol and catecholamine levels, typically seen in patients with depression, may affect placental function by altering uterine blood flow and inducing uterine irritability [36,37]. Dysregulation of the HPA axis associated with depression may also have a direct effect on fetal development [32]. Data on animal studies suggest that stress during pregnancy is also associated with neuronal death and abnormal development of neural structures in the fetal brain, as well as sustained dysfunction of the HPA axis in the offspring [37,38].

Impact of maternal depression on the family unit

Interpersonal difficulties, disruptions in mother-child interactions and attachment due to maternal depression may have a profound impact on infant development [39,40]. Children of depressed mothers are more likely to have behavioral problems and exhibit disruptions in cognitive and emotional development [39,40]. Studies have also shown that depression during pregnancy significantly increases a woman's risk for post-partum depression [25,41]. Antenatal depression, thus may have significant adverse effects that may extend beyond pregnancy and have more significant long-term effects on psychosocial functioning.

Bipolar disorder

Pregnancy and especially the post-partum period are stressful periods for women, and increase the risk of relapse for women with bipolar disorder [7,8]. Bipolar disorder affects 0.5-1.5% of individuals [42].The typical age of onset is late adolescence or early adulthood, placing women at risk for episodes throughout their reproductive years [42]. Bipolar disorder in women presents special diagnostic and treatment challenges to the clinician. The presentation of a woman with bipolar disorder may resemble a depressive disorder, behavioral disregulation, or general medical disorders. Thus it is important to access history of hypomania or mania when determining diagnosis in any woman presenting with psychological symptoms. Symptoms of post-partum psychosis tend to differ from the symptoms typically seen in bipolar mania. Therefore if post-partum psychosis is actually a manifestation of bipolar disorder, accurate diagnosis depends on a knowledge of these differences.

Anxiety disorder

Studies indicate that 19% of men and 31% of women will

develop some type of anxiety disorder during their lifetime [44]. The prevalence rates for panic disorder in women and men are 5% and 2% respectively [44]. Agoraphobia, which often coexists with panic disorder, has a lifetime prevalence rate of 7% in women and 3.5% in men[44]. Fluctuations in reproductive hormone levels during the female life-cycle are thought to be responsible for modulating anxiety. Pregnancy appears to be a protective period for some anxiety disorders, including panic, while for others such as OCD, it may be a trigger [44]. Some studies however, have shown an increase in both panic disorder and OCD in pregnant women, especially in the postpartum period [10,11]. Hormonal changes during pregnancy, such as increased prolactin, oxytocin and cortisol may contribute to the suppression of stress response that occurs during this period [44]. Studies have suggested that women with anxiety related to pregnancy may be at a greater risk for postnatal depression [45]. Hence recognition and management of anxiety disorders in pregnant women may be of interest in the prevention of postnatal depression [45]. Studies have also shown that the mothers of babies who demonstrated poor neonatal adaptation reported higher levels of anxiety and depression at study entry than did mothers of healthy babies [46]. High antenatal maternal anxiety was found to be related to attention-deficit hyperactivity disorder symptoms, externalizing problems, and anxiety in 8-9 year olds [47]. Childbirth qualifies an extreme traumatic stressor that can result in post–traumatic stress disorder [48]. The reported prevalence of post-traumatic stress disorder after childbirth ranges from 1.5 to 6% [48]. Mothers with post–traumatic stress disorder attributable to child-birth struggle to survive each day while battling terrifying nightmares and flashbacks of the birth, anger, anxiety, depression and painful isolation from the world of motherhood [48]. Hence prompt diagnosis and treatment are crucial to prevent the maternal morbidity which in turn will have an effect on fetal, infant and child development.

Psychotic disorders

Women with psychotic disorders are at an increased risk of obstetric and psychiatric complications [49]. Recent studies have confirmed earlier findings of a low fertility in women with schizophrenia, although fertility is less affected by mood disorders. Psychotic relapse during pregnancy is rare but women with a history of mood disorders (affective psychosis) are at a high risk of post-partum relapse. There is a high risk of obstetric complications, mixed evidence of still-births and neonatal deaths, and there is some weaker evidence of an association with sudden infant death syndrome [49]. In a recent study investigating the psychosocial outcomes of pregnancies in women with a history of psychotic disorder, 27% of women had a psychotic episode and 38% had non-psychotic depression in the first year after birth [50]. Women with non-affective psychosis were at a significantly higher risk of post-natal depression compared with controls [50]. The authors concluded that women with a history of psychotic disorder are at a higher risk of psychiatric illness postpartum, particularly a two fold risk of post-natal depression [50]. It is well known that the potential consequences of an untreated psychotic episode may be severe and may lead to the mother attempting suicide and/or infanticide. For these reasons, clinicians need to help mothers weigh both fetal and neonatal risks of exposure to the drugs against the potential risk they and their infant may incur if the psychiatric illness is not treated [51].

Obstetrician and psychiatric disorders

Keeping in mind the need to treat pregnant women with psychiatric disorders effectively, the obstetrician/gynecologist should be able to recognise psychiatric disorders based on the symptoms presented, the appearance of the patient and responses given by the patient. In depressed women, there will be a persistent, pervasive depressed mood or a decreased interest in pleasurable activities for a period of atleast two weeks, along with crying spells, feelings of hopelessness, helplessness and worthlessness, and suicidal ideations. She may be preoccupied with guilt regarding a lot of acts in the past. There will be a predominant socio-occupational deterioration from her premorbid level of functioning. In bipolar disorder in mania/ hypomania there will be a euphoric/ expansive or irritable mood lasting for 4 days to 1 week or more. There will be grandiose ideas, spending sprees, talking excessively with pressure of speech accompanied by rhyming or punning, dressing up in a flamboyant fashion, and socio-occupational deterioration. In psychotic disorders, there may be suspiciousness, and disorganized, disinhibited or catatonic behavior .The frequent behavioral symptom presentation is of aggressive/ abusive assaultive behavior, fearfulness, suspiciousness, decreased self care, and reluctance to eat. Amongst anxiety disorders, like panic attacks/panic disorder, there are intense episodes of severe anxiety lasting about 5 to 10 minutes with severe autonomic symptoms like palpitations, tremors, feelings of suffocation, sweating etc. These may be accompanied by a feeling of impending doom or anticipatory anxiety. In obsessive compulsive disorder, there are recurrent and intrusive thoughts or images which cause severe distress to the patient and interfere with day-to-day functioning. These may be associated with compulsions which are recurrent voluntary motor actions which help to lessen the anxiety related to the obsessions. These are a few of the presentations of psychiatric disorders which may be associated with pregnancy and would require a psychiatrist referral for diagnosis and management thereof.

Treatment of psychiatric disorders during pregnancy

a) Specific concerns

Psychotropic medications readily cross the placenta. The following factors must be considered before starting psychotropic medications [1,3] –

1. Teratogenesis
2. Toxicity to the neonate
3. Neurobehavioral sequelae
4. Risk of no treatment

and 5. Risk of medication discontinuation

Teratogenesis

A drug is considered teratogenic if exposure during the first 12 weeks of gestation increases the risk for congenital malformations compared with the general population [1]. Most psychotropic medications are categorized as category C, which indicates a deficit of human studies and a warning that risk cannot be ruled out. However, to date there is no evidence that exposure to tricyclic antidepressants (TCAs), fluoxetine or newer selective serotonin reuptake inhibitors (SSRIs) during pregnancy increase the risk of intra-uterine fetal death [1,52,53]. Also, there is no evidence to date to implicate TCAs, fluoxetine, or the newer SSRIs as causes of major birth defects in humans or animals [1,52-55]. A recent study conducted by Sanz and coworkers [56] found an association between SSRIs, especially paroxetine, and neonatal withdrawal syndrome, especially neonatal convulsions. By November 2003, a total of 93 suspected cases of SSRI induced neonatal withdrawal syndrome had been reported, and were regarded as enough information to confirm a possible causal relation. Sixty-three of the cases were associated with paroxetine, 14 with fluoxetine, nine with sertraline, and seven with citalopram [56]. The authors concluded that SSRIs, especially paroxetine, should be cautiously employed in the treatment of pregnant women with a psychiatric disorder [56]. However, a study conducted recently, evaluating the pregnancy outcome of women exposed to bupropion during pregnancy, indicated that bupropion, does not increase the rates of major malformations above baseline [57].

Toxicity to the neonate

Transient distress syndromes associated with exposure to or withdrawal from psychotropics have been documented in case reports; the incidence of these adverse events appears to be low [1]. Benzodiazepine withdrawal syndromes consist of jitteriness, autonomic deregulation and seizures [58,59]. Impaired temperature regulation, apnea, lower apgar scores, muscular hypotonia, and failure to take feed have also been reported in benzodiazepine exposed infants [60,61]. Pearson and colleagues [62] reviewed records of 65 infants exposed to TCAs and newer SSRIs during pregnancy; no differences were found in acute neonatal outcome as measured by apgar scores, birth weight, gestational age, and cesarean section rates, in comparison with a control group [62]. Prenatal growth and birth weight of infants exposed to TCAs and newer SSRIs during the first trimester appear comparable to those of infants exposed to drugs identified as non-teratogens [52]. There is a need for large samples to be studied before any causal link can be established between a particular medication and a given perinatal syndrome.

Neurobehavioral Sequelae

Data from animal studies have shown that changes in neurotransmitter function and behavior occur after prenatal exposure to psychotropic agents [1]. However, Nulman and colleagues [63], in one prospective study found no neurobehavioral differences in terms of temperament, overall behavior or cognitive function in children exposed to antidepressants (fluoxetine or TCAs) during pregnancy versus unexposed children of 4 years age.

Risk of not treating depression during pregnancy

Studies have noted an association between maternal depression and factors that predict poor neonatal outcome, including preterm birth, lower birth weight, smaller head circumference, and lower apgar scores [1,33,64,65]. Increased cortisol and catacholamine levels frequently seen in depressed individuals may affect placental function by altering uterine blood flow and increasing uterine irritability [53] . Birth outcomes are also affected by maternal stress mediated by peptides derived from an activated hypothalamic-pituitary-adrenal axis, such as adrenocorticotrophic hormone and beta-endorphin [1,53] . Animal studies have indicated that maternal stress during pregnancy is associated with neuronal death, abnormal development of neural structures in the fetal brain, and sustained disfunction of the HPA axis in the offspring [37,38,66]. Depression during the post-partum period may also affect maternal-infant attachment and thereby affect later infant development. Data indicate that children of depressed mothers are more likely to display behavioral problems and exhibit disruptions in motor, cognitive and emotional development [39,40].

Risks of psychotropic drug discontinuation during pregnancy

Discontinuation of maintenance psychotropic medications during pregnancy has been associated with high rate of relapse [1,29,67]. Approximately 50% of patients with bipolar disorder maintained on lithium experience a recurrence within 6 months

of lithium discontinuation [68]. This risk appears to be particularly high in the setting of abrupt as opposed to a more gradual discontinuation of a mood stabilizer [56]. Higher risk of suicide has been associated with lithium discontinuation in patients with bipolar disorder [69]. However, in women with milder illnesses, medication discontinuation may be an appropriate choice and psychotherapy may be considered, whereas in women with more severe illness ongoing treatment may be necessary [3]. However, pharmacological treatment should be pursued when the perceived risks associated with psychiatric illness in the mother outweigh the risks of fetal exposure to a particular medication [22].

b) Treatment of specific psychiatric disorders

1. Major depression:

Psychotherapies: Interpersonal therapy (IPT) addresses four major problem domains with respect to human psychosocial functioning – grief, interpersonal disputes, role transitions, and interpersonal deficits [3,70]. Keeping in mind the importance of interpersonal relationships in couples expecting a child, and the significant role of transitions that take place during pregnancy and subsequent to delivery, IPT is ideal for the treatment of the depressed pregnant women. A study on IPT in depressed pregnant women, revealed that IPT significantly reduces the severity of depressive symptoms and induced remission in all patients [3,71]. It was also seen that none of the women (n=10) developed post-partum depression. A more recent controlled clinical trial of IPT versus parenting education program found that the interpersonal psychotherapy treatment group showed significant improvement compared to the parenting education control program on measures of mood at termination, thereby concluding that IPT is an effective method of antidepressant treatment during pregnancy [72,73]. Cognitive behavior therapy (CBT) has also been reported to be beneficial [74]. St-Andre, selected four psychotherapy themes during brief conflict focussed interventions with pregnant women and their families [75]. The first theme was conflict over increased dependency needs, second was narcissistic disturbances and pregnancy, third was reconciliative themes in pregnancy, and fourth was, working through losses while giving life. The emphasis was on the developmental receptivity of pregnant women to psychotherapeutic interventions [75].

Antidepressant treatment: Antidepressants during pregnancy are indicated for women whose symptoms interfere with maternal well being and functioning. Medication choice is based on prior treatment response. During pregnancy, fluoxetine is usually the first line antidepressant choice, based on its having the most existent literature supporting its reproductive safety [1,3,54,76-78]. Other first-line choices include TCAS, particularly nortryptiline and desipramine, as they are less anticholinergic and therefore less likely to exacerbate orthostatic hypotension during pregnancy [77]. There is a growing literature on the reproductive safety of the newer SSRIs and these agents may be useful in certain settings.[1,53,78,79]. However, the data are less robust for the other medication including sertraline, paroxetine, fluvoxamine, citalopram and venlafaxine [1]. The overall numbers remain small when looking for a potentially rare complication of exposure. Some authors suggest that the older SSRIs and venlafaxine seem to be devoid of teratogenic risks [4]. Possible consequences related to exposure to SSRIs via the placenta and breast milk on neonatal adaptation, and infant's long-term neurocognitive development is still controversial. Few data are available for monoamine oxidase inhibitors, bupropion, nefazodone, or mirtazapine [1]. However these agents may be considered, in patients who have not responded to either fluoxetine or a TCA, acknowledging that information regarding their reproductive safety is limited. Simplified dosing schedules i.e. using one drug instead of two drugs, and an adequate dosage of medication must be given. During pregnancy, changes in plasma volume, as well as increases in hepatic metabolism and renal clearance may significantly affect drug levels [80,81]. Investigators have found a significant reduction (upto 65%) in serum levels of TCAs [82,83]. Sub-therapeutic levels are associated with depressive relapse [83]. Similarly, many women taking SSRIs during pregnancy require an increase in SSRI dosage to sustain euthymia [84]. Based on a number of anecdotal reports of toxicity in infants born to mothers treated with antidepressants, some authors have recommended discontinuation of antidepressant medications several days or weeks before delivery to minimize the risk of neonatal toxicity. Given the low incidence of neonatal toxicity with most antidepressants, this practice carries significant risk because it withdraws treatment from patients precisely as they are about to enter the post–partum period, a time of heightened risk for affective illness [3].

Electro-convulsive therapy (ECT): Severely depressed patients with acute suicidality or psychosis require hospitalization, and electro-convulsive therapy is frequently the treatment of choice [3]. ECT use during pregnancy is found to be safe and efficacious [3,85-88]. There have been reports of premature labor with ECT use during pregnancy [3]. However, there are no reports of premature rupture of membranes caused by ECT. ECT may be considered as an alternative to conventional pharmacotherapy for women who wish to avoid extended exposure to psychotropic medications during pregnancy or for those women who fail to respond to standard antidepressant therapy [3]. In a review of 300 case reports of ECT during pregnancy, it was found that ECT was a relatively safe and efficacious treatment during pregnancy, if steps are taken to decrease potential risks [86]. Preparation for ECT during

pregnancy should include a pelvic examination, discontinuation of non-essential anticholinergic medication, uterine tocodynamometry, intravenous hydration, and administration of a nonparticulate antacid. During ECT, elevation of the pregnant woman's right hip, external fetal cardiac monitoring, intubation, and avoidance of excessive hyperventilation are recommended [86] .

2. Bipolar disorder

Special treatment options for bipolar disorder in pregnant women need to be considered. A risk of fetal malformation exists when some mood stabilizers are used during conception and/or during the first trimester of pregnancy. Neurobehavioral teratogenicity and neonatal toxicity is also possible [43]. Careful treatment management is necessary to reduce the risks to the fetus/infant and to effectively manage bipolar disorder in the mother.[43] . Relapse rates as high as 30-50% have been found in the post-partum period in women with bipolar disorder [1,7,8]. Relapse rates of approximately 50% within 6 months of lithium discontinuation were found in a study of pregnant bipolar women [54]. The first-line choice in pregnant women with bipolar disorder is lithium. Reports from the International Register of Lithium babies estimated the risk for cardiac anomalies (Ebstein's) to be 400 times higher than in the general population [1,89-90]. However, recent data suggested a more modest risk and re-examination of the data estimates the risk to be between 1 in 2,000 (0.05%) and 1 in 1,000 (0.1%) [1,91]. Compared to the other mood stabilizing options during pregnancy, lithium carries the lowest risk [1] . Anticonvulsants are the other choice for treating bipolar disorder. However, anticonvulsant exposure by the fetus is associated not only with multiple congenital anomalies, but also with relatively high rates of serious central nervous system lesions. 0.5 to 1% risk for neural tube defects is seen with maternal carbamazepine use [1,92]. An increased risk for craniofacial anomalies, microcephaly, and growth retardation is also observed [1,93] . A 1-6% risk for neural tube defects, as well as risk for craniofacial abnormalities, cardiovascular malformations, limb defects, genital anomalies, and hydrocephalus have been associated with valproic acid use [1,94]. No significant behavioral problems were found in a 5-year follow-up study of children exposed to lithium during the second and third trimesters in utero [95]. A study using carbamazepine in pregnant women with bipolar disorder revealed neurobehavioral disfunction, whereas another study reported clear cognitive deficits, including depressed IQ and developmental delay, in children exposed in utero to carbamazepine compared to non-exposed children [1,93]. Divalproex was not significantly more effective than no drug for the prevention of post-partum episodes of bipolar disorder [96]. Sufficient data does not exist for the newer anticonvulsants, such as gabapentin and lamotrigine. A recent study by Bowden et al [97] to assess the safety and tolerability of lamotrigine for bipolar disorder found that few patients experienced adverse events with lamotrigine, and the incidence of withdrawal because of adverse events was low. Serious rash occurred rarely (0.1%), thereby concluding that lamotrigine is effective for bipolar depression [97].

Women with a history of a single episode of mania and sustained well-being, may be able to remain off psychotropics during pregnancy. However, women with a history of recurrent illness or severe symptoms requiring hospitalization should remain on medications during pregnancy, as a recurrence could place both mother and fetus at risk [1]. Amongst the mood stabilizers, lithium should be considered first. However, if the use of carbamazepine or valproic acid is required during pregnancy, high dosage folic acid (4 mg per day) may partially reduce the risk for spina-bifida [98]. Generally, it is recommended, that pregnant women should avoid anticonvulsant exposure. Another strategy in pregnant women controlled with lithium would be to avoid lithium during the first trimester, and to resume the treatment during the second trimester [99]. An ultrasound at 16-18 weeks of gestation is recommended to detect congenital anomalies in fetuses of women exposed to mood stabilizing agents during the first trimester [91]. There is a high risk of relapse in post-partum women with bipolar disorder. The risk increases to almost 70% when women are ill with symptoms of hypomania, mania or depression during pregnancy [99]. Risk of relapse is significantly reduced in the post-partum period with lithium prophylaxis [100]. Earlier reintroduction of lithium during the third trimester may be more protective than reinitiation after delivery [99].

3. Anxiety disorders

Psychotherapies : CBT is found to be efficacious for panic disorder and OCD in both pregnant and non-pregnant women [101]. Tapering of medication or lower dosages of medication may be possible with adjunctive treatment with CBT during pregnancy. Similarly, for mild cases of OCD, pregnant women may do well with behavioral technic. However, moderate to severe symptoms may require maintenance pharmacological treatment.

Anxiolytics : A slow taper of antipanic medications (over 2 weeks), may be possible in mild cases of panic disorder. However, maintenance medication may be necessary in patients with severe panic disorder. In such cases, fluoxetine or a TCA is a reasonable treatment option [102]. In patients who do not respond to these antidepressants, benzodiazepine use may be considered. Patients with moderate to severe OCD require maintenance pharmacological treatment. Fluoxetine is an ideal first choice. Clomipramine may also be considered. but may aggravate orthostatic hypotension. Some data link

clomipramine with neonatal seizure at the time of labor and delivery [7,103]. Benzodiazepine usage during pregnancy is controversial [1]. Some studies suggest an increased risk for cleft lip and cleft palate from first trimester exposure to benzodiazepines [104,105]. However other studies have found no increased risk for organ malformation [60,105]. Some studies also indicate that late third trimester exposure may be associated with neonatal toxicity syndromes, including muscular hypotonia, failure to feed, impaired temperature regulation, apnea, and depressed apgar scores [60,61]. Dosages associated with toxicity are usually greater than or equal to 2 mg a day of clonazepam or the equivalent dosage of other benzodiazepines. A recent study evaluated clonazepam use in pregnancy and the risk of malformations [106]. This study did not observe an increase in major malformations in births exposed to clonazepam monotherapy [106]. Benzodiazepines have the advantage over antidepressants of possible intermittent use.

4. Psychotic disorders

Neuroleptics should be considered as psychosis can be an obstetric and medical emergency. Earlier studies have not associated neuroleptic use with teratogenic risk [107]. However, higher risk of congenital malformations after first trimester exposure to low potency neuroleptics, was observed in a meta-analysis [104]. Hence in pregnant women with psychotic illnesses, higher potency agents are recommended over lower potency neuroleptics. Fewer data are present for atypical neuroleptic medications in pregnancy including olanzapine, risperidone or quetiapine. Clozapine use in pregnant women has been investigated with some studies reporting no evidence of congenital malformations [108-111]. Similarly, a recent review showed that olanzapine and clozapine apparently do not increase the teratogenic risk if administered to pregnant women, while evidence on quetiapine, risperidone, aripiprazole, and ziprasidone is still limited. Some studies suggest increased hyperglycemic risk for pregnant women related to atypical antipsychotic therapy during gestation [51]. The study concluded that atypical antipsychotics in pregnancy and breast feeding do not show evident advantages in safety when compared to typical neuroleptic agents [51]. Some reports have documented transient extrapyramidal symptoms in neonates exposed to neuroleptic drugs at or around the time of delivery [112]. Studies have shown that infants exposed in-utero to neuroleptics have been noted to have normal motor development [113]. During the first trimester, mild intermittent symptoms of psychosis may be managed with neuroleptics as needed .

Table 1. Information regarding use of pharmacotherapeutic agents during pregnancy.

Major depression	
1st line drugs :	fluoxetine, tricyclic antidepressants particularly nortryptilline and desipramine
2nd line drugs :	sertraline, paroxetine, fluvoxamine, citalopram and venlafaxine
	Drugs best avoided due to lack of sufficient data : monoamine oxidase inhibitors, bupropion, nefazodone and mirtazapine
Bipolar disorder	
1st line drugs :	lithium (possible risk- cardiac anomalies 0.05-0.1 %)
2nd line drugs :	carbamazepine (possible risks–multiple congenital anomalies, neural tube defects 0.5-1%, craniofacial anomalies, microcephaly, growth retardation), valproic acid (possible risks – neural tube defects, craniofacial abnormalities, CVS malformations, limb defects, genital anomalies and hydrocephalus).
	Drugs best avoided due to lack of sufficient data : divalproex, lamotrigine, gabapentine
Anxiety disorders	
1st line drugs :	fluoxetine, tricyclic antidepressants
	Drugs best avoided due to lack of sufficient data – benzodiazepines (possible risks – cleft lip, cleft palate, toxicity syndromes including muscular hypotonia, failure to feed, impaired temperature regulation, apnea and depressed apgar scores).
Psychotic disorders	
1st line drugs :	higher potency antipsychotics
2nd line drugs :	clozapine, olanzapine
	Drugs best avoided due to lack of sufficient data - quetiapine, risperidone, aripiprazole and ziprasidone

Conclusion

Numerous psychiatric disorders have been found to be associated with pregnancy. In the present review, we have attempted to highlight some of the common psychiatric disorders which are seen in pregnant women, and various factors to be considered regarding the use of psychotropic medications. Several lacunas exist regarding the use of newer medications during pregnancy due to paucity of literature regarding studies related to their use. The overall consensus is to prefer nonpharmacolgical measures in milder cases of psychiatric disorders. However, if the psychiatric disorder is of a severe intensity, then pharmacotherapy is a must and it outweighs the small possibility of congenital malformation. With the newer psychotropic drugs having fewer side effects, the clinician has a vast array of options available, which allow the effective treatment of pregnant women with psychiatric disorders.

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