Obstetrics and Gynecology Patients: Menstrual Cycle, Pregnancy, and Postpartum-Related Psychiatric Disorders

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31.1 Introduction

Women have a significantly higher risk for developing mood disorders with a lifetime prevalence that is approximately twice that of men. Sex difference in the rates of depression begins to appear in adolescence. Although reasons for this gender difference are not fully understood, the changing level in reproductive hormones throughout a woman's life may be playing a direct or indirect effect on her mood. Studies on bipolar disorder suggest that women are more likely than men to be rapid cyclers (Arnold 2003), which is attributed to the increased occurrence of hypothyroidism and menstrual cycle irregularities in women. Pregnancy and the postpartum period are considered to be vulnerable times in a woman's life with significant increase and drop in reproductive hormones and increased risk of psychiatric symptoms. Oral contraceptives, hormone replacement therapy, and menopause dampen the cyclicity of ovarian function and can cause mood symptoms. Reproductive hormones modulate neuroendocrine, neurotransmitter, and circadian rhythms, all of which have been implicated in the pathophysiology of mood disorder. Changes or variability in

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reproductive hormones rather than absolute level increases the risk for symptoms in vulnerable individuals. Depression occurring in association with the reproductive cycle may sensitize a woman to future depression.

31.2 Menstrual Cycle–Related Affective Illness

31.2.1 Premenstrual Dysphoric Disorder

Premenstrual Dysphoric Disorder (PMDD) is a constellation of affective, behavioral, cognitive and somatic symptoms with a regular cyclical relationship to the luteal phase of the menstrual cycle. 90 % of women report at least mild premenstrual symptoms, 20–30 % of women may have moderate-to-severe symptoms that meet the criteria for premenstrual syndrome (PMS), but about 3–8 % of menstruating women can develop more severe and disabling symptoms that meet criteria for PMDD, causing impairment in their social and occupational functioning (Rapkin and Lewis 2013).

According to DSM-5 (2013), diagnosis of PMDD requires the presence of five of the following 11 symptoms, with one severe mood symptom causing functional impairment: (1) depressed mood, feelings of hopelessness, or self-deprecating thoughts; (2) marked anxiety, tension, feelings of being "keyed up" or "on edge"; (3) marked affective lability, such as feeling suddenly sad or tearful, or increased sensitivity to rejection; (4) persistent marked anger or irritability or increased interpersonal conflicts; (5) decreased interest in usual activities (work, school, friends, hobbies); (6) subjective sense of difficulty in concentration; (7) lethargy, easy fatigability, or marked lack of energy; (8) marked change in appetite, overeating, or specific food cravings; (9) hypersomnia or insomnia; (10) subjective sense of being overwhelmed or out of control; (11) other physical symptoms such as breast tenderness, swelling, headache, joint or muscle pain, sensation of "bloating" or weight gain. Impairment in home, social, and occupational functioning related to the symptoms must be present for most menstrual cycles over the past year, and symptoms must be documented prospectively for at least two menstrual cycles to confirm the premenstrual timing of the symptoms and the postmenstrual symptom-free-interval.

The cause of these symptoms is not fully understood. Absence of symptoms in premenarchy, postmenopause and ovariectomized women indicates the role of gonadal sex steroids, particularly progesterone in causing the symptoms. Symptoms could be the result of exaggerated or abnormal response to normal hormonal fluctuations in susceptible women. Etiology of this "differential sensitivity" may be multifactorial and partially genetically determined. A recent study (Huo et al. 2007) demonstrated an allelic variation on the estrogen receptor α gene in women with PMDD when compared with control women. In addition, the allelic variation was only significant in women who had a valine/valine genotype for the catechol-*O*-methyltransferase enzyme. This significant study may identify a source of abnormal estrogen signaling during the luteal phase that leads to premenstrual affective, cognitive, and somatic symptoms.

The role of specific neurotransmitter, neuroendocrine, and neurosteroidal peptides in causing PMDD is not fully known. Metabolites of progesterone (allopregnanolone or ALLO and pregnanolone) have a positive modulating effect on the GABA neurotransmitter system in the brain and have been implicated in the pathophysiology of PMDD. Decreased peripheral levels of ALLO have been found in the luteal phase of affected women in some studies (Klatzkin et al 2006). Serotonergic dysregulation has been hypothesized as another etiological factor in causing PMDD. Studies have found lower density of brain serotonin receptors (Jovanovic et al 2006), and lower peripheral platelet uptake of serotonin (Ashby et al. 1988) in affected women. Tryptophan depletion in women with PMDD has been shown to exacerbate the symptoms of PMS (Menkes et al. 1994). Also, SSRIs and SNRIs have proven to be effective in the treatment of PMDD.

A recent study using fMRI and PET showed greater dorsolateral prefrontal cortex activation in patients with PMDD, and this correlated with PMDD severity, symptoms, age at onset and disease burden (Baller et al. 2013).

31.2.1.1 Clinical Course and Burden of illness

Premenstrual symptoms are described in women from menarche to menopause, but it is unclear whether symptoms remain stable or increase in severity with age. Symptoms should be assessed prospectively over two consecutive cycles to ensure that symptoms are premenstrual. It is important to rule out other medical or gynecological causes for the symptoms. Patients' dietary habits, amount of physical activity, and drug/alcohol use should be determined as part of the initial evaluation. Women who experience PMDD have a greater risk for future depression during pregnancy, postpartum, and perimenopausal period. Premenstrual symptoms can significantly affect health related quality of life and may result in increased health care utilization and decreased occupational productivity (Borenstein et al. 2003).

31.2.1.2 Treatment

Treatment involves education, lifestyle changes, support, and pharmacologic management of symptoms (Pearlstein and Steiner 2008).

31.2.1.2.1 Lifestyle Modifications, Nutritional Supplements, and Psychosocial Treatments

Education, support groups, biofeedback, massage, exercise both aerobic and anaerobic, reflexology, acupuncture have all been found to have some effect in reducing the symptoms.

Common dietary recommendations include increased consumption of complex carbohydrates, frequent snacks, reduced consumption of refined sugar and artificial sweeteners and caffeine (Sayegh et al. 1995).

Among dietary and herbal supplementations, the strongest evidence exists for the benefit of chasteberry or *V. agnus castus* (Dante and Facchinetti 2011). Other vitamins and minerals shown to be somewhat effective include B_6 (50–100 mg/day), calcium carbonate 1,200 mg/day in divided doses, magnesium, vitamin E 400 units/day, L-Tryptophan 6 g per day, fish oil and soy isoflavones.

Cognitive behavioral therapy (CBT) is consistently reported to be an effective treatment for women with PMDD (Hunter et al. 2002).

31.2.1.2.2 Pharmacological Treatment

Pharmacological treatment focuses on elimination of hormonal fluctuations with ovulation suppression treatments or correcting the neurotransmitter dysregulation with antidepressant or anxiolytic medications.

YAZ, an oral contraceptive containing ethinyl estradiol 20 μg and drospirenone 3 mg, administered as 24 days of active pills followed by a 4-day hormone-free interval (24/4), has reported superiority in reducing premenstrual emotional and physical symptoms when compared with placebo (Rapkin 2008). In 2006, YAZ received United States Food and Drug Administration (FDA) approval for the treatment of PMDD in women desiring oral contraception.

Gonadotropin-releasing hormone (GnRH) agonists suppress ovulation by downregulating GnRH receptors in the hypothalamus. GnRH agonists are administered parenterally (e.g., subcutaneous monthly injections of goserelin, intramuscular monthly injections of leuprolide, daily intranasal buserelin). GnRH agonists have been reported to be superior to placebo in 8 of 10 published randomized controlled trials in women with PMS or PMDD (Backstrom et al. 2003). They should be used only in patients who are resistant to other forms of treatment as they induce menopause and the side effects related to it, including hot flashes, vaginal dryness, depression, headache, osteoporosis, and increased risk for cardiovascular disease.

Oophorectomy and prolonged anovulation from danazol, a gonadotropin inhibitor, are not common treatments for PMDD, largely because of the medical risk associated with prolonged hypoestrogenic state, which leads to the same long-term health issues as those arising from use of GnRH agonists.

For physical symptoms, nonsteroidal anti-inflammatory drugs (NSAIDs) and diuretics, especially spironolactone, have been found to be helpful. For mood symptoms, selective serotonin reuptake inhibitors (SSRIs) have been found to be effective in multiple controlled trials (Marjoribanks et al. 2013). The SSRI dosages that are effective for PMDD are similar to or slightly lower than the dosages recommended for the treatment of major depressive disorder (MDD). Continuous dosing and intermittent late luteal phase dosing have both been shown to be effective. With intermittent dosing the antidepressant is started approximately 14 days before the onset of menses and continued until the onset of menses or shortly thereafter. Benzodiazepines can be effective for severe anxiety symptoms.

31.2.2 Perimenopause-Related Affective Illness

The menopausal transition is often marked by somatic symptoms (aches and pains, myalgia, fatigue), physiologic symptoms (hot flashes and nighttime awakenings, sleep disturbances, urogenital complaints), and psychological symptoms. The most prevalent mood symptoms during this period include irritability, tearfulness, anxiety, depressed/labile mood, lack of motivation and energy, poor concentration, and interrupted sleep.

The perimenopausal period is associated with a higher vulnerability for depression with risk rising from early to late perimenopause and decreasing during postmenopause. Women with past history of depressive disorder, premenstrual syndrome, oral contraceptive-induced dysphoria and depression associated with pregnancy and postpartum have a higher risk of developing depression during menopausal transition (Avis et al. 1994; Stewart and Boydell 1993). The perimenopausal period is associated with a two- to fourfold increased risk for the development of new onset depression in women with no previous history of depression (Cohen et al. 2006; Freeman et al. 2006; (Schmidt et al. 2004). Depressive symptoms can recur in women with bipolar disorder during this time (Khan et al. 2007). Also, risk of suicide in women increases from age 45 to 64 (Usall et al. 2009).

Untreated depression during perimenopause is associated with increased risk for medical illness including heart disease and stroke in women (Wassertheil-Smoller et al. 2004). Also, studies have shown decreased bone density in these women (Jacka et al. 2005, Eskandari et al. 2007). Increased risk for fall combined with osteoporosis results in higher rates of fracture and disability (Silverman et al. 2007).

Hormonal transition to menopause coexists with major stressors and social role changes in midlife. This complex interplay of biological and psychological factors increases vulnerability to develop psychiatric syndromes in susceptible women. Risk factors for developing depression during perimenopause include demographic factors (Caucasian race and lower educational level), psychiatric factors (history of depression), psychosocial factors (empty nest syndrome, changing roles, loss of parents and partner, other stressful life events, unhealthy lifestyle, negative attitudes regarding aging/menopause), and menopausal factors (vasomotor symptoms and other physical symptoms, premenstrual syndrome, early natural menopause, menopausal transition ≥ 27 months, abrupt/surgical menopause).

During the years leading to menopause, the estrogen level changes rapidly with decreasing levels of estradiol production by the ovaries, declining levels of androgens and increasing levels of pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Ovarian hormones modulate serotonin and noradrenaline neurotransmission. It has been postulated that changes in these hormonally mediated neuromodulatory effects may heighten the risk for mood disorders in women with sensitivity to normal hormonal fluctuations (for example during the premenstrual period, puerperium, and perimenopause).

31.2.2.1 Treatment

Routine screening of at-risk population followed by careful assessment for depressive symptoms can help identify the presence of MDD during menopausal transition. Recognition of menopausal

symptoms, with or without depression, is important given their potential impact on quality of life.

Intervention for depressive symptoms during perimenopause depends on the severity of symptoms. Mild depressive symptoms usually respond to psycho-education/counseling, life style changes including diet and exercise, minimizing physical discomfort, optimizing general health and improving social support. Cognitive behavior therapy, supportive psychotherapy and referral to support groups can help women deal with the associated psychosocial stressors.

Moderate to severe symptoms of depression may require pharmacotherapy, and or hormone replacement (Parry 2010).

31.2.2.1.1 Pharmacologic Treatment

Antidepressants: The serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) have been found to be effective to treat depressive symptoms as well as the some of the physical symptoms like hot flashes and are considered the first line treatment for perimenopausal depression.

Hormone Replacement: Although antidepressant medication is the mainstay of treatment, adjunctive therapy, especially with estrogen replacement, may be indicated in refractory cases, and may speed the onset of antidepressant action (Schneider et al. 1997; Rasgon et al. 2002). Although some antidepressants improve vasomotor symptoms, in general they are not as effective as estrogen alone for relieving these symptoms. Estrogen therapy has been shown to be effective in improving mood and in alleviating hot flashes in symptomatic peri- and postmenopausal women but its use may be accompanied by increased risk of stroke, cardiovascular events, breast cancer, and pulmonary embolism. Certain subpopulations of women might preferentially benefit from hormonal interventions such as women with other clinical indications for the use of estrogen replacement therapy (ERT), or women with pre-existing clinical conditions such as sexual dysfunction, which could get worse with the isolated use of antidepressants. The active form of estrogen, 17-beta estradiol, crosses the blood–brain barrier and exerts potential beneficial effects on mood, sleep, cognitive function, and vasomotor symptoms.

31.3 Psychiatric Disorders during Pregnancy

31.3.1 Vignette

A 32-year-old woman who was 22 weeks pregnant was admitted for fetal monitoring for twin pregnancy complications. The patient had a history of bipolar disorder and borderline personality disorder and had been prescribed valproic acid, quetiapine, clonazepam, and sertraline in the past but discontinued all her medications after she found out that she was 7 weeks pregnant. This was her seventh pregnancy and was unplanned. She had a history of repeated suicide attempts. During the psychiatric interview she reported feeling overwhelmed, depressed, anxious, crying easily, having insomnia, loss of appetite, and occasional suicidal thoughts, but no psychotic symptoms. When restarting her medications was discussed, the patient adamantly refused to take any psychotropic medications. She stated that she had been on psychotropic drugs during her last pregnancy, and her now 2-year-old son from that pregnancy was recently diagnosed with autism.

31.3.2 Introduction

The prevalence of mood disorder in women is similar in pregnant and non-childbearing women. The prevalence of major depression in pregnant women ranges from 3.1 % to 4.9 % and that of major or minor depressive episodes from 8.5 % to 11 % (Gaynes et al. 2005). The incidence of major or minor depression during pregnancy is about 14.5 %, major depression being about 7.5 %. Many women are advised to stop taking psychotropic medications during pregnancy or before conception because of our limited knowledge of their safety during pregnancy. Acute affective or psychotic disorders during pregnancy

can adversely affect the pregnancy, fetus, and the family as a whole.

31.3.2.1 Negative Consequences of Untreated Psychiatric Illness

Maternal negative consequences: Maternal negative consequences of untreated psychiatric illness during pregnancy include lack of self-care, poor compliance with prenatal care (Zuckerman et al. 1989), lower than expected weight gain, use of tobacco, alcohol, and illicit substances, increased risk of being a victim of violence, deciding to abort due to depression, and increased risk for self-injurious behavior and suicide (although suicide risk may be lower than in non-pregnant women (Marzuk et al. 1997)).

Negative consequences on the family unit: Psychiatric illness in the pregnant mother can affect the family as a whole causing interpersonal problems, marital discord, disruption in the mother–child interaction, and attachment problems.

Obstetric and neonatal complications: Untreated psychiatric illness during pregnancy has been reported to cause placental abruption, preeclampsia, higher need for epidural anesthesia, higher incidence of operative deliveries, preterm birth, low birth weight, smaller head circumference, lower Apgar score at birth, higher incidence of neonatal intensive care unit (NICU) admissions, and impairment in neonatal neurobehavioral functioning such as irritability in newborn, unconsolability, and excessive crying (Zuckerman et al. 1990). The exact etiology for these complications is unclear. It is hypothesized that increased stress, depression, and anxiety during pregnancy can result in increased maternal levels of cortisol and catecholamines which pass through the placenta and may adversely affect the placental function. This may explain the increased incidence of uterine irritability, preterm labor, and low birth weight. Maternal anxiety in pregnancy has shown to increase the uterine artery resistance index (Teixeira et al. 1999).

Long-term effects: Childhood behavioral problems have been reported in infants of mothers with untreated psychiatric illness. Children whose mothers experienced high levels of anxiety in late pregnancy exhibited higher rates of behavioral and emotional problems during early childhood, which persisted through middle childhood, after controlling for obstetric risks, psychosocial disadvantage, and postnatal anxiety and depression (O'Connor et al. 2003). Poor growth and increased risk for infection has been reported in children exposed to maternal depression (Rahman et al. 2004). Elevated cortisol levels, increased stress responsiveness, difficult temperament, language and cognitive impairment, impulsivity, aggressive behaviors, dysphoria, sleep problems, attention-deficit disorder have all been reported in children exposed to maternal depression during pregnancy (Huot et al. 2004).

Placental transmission of stress hormones to the fetus from maternal depression could affect fetal brain development which could explain the increased behavioral/emotional problem in children exposed to maternal depression and anxiety during pregnancy.

31.3.3 Risk Factors for the Emergence or Exacerbation of Psychiatric Disorders during Pregnancy

Personal and family history of affective illness, discontinuation of maintenance psychotropic medications during pregnancy, having anxiety, younger age, living alone, multiple children, marital discord, being exposed to domestic violence, recent adverse life events, inadequate psychosocial support, lower socioeconomic status, and unwanted pregnancy have been reported to increase the emergence or exacerbation of psychiatric illness during pregnancy.

31.3.4 Clinical Features of Psychiatric Disorders during Pregnancy

There is a significant overlap between prepartum and postpartum depression. Women with depression during pregnancy have an elevated risk of

postpartum depression (Gotlib et al. 1989; Koutra et al. 2014). Diagnostic criteria for depressive disorders during pregnancy are similar to depression during other times in a woman's life. Anxiety is common during pregnancy especially when comorbid with depression. Diagnosis of depression during pregnancy can be complicated by the significant overlap of the neurovegetative symptoms of depression with pregnancy, such as sleep disturbance, low energy, appetite change, and decreased libido. The clinical features that would help to make the diagnosis of depression include anhedonia, feelings of guilt, hopelessness, and suicidal thoughts. Suicidal behavior or a suicide attempt in women with clinical depression during pregnancy is found to be relatively lower compared to that in non-pregnant women (Appleby 1991; Marzuk et al. 1997). Women with a history of recurrent major depression who are on maintenance antidepressant medication and who discontinue their medication either before conception or during pregnancy are at significantly high risk for relapse (Cohen et al. 2004).

Pregnancy is now considered a time for an increased risk for relapse of bipolar depressive and manic episodes, especially following discontinuation of mood stabilizing maintenance treatment. The risk also increases sharply during the postpartum period (2.9 times). Recurrence risk is greater after rapid than after gradual discontinuation of lithium and for patients with more prior affective episodes (Viguera and Nonacs 2000).

Mild to moderate anxiety symptoms are common during pregnancy, but severe anxiety symptoms need prompt diagnosis and treatment, as anxiety can have a deleterious effect on pregnancy and the fetus and increase the risk for postpartum anxiety and depression (Heron et al. 2004). Similarly, women who discontinued treatment for panic disorder and obsessive compulsive disorder are three times more likely to relapse compared to those who maintained treatment during pregnancy (Roy-Byrne et al. 1989).

Posttraumatic stress disorder (PTSD) has been reported in women with traumatic birth experience including prolonged labor, severe pain during childbirth, and loss of control during delivery. It can affect a woman's decision on future pregnancy and her ability to breast-feed, and impair parent–child bonding (Beck 2004)

Psychotic disorders during pregnancy are associated with significant maternal and fetal morbidity and mortality. A new onset of psychosis during pregnancy requires systematic diagnostic evaluation to rule out secondary causes of the symptoms. It also increases the risk for postpartum psychosis. Acute psychosis during pregnancy is both an obstetric and a psychiatric emergency and needs prompt evaluation and treatment to reduce the morbidity and mortality associated with it.

31.3.5 Diagnosis and Treatment of Psychiatric Disorders during Pregnancy

Appropriate management of psychiatric disorder during pregnancy should involve prompt diagnosis, treatment and collaboration between the patient, family, obstetrician, and psychiatrist. Discussion with the patient and family should involve morbidity and mortality associated with untreated psychiatric illness, the risks and benefits of psychotropic medications including the risk of discontinuation of psychotropic medication, and alternative treatments available. These discussions should be initiated prior to conception in patients with a history of psychiatric illness and who are already on psychotropic medications.

Clinicians face specific challenges in treating pregnant women with psychiatric illness. All medications readily cross the placenta. Physiologic changes in a woman's body during pregnancy can alter the pharmacokinetics and pharmacodynamics of drug treatment. It is common for women to avoid or discontinue psychotropic agents either before conception or during pregnancy. The threshold for treating a psychiatric condition during pregnancy with medication tends to be higher compared to a non-psychiatric medical illness. Treatment with psychotropic medications is usually reserved for psychiatric conditions that cause severe impairment in maternal functioning. Treatment should be individualized after a collaborative and ongoing discussion with the patient

and her partner. Even if the decision is made to discontinue treatment, patients should be followed closely during pregnancy and in the postpartum period for early detection of relapse and rapid intervention, which may significantly reduce the morbidity.

31.3.5.1 General Guidelines for Treatment during Pregnancy

The choice of treatment with psychotropic medication during pregnancy is based on the severity of symptoms, patient's level of functioning, period of clinical stability with and without treatment, past history of treatment discontinuation and time to relapse, time to recovery with reintroduction of treatment, previous medication trials and responses, risk and benefits of treatment, and wishes of the patient.

Non-pharmacologic interventions such as CBT and interpersonal therapy (IPT) have proven efficacy for mild to moderate depression and anxiety and should be considered as a first-line treatment for these conditions whenever possible (Spinelli 1997). Both IPT and CBT can also be used to taper the dose of antidepressant or anti-anxiety medications prior to conception to decrease the risk of relapse.

None of the psychotropic medications are Food and Drug Administration (FDA) approved for use during pregnancy. General guidelines for use of psychotropic medications during pregnancy include: (1) select the safest medication with documented safety; (2) use the minimum effective dosage; (3) avoid abrupt discontinuation of medication; (4) simplify the medication regimen and avoid polypharmacy; (5) if medications were discontinued during pregnancy, consider restarting them postpartum, as this is the period of high risk for relapse.

Risks associated with the use of psychotropic medication during different stages of pregnancy include:

1. pregnancy loss
2. teratogenicity with exposure in the first 12 weeks
3. adverse pregnancy and delivery outcomes
4. perinatal syndrome or neonatal toxicity
5. long-term neurobehavioral sequelae in the exposed infant including cognitive, emotional, and behavioral problems

Antidepressants

Reported adverse outcomes with the use of antidepressants during pregnancy (Chaudron 2013) are associated with:

1. Increased risk for pregnancy-induced hypertension with or without preeclampsia with the use of SSRI during late pregnancy (Toh et al. 2009; DeVera and Berard 2012).
2. Slight increase in the risk for spontaneous abortion with the early pregnancy exposure to antidepressants: 12.4 % (exposed) versus 8.7 % (unexposed) (Gentile 2008). In a more recent meta-analysis (Ross et al. 2013), no significant association between antidepressant medication exposure during early pregnancy and spontaneous abortion was found.
3. Structural malformation: In a recent meta-analysis (Grigoriadis et al. 2013a), no associated risk of congenital malformation was found with exposure to antidepressants during early pregnancy. Conflicting association was reported with first trimester exposure to paroxetine (FDA Category D) and increased risks of cardiac malformations. Combination of an SSRI and a benzodiazepine may increase the risk for congenital heart defects.
4. Lower birth weight, small size for gestational age, slower rates of head growth, preterm birth, lower Apgar scores have been reported with antidepressant exposure during pregnancy (Ross et al. 2013).
5. There is a significant association between exposure to antidepressants during late pregnancy and overall occurrence of poor neonatal adaptation syndrome (PNAS) which manifest as irritability, jitteriness, poor muscle tone, weak cry, respiratory distress, hypoglycemia, temperature instability, low Apgar scores, and seizures. Studies of third trimester exposure to SSRIs and SNRIs have demonstrated such effects (Zeskind and Stephens 2004). These symptoms start within hours of delivery, but generally require only supportive care and fully abate within 1–2 weeks. Poor neonatal adaptation may occur in 30 % of infants with

exposure to SSRIs, with higher rates evidenced in premature infants (Grigoriadis et al. 2013b).

6. Persistent pulmonary hypertension (PPH) of the newborn with exposure to SSRI after 20 weeks: Persistent pulmonary hypertension in the newborn occurs when the pulmonary vascular resistance fails to decrease after birth and the ductus arteriosus remains open to ensure circulation. Mortality ranges from 5 % to 10 %. Perinatal risk factors for persistent pulmonary hypertension of the newborn include meconium aspiration, maternal overweight, smoking, diabetes, or use of nonsteroid anti-inflammatory drugs during pregnancy. PPH with exposure to SSRI was first reported in 2006 (Chambers et al. 2006). Since then studies have shown conflicting results on the increased risk of PPH with later gestational exposure to SSRI. A recent population based cohort study from the health registers from five Nordic countries involving 1.6 million births found an absolute risk increase from 1.2/1,000 base rate to 3/1,000 in SSRI exposed newborns. It was a class effect with no difference between the SSRIs (Kieler et al. 2012).
7. Long-term growth, IQ, and behavioral problems: Most studies show no association with use of SSRIs or TCAs during pregnancy and long-term neurobehavioral problems and IQ in exposed children (Pederson et al. 2013; Nulman and Rovet 2002; Nulman et al. 1997; Nulman et al. 2012). There is a recent report of twofold increased risk of autism spectrum disorder associated with SSRI treatment (Croen et al 2011) and subtle impairment in motor development with fetal exposure to antidepressants (Casper 2003).

31.3.5.2 APA and ACOG Guidelines for Treating Depression during Pregnancy (Yonkers et al. 2009)

Women thinking about getting pregnant: For women on medication with mild or no symptoms for 6 months or longer, it may be appropriate to taper and discontinue medication before becoming pregnant.

Medication discontinuation may not be appropriate in women with a history of severe, recurrent depression or who have psychosis, bipolar disorder, other psychiatric illness requiring medication, or a history of suicide attempts. Women with suicidal or acute psychotic symptoms should be referred to a psychiatrist for aggressive treatment.

Pregnant women currently on medication for depression: Psychiatrically stable women who prefer to stay on medication may be able to do so after consultation between their psychiatrist and ob-gyn to discuss risks and benefits. Women who would like to discontinue medication may attempt medication tapering and discontinuation if they are not experiencing symptoms, depending on their psychiatric history. Women with a history of recurrent depression are at a high risk of relapse if medication is discontinued. Women with recurrent depression or who have symptoms despite their medication may benefit from psychotherapy to replace or augment medication. Women with severe depression (with suicide attempts, functional incapacitation, or weight loss) should remain on medication. If a patient refuses medication, alternative treatment and monitoring should be in place, preferably before discontinuation.

Pregnant and not currently on medication for depression: Psychotherapy may be beneficial in women who prefer to avoid antidepressant medication. For women who prefer taking medication, risks and benefits of treatment choices should be evaluated and discussed, including factors such as stage of gestation, symptoms, history of depression, and other conditions and circumstances (e.g., smoking, difficulty gaining weight).

All pregnant women: Regardless of circumstances, a woman with suicidal or psychotic symptoms should immediately be hospitalized and see a psychiatrist for treatment.

Benzodiazepines

Abrupt discontinuation of benzodiazepines during pregnancy can result in rebound anxiety symptoms and potentially serious withdrawal symptoms. If the patient and clinician decide to

stop *a* benzodiazepine during pregnancy, it has to be gradually tapered over 2 weeks or more. Adjunctive CBT could be helpful to prevent relapse of symptoms. SSRIs and SNRIs should be tried as first-line agents for treatment of anxiety disorders, but patients may need augmentation with *a* benzodiazepine especially during the first few weeks of treatment till the antidepressant starts working.

Reported adverse outcomes with the use of benzodiazepines during pregnancy include:

1. *Teratogenic Effects:* Initial reports suggested that there may be an increased risk of cleft lip and palate with the use of benzodiazepines during first trimester. More recent studies and meta-analysis suggest a very modest increase in risk of oral cleft, 0.7 %, which represents a tenfold increased risk in relation to general population (Altshuler et al. 1996). All benzodiazepines are FDA Class D medications and should be used only if the maternal benefit outweighs the fetal risk. Currently, no systematic data are available on the reproductive safety of non-benzodiazepine anxiolytic agents, such as buspirone and hypnotic agents like zolpidem and zaleplon. Therefore, these medications are not recommended for use in pregnancy.
2. *Perinatal Toxicity:* Maternal use of BZD and/or benzodiazepine receptor agonists may increase the risk for preterm birth and low birth weight (Wikner et al. 2007). Late-trimester use and exposure to benzodiazepine during labor is associated with increased risk for floppy baby syndrome or marked neonatal withdrawal symptoms. Symptoms of floppy baby syndrome can include mild sedation, hypotonia, neonatal apnea, reluctance to suck, low Apgar score, cyanosis, and temperature dysregulation. Symptoms of neonatal withdrawal include hypertonia, hyperreflexia, restlessness, irritability, abnormal sleep patterns, inconsolable crying, tremors or jerking of the extremities, bradycardia, cyanosis, suckling difficulties, apnea, risk of aspiration when fed, diarrhea and vomiting, and growth retardation. This neonatal withdrawal can appear within a few days to 3 weeks after birth and can last up to several months because of slow neonatal metabolism. Infrequent use of benzodiazepines does not seem to cause this problem.
3. *Long-term neurobehavioral effects:* Data on long-term neurobehavioral sequelae following exposure to benzodiazepines in utero are scant and reports are mixed. In one study involving 550 children exposed to benzodiazepines and followed up to 4 years of age, there was no adverse effects on neurobehavioral development and IQ (McElhatton 1994).

31.3.5.3 Management of Bipolar Disorder during Pregnancy

It is challenging for clinicians to treat patients with a history of bipolar disorder who plan to conceive or who are pregnant. Because most mood stabilizers and atypical antipsychotic drugs have been categorized as FDA category C (human fetal teratogenicity cannot be ruled out) or category D (positive risk of human fetal teratogenicity has been demonstrated). Relative risk associated with the use these medications should be weighed against potential benefits and the likely morbidity and mortality associated with untreated bipolar illness. Treatment should be individualized with collaborative discussion with the patient and her partner and making an informed decision.

31.3.5.3.1 Mood Stabilizers

Lithium

Teratogenic Effect (Class D): (Gentile 2012) The risk of major congenital anomalies in lithium-exposed babies is about 4–12 % compared to 2–4 % in the general population. The use of lithium during the first trimester is associated with the risk of Ebstein anomaly, which is characterized by right ventricular hypoplasia and congenital downward displacement of the tricuspid valve into the right ventricle. Initially, this risk was thought to be approximately 400 times higher than in the general population, but recent epidemiologic data point to a risk of 4.45–7.6/1,000 live births. Report from the registry on 225 lithium babies identified 25 cases of congenital

anomalies (11.1 %) of which 18 babies (8 %) had cardiovascular defects and six (2.7 %) had Ebstein anomaly. Prenatal screening with high-resolution ultrasound and fetal echocardiography is recommended at around 16–18 weeks of gestation to screen for cardiac anomalies in the fetus exposed to lithium.

Pregnancy and delivery outcome: Lithium use during the second and third trimesters of pregnancy has been reported to cause polyhydramnios, premature delivery, thyroid abnormalities including nontoxic goiter and hypothyroidism and nephrogenic diabetes insipidus in the fetus.

Neonatal outcome: The lithium exposed newborn can develop floppy baby syndrome, with lethargy, muscular hypotonia, impaired breathing, and cyanosis. The higher the maternal lithium level, the greater the fetal complications detected.

Long-term neurobehavioral effects: Limited data are available on the neurobehavioral sequelae from lithium exposure during pregnancy. Two small studies (Van der Lugt et al. 2012; Schou 1976) showed normal growth, behavior and development in lithium exposed children indicating that continuing lithium therapy during pregnancy does not pose significant risk to the neurological, cognitive and behavioral development of exposed children.

General guidelines for using lithium: To minimize lithium-induced fetal complications, prescribe the minimum effective dose, use sustained-release lithium in divided doses to avoid peak concentrations, avoid diuretics with lithium, discontinue use of lithium 24 h before delivery and resume use after delivery to prevent postpartum decompensation, and maintain intravenous hydration during labor and delivery. Recent guidelines on the use of lithium during pregnancy suggest gradual tapering of lithium over a period of 2 weeks pre-pregnancy in patients with mild and stable forms of bipolar disorder. In patients with a moderate risk for relapse, tapering, and discontinuing lithium during embryogenesis can be tried. In patients with severe form of illness with multiple episodes of affective instability or who relapse on medication discontinuation, maintaining lithium throughout pregnancy is recommended, as the risk associated with lithium teratogenicity is outweighed by the risk associated with lithium discontinuation and relapse (Cohen et al. 1994; Cohen 2007; Armstrong 2008). Relapse of bipolar disorder during pregnancy is potentially dangerous to both mother and fetus, as it would require aggressive treatment including hospitalization and exposure to multiple psychotropic agents at higher dosages.

Valproic Acid

Teratogenic risk (Class D): The incidence of major congenital malformation is about 11 %. The rates of neural tube defect range from 3 % to 5 %, which is more than 50 times above the base rate of 0.05 % in the general population. This is of particular concern because the formation of the neural tube occurs during the first month of pregnancy, even before the diagnosis of pregnancy is made. Thus, women in their reproductive years who are on valproate should have reproductive counseling before deciding to get pregnant. Other congenital anomalies associated with exposure to valproate include craniofacial abnormalities, cardiovascular malformation, skeletal abnormalities, limb defects, genital anomalies, and CNS structural abnormalities including hydrocephalus. There is also an increased risk for minor malformations with exposure to valproate including rotated ears, flat nasal bridge, fingernail hypoplasia, which tend to disappear over time (Jager-Roman et al. 1986). Specific risk factors for teratogenesis include high maternal daily doses or serum concentrations, low folate level, and exposure to multiple anticonvulsants.

Perinatal toxicity: Perinatal toxicity reported with valproate exposure include intrauterine growth retardation, neonatal hypoglycemia, coagulopathies, neonatal hepatotoxicity, and hyperbilirubinemia and neonatal withdrawal syndrome, with irritability, jitteriness, hypertonia, feeding difficulties, seizures, and vomiting (Ebbesen et al. 2000; Thisted and Ebbesen 1993).

Long-term neurobehavioral effects: Data collected from the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study have shown lower IQs and increased risk of marked intellectual impairment among valproate-exposed children evaluated at 6 years of age (Bromley et al. 2013).

The use of valproate in pregnancy is relatively *contraindicated,* and pregnant women with first trimester exposure to valproate should have a high-resolution fetal sonogram and echocardiogram performed at 16–18 weeks of gestation along with a serum α-fetoprotein level to detect neural tube defects followed by amniocentesis if necessary to detect spina bifida. Supplementation with folic acid 4 mg daily is recommended. Prophylactic vitamin K supplementation 10–20 mg/day in the last month before delivery as well as 1 mg IM vitamin K administered to neonates is recommended because of the potential for valproate-induced coagulopathies. Lower doses of valproate (<1,000 mg/day) with serum levels <70 μg/ml and divided doses may reduce the risk of teratogenicity.

Carbamazepine (Class D)

Carbamazepine has been associated with about 0.5–1.0 % risk of spina bifida. The overall incidence of congenital malformation is about 5.7 %. Common teratogenic effects include microcephaly and other craniofacial defects, fingernail hypoplasia, cardiac abnormalities, coagulopathies, growth retardation, and possible developmental delays (Jones et al. 1989). A higher frequency of congenital anomalies is reported when carbamazepine is administered with valproate. Carbamazepine is relatively contraindicated during the first trimester of pregnancy.

Lamotrigine (Class C)

The risk of malformation with lamotrigine monotherapy during the first trimester, based on data from the lamotrigine pregnancy registry established by the manufacturer, is about 2.5 %. There have been recent reports of increased prevalence of cleft lip and/or cleft palate in infants exposed to lamotrigine during the first trimester of pregnancy.

Topiramate (Class D)

Data from the North American Antiepileptic Drug Pregnancy registry and UK Epilepsy and pregnancy registry show 4–5 % increased risk of major malformation in women exposed to topiramate, with a predominance of oral cleft (11times higher).

31.3.5.3.2 Antipsychotics

First Generation Antipsychotics (FGA) and Second Generation Antipsychotics (SGA)

Teratogenic risk: Antipsychotic medications are classified as FDA class C medications and have been associated with a small possible increase in the risk for birth defects as a whole, with no significant differences in malformation risk between classes and/or single medications. There are reports of increased risk of therapeutic abortions (Mckenna et al. 2005).

Perinatal effects: The use of both SGAs and FGAs during late pregnancy has been associated with increased rates of perinatal complications including low birth weight babies and extrapyramidal symptoms in the newborn. There are several reports of transient extrapyramidal side effects (EPSs), including motor restlessness, tremors, difficulty with oral feeding, hypertonicity, dystonic movements, and parkinsonism in neonates exposed to FGA in utero. But these symptoms are short lived, and infants were noted to have normal motor development. SGAs increase the risk for metabolic syndrome and the complications associated with it. Quetiapine showed the lowest amount of placental passage in a comparative study with both FGAs (haloperidol) and SGAs (risperidone and olanzapine) (Newport et al. 2007).

Reports on long-term neurobehavioral consequences of exposure to antipsychotics are limited and inconclusive.

Clozapine: Clozapine is FDA class B medication. Reproductive studies in animals at doses approximately two to four times the human dose revealed no harm to the fetus. In humans, information on the safety of clozapine in human pregnancies has been available since the early 1990s. Single cases of major malformations, gestational metabolic complications, poor pregnancy outcome, and perinatal adverse reactions associated with exposure to clozapine during various stages of pregnancy have been reported, though solely from case reports

and/or small case series studies (Nguyen and Lalonde 2003; Gentile 2010). The potential for clozapine-induced agranulocytosis warrants monitoring of the white blood count (WBC) in exposed newborns, although there have been no reports of leukopenia or agranulocytosis in such infants.

31.3.5.4 Treatment of Psychosis during Pregnancy

Independent of any safety considerations, treatment of psychosis during pregnancy becomes a psychiatric emergency because of the increased risk for harm to mother and baby. Antipsychotics are frequently administered to control the symptoms. Safety data on the use of FGAs are available for last 40 years and should be preferably used to treat new onset psychotic symptoms during pregnancy. If patients had been on certain antipsychotics before pregnancy, it is preferable to continue the same medication during pregnancy because trying new medication during pregnancy can result in exacerbation of symptoms.

31.3.5.5 Electroconvulsive Therapy During Pregnancy

Electroconvulsive therapy (ECT) is a relatively safe and effective treatment during pregnancy when done in collaboration with a multidisciplinary team and taking steps to minimize potential risks. It is indicated for severe psychotic depression and agitated mania with risk of impulsivity and self-harm.

A study that reviewed 300 case reports from 1942 to 1991 reported complications in 28 of the 300 cases that underwent ECT during pregnancy. These complications included transient benign fetal arrhythmias, mild vaginal bleeding, abdominal pain, self-limited uterine contractions, premature labor, miscarriage, stillbirth and neonatal death, neonatal respiratory distress, and teratogenicity (Miller 1994). Transient hypertension during seizures may increase the risk of abruption (Sherer 1991). Without proper preparation there is an increased likelihood of pulmonary aspiration from delayed gastric emptying during pregnancy, aortocaval compression during later stages of pregnancy, and fetal hypoxia from respiratory alkalosis. Pregnancy may alter the seizure threshold in unpredictable ways. Progesterone-driven hyperventilation with compensatory alkalosis, electrolyte disturbances, sleep disturbance, fatigue, and stress can lower the seizure threshold.

31.3.5.5.1 Effects of Medications Used in ECT

Muscle Relaxants: Succinylcholine, which is used most commonly as a muscle relaxant during ECT, in ordinary doses does not cross placenta in detectable amounts.

Anticholinergic Agents: Atropine or glycopyrrolate is administered before ECT to prevent excessive vagal bradycardia and to decrease oropharyngeal and tracheal secretions. Atropine and to a lesser extent glycopyrrolate quickly cross the placenta and can cause fetal tachycardia and decreased heart rate variability. Glycopyrrolate, because of its minimal effect on fetal heart rate, is preferred during pregnancy. Also these drugs can reduce lower esophageal sphincter tone, thus increasing the risk of regurgitation and aspiration.

Barbiturates: Short-acting barbiturates in doses administered during ECT have no known adverse effect unique to pregnancy.

Preparation for ECT during pregnancy should include a pelvic exam, discontinuation of nonessential anticholinergic medication, monitoring for uterine contractions, intravenous hydration, and administration of nonparticulate antacid. During ECT, elevation of the pregnant woman's right hip, external fetal cardiac monitoring, intubation (if beyond first trimester), and avoidance of excessive hyperventilation are recommended. Recheck for uterine contraction and vaginal bleeding after ECT is administered. Informed consent for ECT should include the patient's capacity to understand and rationally evaluate risks and benefits to herself and the fetus.

31.4 Postpartum Psychiatric Disorders

The postpartum period is a time of increased vulnerability to psychiatric illness in the life cycle of women. About 85 % of women experience some

kind of mood symptoms during this period, but in most cases symptoms are transient and mild. 10–15 % of women experience more severe and disabling symptoms, which, if unrecognized and untreated, can place both the mother and the newborn at risk, have a negative impact on the family as a whole, and have been associated with long-term effects on child development and well-being (Murray 1992).

Postpartum affective illness is clinically indistinguishable from affective illness occurring at other times during a woman's life. The risk for postpartum psychiatric illness is highest during the first 3 months after delivery, but the risk remains high during the first year after delivery.

Postpartum psychiatric disorders include:
Postpartum blues: incidence 50–85 %
Postpartum depression: incidence 10–15 %
Postpartum psychosis: incidence 0.1–0.2 %

31.4.1 Postpartum Blues (PPB), also called "Baby Blues"

This is a common benign, transitory, and self-limited condition occurring during the first 10 days postpartum. It peaks between days 3 and 5. Postpartum blues appear to be a specific affective syndrome associated with childbirth. Symptoms include rapidly fluctuating mood, tearfulness, irritability, anxiety, somatic symptoms, and sleeplessness. The central feature of postpartum blues is the marked lability of mood with increased emotional reactivity to stimuli, such as crying or becoming irritable, profoundly joyful, or sad, in response to stimuli that would normally not provoke such intense reactions.

Relationship to Other Affective Illness: History of depressive episodes, depression during pregnancy, premenstrual depression, family history of depression can increase the risk for PPBs. Women who experience severe postpartum blues have three times greater likelihood of developing postpartum depression (Henshaw et al. 2004).

31.4.1.1 Etiology

Psychosocial Factors: The role of demographic variables, current stressors, obstetric complications, and social support in causing PPBs appears to be minimal. It occurs across all social classes and cultures even though the incidence may vary. Psychosocial factors have been shown to influence the intensity of blues (M'Bailara et al. 2005)

Biologic Factors: The timing of symptoms coincides with a period of dramatic drop in the hormonal level, which points to a physiological cause for PPBs. The abrupt withdrawal of the hormones estrogen and progesterone in the immediate postpartum period may have a direct or indirect effect via neurotransmitters in causing the mood symptoms. It is the magnitude of drop rather than the absolute levels that cause the symptoms. One study found a greater drop in free estriol levels in women who developed postpartum blues compared to women who did not (O'Hara et al. 1991). Mood symptoms may be related to the large drop in the β-endorphin causing an endogenous opioid withdrawal state (Brinsmead et al. 1985). There is evidence of lower levels of free plasma tryptophan, a precursor of serotonin, in the early postpartum period that may trigger the blues in vulnerable women (Bailara et al. 2005).

31.4.1.2 Treatment

No specific treatment is indicated as symptoms are benign and resolve spontaneously. Support and reassurance could help. It usually does not affect the mother's functional ability to care for self and her newborn. If symptoms are severe or prolonged over 2 weeks, blues may indicate the onset of postpartum depression.

31.4.2 Postpartum Depression

The prevalence of postpartum depression (PPD) is 10–15 %. DSM-5 diagnostic criteria for PPD include symptoms of major depression lasting for more than 2 weeks with peripartum onset.

31.4.2.1 Risk Factors

Risk factors for PPD include low socioeconomic status, financial stress, marital discord, inadequate social and spousal support (both emotional and instrumental support), child care stress, stressful life events during pregnancy or early postpartum. Immigrant women who are culturally and physically separated from their support system are at risk for postpartum depression (Dennis et al. 2004). Other risk factors include very young or older age, having twins, a history of premenstrual dysphoric disorder, severe postpartum blues, depressive symptoms during pregnancy, anxiety symptoms during pregnancy, a personal history of mood disorder especially bipolar disorder (risk of recurrence is 30–50 %), a history of postpartum depression (rates of recurrence are as high as 40 %) (Cooper and Murray 1995), a family history of mood disorder, history of recurrent episodes of depression, and discontinuation of antidepressant medications during pregnancy (Robertson et al. 2004).

31.4.2.2 Clinical Features

Onset of symptoms of PPD is insidious within the first 3 months after delivery. Symptoms are more pervasive and interfere with the mother's ability to care for self and her newborn. Symptoms include depressed mood, irritability, tearfulness, emotional lability, sleep disturbance, fatigue, loss of appetite, poor concentration, feelings of inadequacy, guilt, lack of pleasure, lack of interest in the baby, and ambivalent or negative feelings toward the infant. Suicidal ideation is common but suicide attempts are relatively infrequent in women with nonpsychotic depression. Anxiety symptoms are prominent and may present with generalized anxiety disorder, panic disorder, or hypochondriasis. Woman may experience intrusive obsessive ruminations involving the child, often violent in nature, such as thoughts about smothering the baby or dropping the baby down the stairs. These thoughts are ego-dystonic and very distressing, and women appear to go out of their way to ensure their child's safety. Reality testing remains intact. Severity of depression may decrease over time, but in 30 % of women symptoms could persist for as long as 2 years with persistent psychosocial stress.

31.4.2.3 Etiologic Factors

Etiologic considerations of general depression hold in addition to the biology and psychology of the postpartum period.

31.4.2.3.1 Biologic Factors

During pregnancy, levels of estrogen, progesterone, β-endorphin, human chorionic gonadotropin (HCG), and cortisol rise steadily, peaking near term. There is a rapid decline in the levels of these hormones with the removal of the placenta. Estrogen and progesterone levels drop 200-fold, reaching pre-pregnancy levels by the fifth postpartum day. Estrogen and progesterone are known to influence neurotransmitter functions in the brain. The sudden drop in hormones may increase the risk of developing mood symptoms in a subpopulation of women who are vulnerable to changes in hormonal state.

7 % of women develop abnormal thyroid function in the postpartum period, compared to 3–4 % in the general population. Approximately, 12 % of postpartum women have thyroid antibodies, which may be due to a rebound immune phenomenon after the sharp drop in the cortisol levels after delivery. In one study 43 % of antibody-positive women developed depressive symptoms compared to 28 % of antibody-negative women (Harris et al. 1992). Antibody-positive women should be followed with thyroid function testing beyond the postpartum period, as many patients with anti-thyroid antibodies go on to develop overt hypothyroidism within 4 years. Diminished thyroid function may affect postpartum mood through its association with diminished central serotonin activity.

31.4.2.3.2 Psychosocial Factors

Psychosocial variables appear to play a major role in the etiology of postpartum depression. Inadequate social support, marital discord, and stressful life events during pregnancy and around the time of delivery increase the likelihood of postpartum depression (O'Hara 1986).

31.4.2.3.3 Cultural Influences

Culture influences individual's identity, expression of symptoms, the nature of social support and stressors, and the treatment relationship between the patient and the clinicians. Different cultures follow different rites of passage to parenthood, which may include ceremonies, rituals, seclusion, rest, solicitude, and return to the home of origin. A major function of these rituals is to provide support during times of emotional and physical vulnerability. This lessens the likelihood of developing depressive symptoms during the vulnerable period. Migration, individuation, and separation from the family of origin can reduce the social support and increase the emotional burden on both partners in the postpartum period. During assessment, clinicians should ask patients about cultural background, social support network, and traditional antepartum and postpartum practices.

31.4.2.4 Consequences of Untreated Postpartum Depression

Untreated postpartum depression can result in a disturbed mother–infant relationship, *future* psychiatric morbidity in the child (depression, conduct disorder, lower IQ), marital tension, vulnerability to future depression, and suicide/homicide.

A disturbed mother–infant relationship as a result of postpartum depression can result in both short- and long-term consequences. Maternal characteristics including emotional availability, accepting attitude, and responsiveness and sensitivity to the infant's signals and needs are critical during the first year of life. These characteristics result in a secure mother–infant bonding that is associated with a positive outcome in the child. If the mother has postpartum depression, she may have difficulty interacting with her infant, or she may manifest a lack of interest, neglect, negativity toward the infant, and less sensitivity and responsiveness to the infant's needs. Infants of mothers with PPD show decreased eye gaze during feeding, less reciprocity and playfulness with their mothers, limited engagement with the environment, and more muted affective expressions (Feldman et al. 2009).

Long-term effects on children of mothers with postpartum psychiatric illness include behavioral problems, sleep disturbances, feeding problems, and temper tantrums, which may persist over time. Several studies have documented less optimal cognitive development in offspring of mothers with postpartum mood disorder, including lag in developing the concept of object permanence and developmental delays in intellectual functioning. It can also cause social and interpersonal functional impairment, including reduced quality of interaction with their mothers, less sociability with strangers, and insecure attachment patterns (Edhborg et al. 2003; Cicchetti et al. 1998). Exposure to maternal stress, especially postpartum depression early in infancy, predisposes children to increased hypothalamic-pituitary-adrenal axis (HPA) function with an increase in cortisol level during a period of concurrent stress. These children were found to be at increased risk for emotional and behavioral difficulties at the end of the first grade in school (Essex et al. 2002).

31.4.2.5 Course and Prognosis

The duration of postpartum depression is variable. Episodes are often short lived and may last no more than 3 months. Women with a history of recurrent major depressive disorder (MDD) and with severe symptoms can have a more protracted course. Postpartum depression has a good prognosis with early diagnosis and treatment. There is a 40 % risk of recurrence with subsequent childbirth (Wisner et al. 2004a). There is also risk of recurrence of episodes unrelated to pregnancy and childbirth.

Exposure to maternal depression in the early postpartum months may have an enduring influence on the child's psychological development and can cause emotional, behavioral, cognitive, and interpersonal problems later in life.

31.4.2.6 Treatment of Postpartum Depression

Primary Prevention: Primary prevention involves identifying risk factors and taking measures to prevent these factors from causing or contributing to postpartum depression. It includes:

1. Screening for antenatal depression, history of postpartum depression, family history of depression.

2. Screening for other risk factors, such as age, social support, financial status, negative life events.
3. Screening for thyroid antibodies and thyroid function.

Providing continuity of care, education, support groups, continuous early and late antenatal care with additional focus on psychosocial issues, and timely postnatal counseling can help reduce the risk. Brief, group psychotherapy for pregnant, socially disadvantaged women who have one or more risk factors of depression, a single individual psychotherapy session shortly after birth for women who had elevated depressive symptoms, and extended home visits by nurses/midwifes to vulnerable families have all been found to be effective strategies for preventing postpartum depression. Interpersonal therapy has proven efficacious in the prevention of postpartum depression, with focus on role transition, conflict with other role interests, and maladaptive interpersonal patterns (Dennis and Dowswell 2013).

For women with history of recurrent major depression or postpartum depression or depression during pregnancy, prophylactic antidepressant treatment has been found to reduce the recurrence of postpartum major depression (Wisner and Wheeler 1994; Wisner et al. 2004b).

Secondary Prevention: Secondary prevention involves early diagnosis and treatment to minimize the consequences of postpartum depression. Most women do not report their symptoms to health care providers, and less than one third of women with PPD receive any type of intervention. Screening all women for depression during the postpartum period is advisable. The Edinburgh Postnatal Depression Scale is a 10-item self-rated questionnaire that has been used extensively for detection of PPD (Cox et al. 1987) (see Appendix at end of chapter). A score of 12 or more on this scale or an affirmative answer on question 10 (presence of suicidal thoughts) raises concern and indicates the need for more thorough evaluation. It can be integrated in the follow-up obstetric visit at 6 weeks and subsequent pediatric well-baby visits, which can significantly improve the detection of PPD (Chaudron et al. 2004).

Mild to moderate postpartum depression can be managed by psychological interventions like interpersonal therapy, cognitive behavioral therapy, self-help networks, peer and partner support, and nondirective counseling. Other interventions, such as relaxation/massage therapy, exercise, and mother–infant relationship therapy, have also been found to be helpful. Biologic interventions are usually indicated for moderate to severe depression including antidepressant medications, hormone therapy, and ECT.

Interpersonal Therapy: Evidence supports the effectiveness of interpersonal psychotherapy in treating mild to moderate postpartum depression (O'Hara et al. 2000). It also improves social adjustment in these patients and represents an alternative to pharmacotherapy, particularly for women who are breast-feeding. Interpersonal therapy has been found to be effective in both individual and group settings. It is time limited and focuses on role transition, integrating a new role with the established roles, exploring feelings and ambivalence about these roles, assessing satisfaction with relationships, defining patient's expectations of others, and renegotiating relationships.

Cognitive Behavioral Therapy: Cognitive behavioral therapy in individual or group settings has been shown to be effective in treating mild to moderate postpartum depression (Appleby et al. 1997; Prendergast and Austin 2001). It is time limited and focuses on negative thoughts, negative perceptions of self and infant, cognitive restructuring, and behavioral modification.

Other Psychosocial Interventions: Companionship and belonging to a support group have a protective effect on postpartum depression. Support groups, peer and partner support (Dennis 2003), telephone-based peer support, and nondirective or supportive counseling administered by public health nurses and social workers have all been found to be effective in reducing the depressive symptoms of PPD. Similarly, maternal/infant massage therapy, exercise, infant sleep interventions, and mother–infant therapy all hold promise

in reducing the symptoms of postpartum depression (Craig and Howard 2009).

Pharmacotherapy: Pharmacotherapy is indicated for moderate to severe depression. Antidepressant medication, especially SSRIs and some SNRIs, has been shown to be effective in treating postpartum depression in randomized controlled and open-label studies (Yonkers et al 2008; Misri et al. 2004). Women with postpartum depression may take longer to respond to treatment and may require more antidepressant agents at the time of response to treatment (Hendrick et al. 2000). The use of psychotropic medications during breastfeeding should be considered on an individual basis, weighing the risks and benefits of nursing, the risks associated with the exposure of the infant to psychotropic medications and understanding the risks associated with untreated maternal psychiatric illness on the mother, child and family as a whole. General principles and specific classes of drug use in lactating women are discussed at the end of this section.

31.4.3 Postpartum (Puerperal) Psychosis

Postpartum psychosis is a psychotic disorder occurring after childbirth. It is primarily a bipolar affective disorder or a variant of it. Evidence from studies of women with a history of bipolar disorder, longitudinal studies of women with puerperal episodes of psychosis, and family studies supports a link between postpartum psychosis and bipolar disorder (Chaudron and Pies 2003).

31.4.3.1 Epidemiology

One to two per 1,000 postpartum women are affected. A constant incidence rate is reported transculturally (Kumar 1994).

31.4.3.2 Risk Factors

Risk factors for postpartum psychosis include primiparity (70–80 % of index cases occur after first childbirth, 35 times more common in primipara), personal and family history of bipolar disorder, women with history of postpartum psychosis, and women with a history of schizophrenia. Perinatal mortality, obstetrical complications, and lack of partner or social support can also increase the risk for postpartum psychosis (Kendell et al. 1987; Nager et al. 2008; Spinelli 2009)

31.4.3.3 Etiology

Transcultural prevalence and occurrence in primipara suggest that biologic factors play a major role in the onset of postpartum psychosis. Family history of affective illness suggests a genetic predisposition for postpartum psychosis. Hormone withdrawal in the postpartum state can lead to dopamine receptor supersensitivity as estrogen increases dopamine receptor binding. Sleep deprivation in the postpartum period may trigger manic and hypomanic states in vulnerable women (Strouse et al. 1992; Sharma et al. 2004).

31.4.3.4 Clinical Presentation

Postpartum psychosis is the most severe form of postpartum psychiatric illness. The presentation of postpartum psychosis is often abrupt and dramatic, with onset of symptoms during the first 48–72 h after delivery. The majority of women with postpartum psychosis develop symptoms within the first 2 weeks postpartum. Symptoms resemble those of a rapidly evolving mania or mixed state. The earliest signs are restlessness, agitation, irritability, and insomnia. The symptoms are characterized by a mixture of delirium, psychosis with confusion and perplexity, emotional lability, delusions, and hallucinations.

Postpartum psychotic depression presents with depressed mood (worst in the morning), tearfulness, significant psychomotor retardation, sleep disturbances with early morning awakenings, appetite disturbances, preoccupation with feelings of guilt and worthless, delusions of the infant being dead or defective, and even hallucinations commanding the mother to harm the baby. In postpartum mania, the woman is excited, euphoric, grandiose, irritable, hyperactive requires little sleep and may have grandiose delusions about her baby, such as having special powers or that the child is either Satan or God.

Compared with episodes of nonpsychotic depression, women with postpartum psychosis who have thoughts of harming their infants are more likely to act on them, as their reality testing is impaired.

Differential diagnosis includes exacerbation of primary psychiatric disorder, toxic, metabolic, or neurologic causes, such as tumors, head trauma, infection, cerebral embolism, seizures, electrolyte disturbances, anoxia, vitamin deficiencies, thyroiditis, and substance-induced psychosis, including that caused by high doses of prescription drugs or recreational drugs.

31.4.3.5 Prognosis

Rate of infanticide associated with untreated postpartum psychosis is estimated to be as high as 4 %. With adequate treatment 95 % women improve within 2–3 months and have a good functional outcome. A 23-year follow-up study showed an increased risk of subsequent episodes in 75 % of patients with an index puerperal episode, most of them unrelated to childbirth. The risk of puerperal recurrence is as high as 30 % (Robling et al. 2000). Medico-legal issues from infanticide secondary to postpartum psychosis can be complicated, as symptoms may remit by the time patient goes for trial.

31.4.3.6 Treatment of Postpartum Psychosis

Postpartum psychosis is a psychiatric emergency and requires major intervention and in most cases hospitalization. Both psychosocial and pharmacologic interventions are necessary. In most cases symptoms should be treated as an affective psychosis. Acute treatment with a mood stabilizer in addition to antipsychotic medication is indicated. Treatment with a mood stabilizer should extend beyond the resolution of active symptoms to reduce the risk of relapse. The infant's clinical status should be regularly monitored if the mother is breast-feeding. A monotherapy regimen should be maintained if possible to minimize side effects and to reduce delayed development from combination treatment. See Lactation and Psychotropic Medications at the end of the Postpartum Psychiatric Disorders section for specific medications.

Electroconvulsive therapy is well tolerated and can work more rapidly than medication in patients with more severe postpartum depression and postpartum psychosis.

In women with a history of postpartum psychosis or bipolar disorder, prophylactic treatment with lithium or other mood stabilizers instituted either prior to delivery (at 36 weeks gestation) or no later than the first 48 h postpartum is found to significantly reduce the relapse rates as well as to diminish the severity of illness (Cohen et al. 1995; Stewart 1988).

31.4.4 Lactation and Psychotropic Medications

Lactation is a unique event during the postpartum period. If the postpartum woman intends to breast-feed, the amount of drug passing into the breast milk becomes an important issue to consider in selecting a psychotropic medication.

Most psychotropic medications pass into breast milk in varying amounts, mostly through the process of passive diffusion. Factors that determine the amount of diffusion into breast milk include maternal dosing and frequency, and the drug's protein binding, lipid solubility, degree of ionization, and molecular weight. The less protein bound, more lipid soluble and more weakly alkaline the drug, the more likely it is to diffuse into breast milk. The higher lipid content of hind-milk makes it likely that the second half of breast milk will have a higher concentration of maternal medication than the first half.

Infant physiology that determines the bioavailability of the drug includes absorption, metabolism, and elimination of drugs. Infants have higher gastric pH, which increases the absorption of basic compounds. They have low serum protein, which would increase the amount of free drug in circulation. Full-term neonatal cytochrome P-450 activity is approximately one half of that found in adults, decreasing the rate of degradation of the medications. Hepatic enzyme immaturity is even more pronounced in premature infants. The newborn kidney is functionally immature, with a glomerular filtration rate (GFR) and tubular secretion

about 20–30 % of adult function, which result in decreased renal clearance. Medications eliminated through the kidneys tend to accumulate in the infant, causing toxic exposure over time. For full-term infants the GFR seen in adults is achieved between the second and fifth months of life. The newborn blood–brain barrier is not fully developed, and lipid soluble agents can be 10–30 times more concentrated in the cerebrospinal fluid (CSF) than in the serum.

The milk to plasma (M/P) ratio is the ratio of medication concentration in milk to the concentration in maternal serum. Compounds that are weakly protein bound, highly lipid soluble, weakly alkaline, and small in molecular size have a higher M/P ratio. Ratios greater than 1 indicate higher milk level than serum level. The higher the M/P ratio, the greater will be the infant's exposure to the medication. A clear correlation between M/P ratio and clinical status has not been established.

31.4.4.1 Treatment Guidelines during Lactation

Before starting psychotropic medications:

1. Explain the potential risks and benefits, ideally to both parents.
2. Refer for a pediatric evaluation to assess the baby's baseline behavior—sleep, feeding, and alertness.
3. Collaborate with the pediatrician and provide education regarding possible infant side effects and interaction with other medications.

The choice of medication is affected by a number of factors, including diagnosis of psychiatric illness, a past history of treatment response, the side-effect profile of the medication, dosing flexibility, and pharmacokinetic characteristics that minimize accumulation of the medication in milk and infant serum. Factors that minimize infant exposure include minimum effective dose, short acting agents, medications without active metabolites, timing the breast-feeding for when the drug levels in milk are lowest, formula supplementation reducing infant exposure while retaining some breast-feeding benefits, and monitoring infant clinical status monthly to ensure general health and normal pediatric development.

31.4.4.2 Specific Drug Use during Lactation

31.4.4.2.1 Antidepressants

SSRIs

From the available data, (Berle and Spigset 2011; Fitelson et al. 2011) SSRIs comprise a relatively safe group of medications that can be used during lactation for postpartum depression and anxiety. Among the SSRIs, sertraline and paroxetine have a uniformly low or non-detectable infant serum level and a lack of reported adverse effects, which makes them good choices for nursing mothers and are usually recommended as first line agents. Paroxetine may have some disadvantages. If the mother needs long-term treatment and subsequently becomes pregnant again, paroxetine is probably not the first choice due to the risk of cardiac defects. Also, among SSRIs, paroxetine has a higher risk for withdrawal symptoms if one or a few doses are missed.

Fluoxetine has an active metabolite-norfluoxetine, with a long half-life which may result in accumulation of the drug in infant serum. It is recommended that when possible, fluoxetine and citalopram should be avoided or used with caution due to the higher infant plasma levels than for other drugs, with the possible risk of adverse effects which are mostly subtle and unspecific and reverse with the discontinuation of the drug. Excessive crying, irritability, decreased feeding and watery stools have been described in a few cases for fluoxetine. For citalopram, hypotonia, colic, decreased feeding and sleep difficulties have been reported in single cases. However, if the mother has been treated with fluoxetine or citalopram previously and the treatment was effective, or if the mother has used one of these drugs during pregnancy, it could also be used in the postpartum period. For venlafaxine, which also result in relatively high infant serum level, no adverse events have been reported. A single case of seizures has been reported in a 6-month-old breast-fed infant after 4 days of maternal bupropion treatment. Also a single case report of necrotizing enterocolitis in a term infant exposed to escitalopram in utero and in breast milk has been published.

No difference in the infant body weight has been reported in several studies of SSRI exposure

through breast milk compared to values from general population (Hendrick et al. 2003). Long-term neurobehavioral data on infant antidepressant exposure through breast milk are lacking. No detrimental long-term effects have been reported in a few studies for factors such as global intelligence quotient, language, behavioral development and neurological development. Little data exist for drugs such as fluvoxamine, venlafaxine, duloxetine, bupropion, and mirtazapine, and these should not be considered as first-line therapies, but they can be used in special cases.

Routine breast milk and/or infant serum sampling for drug concentration analysis is generally not recommended. Clinical monitoring of the infant is indicated if the infant is sick, premature, or has a low body weight.

Tricyclics

The tricyclic antidepressants (TCAs) are useful in the treatment of postpartum depression when the SSRIs have failed, or when the woman has shown a previous good response to these medications. All TCAs are excreted into human breast milk in low concentrations, and a wide range of infant serum levels has been reported. However, no adverse effects have been documented from exposure to amitriptyline, nortriptyline, imipramine, desipramine or clomipramine. Doxepin has an active metabolite with a long half-life and has been reported to cause sedation and respiratory depression in one nursing infant.

31.4.4.2.2 Benzodiazepines

Benzodiazepines are commonly used to treat anxiety and insomnia associated with depression and as an adjunctive treatment for panic attacks, generalized anxiety and obsessive compulsive disorder and psychosis. Mild to moderate postpartum anxiety could be managed with non-pharmacologic interventions such as CBT, relaxation techniques, and environmental stress reduction. For severe anxiety symptoms benzodiazepines may be indicated. Benzodiazepines should be used with caution in lactation because of the risk of sedation, respiratory depression, and withdrawal symptoms. Low doses of medications with no active metabolites like clonazepam, oxazepam, temazepam, and lorazepam are preferred. However, the long half-life of clonazepam may predispose to accumulation in the infant.

In a prospective study of 124 (Kelly et al. 2012) mothers who used benzodiazepines, mainly lorazepam, clonazepam and midazolam while breast-feeding, central nervous system depression including sleepiness, poor latching, limpness or lack of response to stimuli was reported in 2 infants (1.6 %).

31.4.4.2.3 Mood Stabilizers

Lithium

Lithium is secreted into breast milk and levels achieved are nearly half of maternal serum levels. The neonate may be more vulnerable to lithium toxicity because the kidney is relatively immature with decreased renal clearance and high risk for dehydration. Adverse effects reported with lithium include cyanosis, hypotonia, heart murmur, T-wave changes, restlessness, muscle twitches, lethargy and hypothermia. Mild elevation in BUN/Cr and TSH was reported in one study which returned to normal after breast-feeding was discontinued. Long-term effects of sustained lithium levels on the infant are not known. The American Academy of Pediatrics recommends that breast-feeding be undertaken with caution by women undergoing lithium treatment. In a breast-fed infant exposed to lithium, serum concentrations should be monitored (Yonkers et al. 2004; Viguera et al. 2007).

Anticonvulsants

(Chaudron and Jefferson 2000; Yoshida et al. 1999)

Valproic acid

Valproic acid is considered compatible with breast-feeding because of consistent low levels in the breast milk. There is one report of thrombocytopenia and anemia in an infant exposed to mother on valproate. Recent reports on the neurodevelopmental effects, from in utero exposure to valproic acid, increase concern about the long-term effects of valproic acid exposure from lactation on the infant brain. If a nursing mother is taking valproic acid, it is important to monitor maternal and infant serum drug levels and liver function tests every 2 to 4 weeks, or more frequently as indicated by the clinical situation.

Carbamazepine

Carbamazepine is considered compatible with breast-feeding because of low level detected in breast milk. There are two case reports of transient direct hyperbilirubinemia and high concentrations of gamma-glutamyltransferase (GGT). Infants in both cases were exposed to carbamazepine during both pregnancy and through breast milk therefore it is unclear as to whether the adverse effects were the result of in-utero or breast milk exposure. Infants exposed to carbamazepine should be monitored for possible hepatic complications. Maternal and infant serum drug levels and liver function tests should be monitored every 2–4 weeks, or more frequently as indicated by the clinical situation.

Lamotrigine

Lamotrigine is excreted in considerable quantities (60 %) into human breast milk (Newport et al. 2008; Ohman and Vitols 2000; Tomson et al. 1997). Infant serum levels were approximately one-third of maternal levels. None of the infants in these case reports displayed adverse effects. However, lamotrigine has been linked to severe life threatening rashes in children who are treated directly with the drug, and there is a theoretical concern that infants exposed during breast-feeding may also be at risk. Thus, infants exposed to this medication should be observed closely for side effects.

31.4.4.2.4 Antipsychotics

Among the typical antipsychotics haloperidol is excreted in relatively high amounts in breast milk, but also has been shown to have no adverse effects on the infant (Whalley et al. 1981). Chlorpromazine exposure has been associated with drowsiness and lethargy in one infant (Wiles et al. 1978). In one study of seven infants with exposure to chlorpromazine through breast milk, there were no adverse effects reported at 16-month and 5-year follow-up evaluations. Another study showed that infants exposed to haloperidol and chlorpromazine through breast milk exhibited developmental delays at 12–18 months of age (Yoshida et al. 1998a). It is unclear if these delays were due to medication exposure or other factors.

Among the atypical antipsychotics, case reports on risperidone exposure found serum levels to be low to undetectable (Ilett et al. 2004). No adverse effects in any of the exposed infants were reported. With olanzapine exposure, serum levels were low to undetectable in the small number studied. Most infants showed no adverse effects (Croke et al. 2002). In one infant exposed to olanzapine, there was a report of cardiomegaly, jaundice, and sedation. Case reports from quetiapine exposure, breast milk levels were found to be low and there were no reported adverse effects in the exposed infants (Lee et al. 2004). One case report from Clozapine exposure found relatively high accumulation in breast milk (Barnas et al. 1994). Another report attributed delayed speech acquisition to clozapine, after the mother was treated with clozapine both prenatally and during breast-feeding (Mendhekar 2007). Although no cases have been reported of a granulocytosis in nursing infants, it is a theoretical risk.

In a recent meta-analysis (Klinger et al. 2013) of 4 prospective studies, 12 case series, 28 case reports, and 1 pharmaceutical registry, infant outcomes focused on long-term outcome from antipsychotic exposure from breast-feeding. Among 21 antipsychotic drugs used in clinical practice, 7 have no data at all regarding breast-feeding and 6 have data based only on few infant exposures. Only few prospective studies assessing use of haloperidol, chlorpromazine, and olanzapine during breast-feeding were identified. Olanzapine and quetiapine were categorized as acceptable for breast-feeding. Chlorpromazine, haloperidol, and risperidone were categorized as possible for breast-feeding under medical supervision. Breast-feeding cannot be currently recommended for the following medications: aripiprazole, asenapine, clozapine, droperidol, fluphenazine, flupenthixol, iloperidone, lurasidone, paliperidone, perphenazine, pimozide, trifluoperazine, thiothixene, and ziprasidone.

31.4.4.2.5 Hormonal Interventions

Progesterone use has not been supported by randomized controlled studies. Some reports suggest worsening of mood symptoms with synthetic progesterone (Lawrie et al. 1998).

Postpartum estrogen treatment has shown some beneficial effect. Transdermal patch of 17β-estradiol was found to be effective in one double blind placebo-controlled trial ($n=61$)

(Gregoire and Kumar 1996) and sublingual 17β-estradiol was found to be effective in one open-label study ($n=23$) (Ahoka et al. 2001). Effective dosing and the route of administration include using a 200 μg transdermal patch, changed twice weekly, or 1 mg sublingually four times a day. Side effects include changes in breast milk production, thromboembolic events, and endometrial hyperplasia. Efficacy and safety relative to antidepressants have not been established.

31.4.4.2.6 Electroconvulsive Therapy

No randomized controlled trials exist on the use of ECT in postpartum women. It has been advocated by several researchers as an effective treatment option. It is used more commonly in severe drug-resistant psychotic depression. It also has a positive advantage in breast-feeding mothers who do not want to expose their infants to antidepressant medications.

31.4.4.3 Conclusion

The postpartum period increases vulnerability for the development of major psychiatric illness in some women. The consequences of untreated postpartum depression and psychosis can be devastating for the mother, the newborn, and other family members. Screening for risk factors and symptoms can be incorporated into the already existing prenatal and postnatal clinic visits. Instituting effective pharmacologic and nonpharmacologic interventions may limit both maternal and infant morbidity and mortality.

31.5 Special Topics

31.5.1 Hyperemesis Gravidarum

70–85 % of pregnant women develop nausea and vomiting during early pregnancy. In 10 % of these women symptoms may persist throughout pregnancy. Hyperemesis gravidarum is a severe form of nausea and vomiting seen in 0.3–2.3 % of all pregnancies. The condition is defined as uncontrolled vomiting requiring hospitalization for severe dehydration, muscle wasting, electrolyte imbalance (hyponatremia, hypokalemia), low serum urea, ketonuria, and weight loss of more than 5 % of body weight. The symptoms usually peak at 9 weeks of gestation and subside by approximately 20 weeks of gestation. Women who experienced hyperemesis in their first pregnancy have a high risk for recurrence (Trogstad et al. 2005). It can result in a negative pregnancy outcome and can cause considerable distress and disability to the pregnant woman and her family.

Multiple gestation, gestational trophoblastic disease, triploidy, Down syndrome, and hydrops fetalis have been associated with an increased incidence of hyperemesis gravidarum. Multiple medical conditions have been found to play a role in causing or contributing to hyperemesis gravidarum, including gastrointestinal disorders, genitourinary tract diseases, metabolic disorders, neurologic disorders, pregnancy-related conditions like acute fatty liver of pregnancy and preeclampsia, and drug toxicity or intolerance (Quinlan and Hill 2003; Philip 2003)

Negative maternal outcomes associated with hyperemesis gravidarum include splenic avulsion, esophageal rupture, Mallory-Weiss tears, pneumothorax, peripheral neuropathy, and preeclampsia. If not appropriately treated, it may even cause severe adverse effects, including Wernicke encephalopathy, central pontine myelinolysis, and even maternal death.

Negative fetal outcomes include fetal growth retardation, small for gestational age, premature birth, lower birth weight, and low Apgar scores. There are also reports of congenital malformations such as undescended testes, hip dysplasia, Down syndrome, and increased incidence of CNS malformation. Untreated electrolyte disturbance, malnutrition, and maternal weight loss may be the cause for these congenital malformations.

Management of the nausea and vomiting of pregnancy depends on the severity of symptoms and can range from dietary modifications, acupressure, hypnosis, vitamin supplements (pyridoxine), herbal remedies (ginger), and antihistamines (doxylamine) to more aggressive treatments including hospitalization, intravenous fluids, antiemetics (metaclopromide, promethazine, dimenhydrinate, ondansetron), steroids (methylprednisolone), and total parenteral nutrition (Wegrzyniak et al. 2012). There are case reports of positive response to mirtazapine in IV

fluids in treatment resistant cases of hyperemesis gravidarum (Guclu et al. 2005; Leib et al. 2012).

Referral for psychiatric consultation is usually made in cases of repeated hospitalization, multiple medication failures, and presence of significant psychosocial stressors. The role of the psychiatric consultant involves evaluation of the underlying psychosocial stressors, depression, anxiety, or other psychiatric conditions that could be contributing to or worsening the physical symptoms. Appropriate management of the psychiatric comorbidity with medications, weighing the risks and benefits, facilitating support from the staff, family, friends, and support network, and working collaboratively with the treating primary physician can help to alleviate the symptoms.

31.5.2 Fetal Demise

Miscarriage is the most common complication of pregnancy. About one fifth of clinically confirmed pregnancies abort spontaneously. Most women react to this unexpected loss with sorrow and grief. Studies have shown that 22–44 % of these women develop clinically significant levels of depression and anxiety (Thapar and Thapar 1992). Risk for an episode of major depressive disorder among miscarrying women in the 6 months following loss is about 10.9 % compared with 4.3 % of community women (Neugebauer et al. 1997). A majority of women have intense feelings of grief, guilt, and anxiety immediately following miscarriage, which wanes within 4–6 weeks, but some symptoms may persist for longer periods. Miscarriage may represent loss of a pregnancy, a baby, a future child, loss of motherhood, loss of self-esteem, and doubts regarding ability to reproduce. Some women feel responsible for the miscarriage, blame themselves for the loss, and feel excessive guilt and shame.

Clinicians should be aware of the psychological sequelae associated with miscarriage and should provide support and follow-up, as well as access to formal counseling when necessary. Intervention should be focused on grief counseling, support to patients and families, and providing them access to resources in the community. Screening for depression and anxiety initially and at follow-up visits using a general health questionnaire or the Edinburg Postnatal Depression Scale could help with early diagnosis of major psychiatric illness and prompt intervention (Lee et al. 1997).

31.6 Role of Consultation Liaison (CL) Psychiatrist in OB & Gyn Setting

Prevalence of mental disorders in Ob/Gyn practice range from 20 % to 38 % for any psychiatric or substance abuse disorder. Higher rates found in clinics serving low income women. Only 23 % of women diagnosed with depression are adequately treated (Kelly et al. 2001). The CL Psychiatrist can play a major role in consulting and teaching medical students, residents, nursing, and other ancillary staff in recognizing and screening for psychiatric disorders and also to provide supportive care and education to this patient population.

Consultations from the Ob & Gyn service are frequently requested for blunted/flat/odd affect in a pregnant or postpartum woman, lack of bonding with the newborn, bizarre behaviors, depression, anxiety, psychosis, suicidal and homicidal thoughts, suicide attempts, being a victim of abuse or domestic violence, substance abuse, frequent admissions for hyperemesis gravidarum, fetal demise, history of psychiatric diagnosis and psychiatric hospitalization, history of being on psychotropic medications, safety of psychiatric medications during pregnancy and postpartum, involvement of child protective service, safety of the newborn to be discharged with the mother, chronic pain issues and legal/ethical issues related to noncompliance with treatment and capacity to make decisions. Because of the intensity of psychosocial issues involved in these cases collaboration and participation in family meetings, interdisciplinary and ethics committee meetings are sometimes indicated and can help to collaborate care and provide appropriate interventions in a timely manner. This can be a valuable teaching and learning experience.

31.7 Appendix: Postnatal Depression Scale

Edinburgh Postnatal Depression Scale[1] (EPDS)

Postpartum depression is the most common complication of childbearing.[2] The 10-question Edinburgh Postnatal Depression Scale (EPDS) is a valuable and efficient way of identifying patients at risk for "perinatal" depression. The EPDS is easy to administer and has proven to be an effective screening tool.

Mothers who score above 13 are likely to be suffering from a depressive illness of varying severity. The EPDS score should not override clinical judgment. A careful clinical assessment should be carried out to confirm the diagnosis. The scale indicates how the mother has felt ***during the previous week***. In doubtful cases it may be useful to repeat the tool after 2 weeks. The scale will not detect mothers with anxiety neuroses, phobias or personality disorders.

Women with postpartum depression need not feel alone. They may find useful information on the web sites of the National Women's Health Information Center <www.4women.gov> and from groups such as Postpartum Support International <www.chss.iup.edu/postpartum> and Depression after Delivery <www.depressionafterdelivery.com>.

SCORING

QUESTIONS 1, 2, & 4 (without an *)
Are scored 0, 1, 2 or 3 with top box scored as 0 and the bottom box scored as 3.

QUESTIONS 3, 5-10 (marked with an *)
Are reverse scored, with the top box scored as a 3 and the bottom box scored as 0.

Maximum score: 30
Possible Depression: 10 or greater
Always look at item 10 (suicidal thoughts)

Instructions for using the Edinburgh Postnatal Depression Scale:

1. The mother is asked to check the response that comes closest to how she has been feeling in the previous 7 days.
2. All the items must be completed.
3. Care should be taken to avoid the possibility of the mother discussing her answers with others. (Answers come from the mother or pregnant woman.)
4. The mother should complete the scale herself, unless she has limited English or has difficulty with reading.

[1]Source: Cox, J.L., Holden, J.M., and Sagovsky, R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 150:782-786.

[2]Source: K. L. Wisner, B. L. Parry, C. M. Piontek, Postpartum Depression N Engl J Med vol. 347, No 3, July 18, 2002, 194-199

References

Ahoka, A., Kaukoranta, J., Wahlbeck K., Aito M. (2001). Estrogen deficiency in severe PPD: Successful treatment with sublingual physiologic 17 beta estradiol: A preliminary study. *Journal of Clinical Psychiatry, 62*, 5.

Altshuler, L. L., Cohen, L., Szuba, M. P., Burt, V. K., Gitlin, M., Mintz, J. (1996). Pharmacologic management of psychiatric illness in pregnancy: Dilemmas and guidelines. *The American Journal of Psychiatry, 153*, 592–606.

Appleby, L. (1991). Suicide during pregnancy and in the first postnatal year. *British Medical Journal, 302*, 137–140.

Appleby, L., Warner, R., Whitton, A., & Faragher, B. (1997). A controlled study of fluoxetine and cognitive-behavioural counseling in the treatment of postnatal depression. *BMJ, 314*, 932–936.

Armstrong, C. (2008). ACOG guidelines on psychiatric medication use during pregnancy and lactation. *American Family Physician, 78*(6), 772–778.

Arnold, L. M. (2003). Gender differences on bipolar disorder. *Psychiatric Clinics of North America, 26*(3), 595–620.

Ashby, C., Jr., Carr, L. A., Cook, C. L., Steptoe, M. M., Franks, D. D. (1988). Alteration of platelet serotonergic mechanism and monoamine oxidase activity in premenstrual syndrome. *Biological Psychiatry, 24*(2), 225–233.

Avis, N. E., Brambilla, D., McKinlay, S. M., Vass, K. (1994a). A longitudinal analysis of the association between menopause and depression. Results from the Massachusetts Women's Health Study. *Annals of Epidemiology, 4*(3), 214–220.

Backstrom, T., Andreen, L., Birzniece, V., Bjorn, I., Johansson, I. M., Nordenstam-Haghjo, M., Nyberg, S., Sundstrom-Poromaa, I., Wahlstrom, G., Wang, M., Zhu, D. (2003). The role of hormones and hormonal treatments in premenstrual syndrome. *CNS Drugs, 17*(5), 325–342.

Bailara, K. M., Henry, C., Lestage, J., Launay, J. M., Parrot, F., Swendsen, J., Sutter, A. L., Roux, D., Dallay, D., Demotes-Mainard, J. (2005). Decreased brain tryptophan availability as a partial determinant of postpartum blues. *Psychoneuroendocrinology, 31*(3), 407–413. Epub November 21, 2005.

Baller, E. B., Wei, S. M., Kohn, P. D., Rubinow, D.R., Alarcón G, Schmidt, P. J., Berman, K.F. (2013). Abnormalities of dorsolateral prefrontal function in women with premenstrual dysphoric disorder: A multimodal neuroimaging study. *The American Journal of Psychiatry, 170*(3), 305–314.

Barnas, C., Bergant, A., Hummer, M., Saria, A., & Fleischhacker, W. W. (1994). Clozapine concentrations in maternal and fetal plasma, amniotic fluid, and breast milk. *The American Journal of Psychiatry, 151*(6), 945.

Beck, C. T. (2004). PTSD due to childbirth:The Aftermath. *Nursing Research, 53*(4), 216–224.

Berle, J., & Spigset, O. (2011). Antidepressant Use During Breastfeeding. *Current Women's Health Reviews, 7*(1), 28–34.

Borenstein, J. E., Dean, B. B., Endicott, J., Wong, J., Brown, C., Dickerson, V., Yonkers, K. A. (2003). Health and economic impact of the premenstrual syndrome. *Journal of Reproductive Medicine, 48*(7), 515–524.

Brinsmead, M., Smith, R., Singh, B., Lewin, T., & Owens, P. (1985). Peripartum concentrations of beta endorphin and cortisol and maternal mood states. *The Australian & New Zealand Journal of Obstetrics & Gynaecology, 25*(3), 194–197.

Bromley, R., Mawer, G. E., Briggs, M., Cheyne, C., Clayton-Smith, J., Garcia-Finana, M., Kneen, R., Lucas, S. B., Shallcross, R., Baker, G. A. (2013). The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *Journal of Neurology, Neurosurgery and Psychiatry, 84*(6), 637–643.

Casper, R. C. (2003). Fleisher BE, et al; Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. *Journal of Pediatrics, 142*(4), 402–408.

Chambers, C. D., Hernandez-Diaz, S., Van Marter, L. J., Werler, M. M., Louik, C., Jones, K. L., Mitchell, A. A. (2006). Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *New England Journal of Medicine, 354*, 579–587.

Chaudron, L. (2013). Complex challenges in treating depression during pregnancy. *The American Journal of Psychiatry, 170*, 12–20.

Chaudron, L., & Jefferson, J. (2000). Mood stabilizers during breastfeeding: A review. *Journal of Clinical Psychiatry, 61*, 79–90.

Chaudron, L., & Pies, R. (2003). The relationship between postpartum psychosis and bipolar disorder: A review. *Journal of Clinical Psychiatry, 64*, 1284–1292.

Chaudron, L., Szilagyi, P. G., Kitzman, H., Wadkins, H. I., Conwell, Y. (2004). Detection of postpartum depressive symptoms by screening at well-child visits. *Pediatrics, 113*(3), 551–558.

Cicchetti, D., Rogosch, F., & Toth, S. (1998). Maternal depressive disorder and contextual risk: Contributions to the development of attachment insecurity and behavior problems in toddlerhood. *Development and Psychopathology, 10*, 283–300.

Cohen, L. S. (2007). Treatment of bipolar disorder during pregnancy. *Journal of Clinical Psychiatry, 68*(suppl 9), 4–9.

Cohen, L., Friedman, J. M., Jefferson, J., Johnson, E. M., Weiner, M. L. (1994). A re-evaluation of risk of in utero exposure to lithium. *JAMA, 271*, 146–150.

Cohen, L., Nonacs, R. M., Bailey, J. W., Viguera, A. C., Reminick, A. M., Altshuler, L. L., Stowe, Z. N., Faraone, S. V. (2004). Relapse of depression during pregnancy following antidepressant discontinuation: A preliminary prospective study. *Archives of Women's Mental Health, 7*, 217–221.

Cohen, L., Sichel, D., Robertson, L., Heckscher, E., Rosenbaum, J. F. (1995). Postpartum prophylaxis for women with bipolar disorder. *The American Journal of Psychiatry, 152*, 1641–1645.

Cohen, L. S., Soares, C. N., Vitonis, A. F., Otto, M. W., Harlow, B. L. (2006). Risk for new onset of depression during the menopausal transition: The Harvard Study of Moods and Cycles. *Archives of General Psychiatry, 63*(4), 385–390.

Cooper, P., & Murray, L. (1995). Course and recurrence of postnatal depression. *British Journal of Psychiatry, 166*, 191–195.

Cox, J. L., Holden, J. M., & Sagovsky, R. (1987). Detection of postnatal depression: Development of the 10–item Edinburgh Postnatal Depression scale. *British Journal of Psychiatry, 150*, 782–786.

Craig, M., & Howard, L. (2009a). Postnatal depression. *Clinical Evidence (Online), 2009*.

Croen, L. A., Grether, J. K., Yoshida, C. K., Odouli, R., Hendrick, V. (2011). Antidepressant use during pregnancy and childhood autism spectrum disorders. *Archives of General Psychiatry, 68*(11), 1104–1112.

Croke, S., Buist, A., Hackett, L. P., Ilett, K. F., Norman, T. R., & Burrows, G. D. (2002). Olanzapine excretion in human breast milk: Estimation of infant exposure. *International Journal of Neuropsychopharmacology, 5*(3), 243.

Dante, G., & Facchinetti, F. (2011a). "Herbal treatments for alleviating premenstrual symptoms: A systematic review. *Journal of Psychosomatic Obstetrics and Gynaecology, 32*(1), 42–51.

Dennis, C. (2003). The effect of peer support on PPD: A pilot randomized controlled trial. *Canadian Journal of Psychiatry, 48*(2), 115–124.

Dennis, C. L., & Dowswell, T. (2013). Psychosocial and psychological interventions for preventing postpartum depression. *Cochrane Database of Systematic Reviews, 2*, CD001134.

Dennis, C. L., Janssen, P. A., Singer, J. (2004a). Identifying women at-risk for postpartum depression in the immediate postpartum period. *Acta Psychiatrica Scandinavica, 110*(5), 338–346.

DeVera, M. A., & Berard, A. (2012). Antidepressant use during pregnancy and the risk of pregnancy-induced hypertension. *British Journal of Clinical Pharmacology, 74*(2), 362–369.

Ebbesen, F., Joergensen, A., Hoseth, E., Kaad, P. H., Moeller, M., Holsteen, V., Rix, M. (2000). Neonatal hypoglycemia and withdrawal symptoms after exposure in utero to valproate. *Archives of Disease in Childhood (Fetal and Neonatal Ed), 83*, F124–F129.

Edhborg, M., Lundh, W., Seimyr, L., Widstrom, A. M. (2003). The parent-child relationship in the context of maternal depressive mood. *Archives of Women's Mental Health, 6*, 211–216.

Eskandari, F., Martinez, P. E., Torvik, S., Phillips, T. M., Sternberg, E. M., Mistry, S., Ronsaville, D., Wesley, R., Toomey, C., Sebring, N. G., Reynolds, J. C., Blackman, M. R., Calis, K. A., Gold, P. W., Cizza, G. (2007a). Low bone mass in premenopausal women with depression. *Archives of Internal Medicine, 167*(21), 2329–2336.

Essex, M., Klein, M., Cho, E., Kalin, N. H., (2002). Maternal stress beginning in infancy may sensitize children to later stress exposure: Effects on cortisol and behavior. *Biological Psychiatry, 52*, 776–784.

Feldman, R., Granat, A., Pariente, C., Kanety, H., Kuint, J., Gilboa-Schechtman, E. (2009a). Maternal depression and anxiety across the postpartum year and infant social engagement, fear regulation, and stress reactivity. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(9), 919–927.

Fitelson, E., Kim, S., Baker, A. S., & Leight, K. (2011). Treatment of postpartum depression: Clinical, psychological and pharmacological options. *International Journal of Women's Health, 3*, 1–14.

Freeman, E. W., Sammel, M. D., Lin, H., Nelson, D. B. (2006). Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Archives of General Psychiatry, 63*(4), 375–382.

Gaynes, B. N., Gavin, N., Meltzer-Brody, S., Lohr, K. N., Swinson, T., Gartlehner, G., Brody, S., Miller, W. C. (2005a). Perinatal depression: Prevalence, screening accuracy, and screening outcomes. *Evidence Report/ Technology Assessment (Summary), 119*, 1–8.

Gentile, S. (2008). Pregnancy exposure to serotonin reuptake inhibitors and the risk of spontaneous abortions. *CNS Spectrums, 13*, 960–966.

Gentile, S. (2010). Antipsychotic therapy during early and late pregnancy: A systematic review. *Schizophrenia Bulletin, 36*(3), 518–544.

Gentile, S. (2012). Lithium in Pregnancy: The need to treat, the duty to ensure safety. *Expert Opinion on Drug Safety, 11*(3), 425–437.

Gotlib, I., Whiffen, V. E., Mount, J. H., Milne, K., Cordy, N. I. (1989). Prevalence rates and demographic characteristics associated with depression in pregnancy and the postpartum. *Journal of Consulting and Clinical Psychology, 57*(2), 269–274.

Gregoire, A. J. P., & Kumar, R. (1996). Transdermal estrogen for treatment of severe postpartum depression. *Lancet, 347*, 930–933.

Grigoriadis, S., VonderPorten, E. H., Mamisashvili, L., Roerecke, M., Rehm, J., Dennis, C. L., Koren, G., Steiner, M., Mousmanis, P., Cheung, A., Ross, L. E. (2013a). Antidepressant exposure during pregnancy and congenital malformations: Is there an association? A systematic review and meta-analysis of best evidence. *Journal of Clinical Psychiatry, 74*(4), e293–e308.

Grigoriadis, S., VonderPorten, E. H., Mamisashvili, L., Eady, A., Tomlinson, G., Dennis, C. L., Koren, G., Steiner, M., Mousmanis, P., Cheung, A., Ross, L. E. (2013b). The effect of prenatal antidepressant exposure on neonatal adaptation: A systematic review and meta-analysis. *Journal of Clinical Psychiatry, 74*(4), e309–e320.

Guclu, S., Gol, M., Dogan, E., Saygili, U. (2005). Mirtazapine use in resistant hyperemesis gravidarum:

Report of three cases and review of the literature. *Archives of Gynecology and Obstetrics, 272*(4), 298–300.

Harris, B., Othman, S., Davies, J. A., Weppner, G. J., Richards, C. J., Newcombe, R. G., Lazarus, J. H., Parkes, A. B., Hall, R., Phillips, D. I. (1992). Association between postpartum thyroid dysfunction and thyroid antibodies and depression. *British Medical Journal, 305*(6846), 152–156.

Hendrick, V., Smith, L., Hwang, S., Altshuler, L. L., Haynes, D. (2003). Weight gain in breastfed infants of mothers taking antidepressant medication. *Journal of Clinical Psychiatry, 64*, 410–412.

Hendrick, V., Altshuler, L., Strouse, T., Grosser, S. (2000). Postpartum and nonpostpartum depression: Differences in presentation and response to pharmacologic treatment. *Depression Anxiety, 11*, 66–72.

Henshaw, C., Foreman, D., & Cox, J. (2004). Postnatal blues: A risk factor for postnatal depression. *Journal of Psychosomatic Obstetrics, 25*(3–4), 267–272.

Heron, J., O'Connor, T., Evans, J., Golding, J., Glover, V. (2004). The course of anxiety and depression through pregnancy and the postpartum in a community sample. *Journal of Affective Disorders, 80*, 65–73.

Hunter, M. S., Ussher, J. M., Browne, S. J., Cariss, M., Jelley, R., Katz, M. (2002). A randomized comparison of psychological (cognitive behaviour therapy), medical (fluoxetine) and combined treatment for9women with premenstrual dysphoric disorder. *Journal of Psychosomatic Obstetrics and Gynaecology, 23*(3), 193–199.

Huo, L., Straub, R. E., Roca, C., Schmidt, P. J., Shi, K., Vakkalanka, R., Weinberger, D. R., Rubinow, D. R. (2007). Risk for premenstrual dysphoric disorder is associated with genetic variation in ESR1, the estrogen receptor alpha gene. *Biological Psychiatry, 62*(8), 925–933.

Huot, R., Brennan, P. A., Stowe, Z. N., Plotsky, P. M., Walker, E. F. (2004). Negative affect in offspring of depressed mothers is predicted by infant cortisol levels at 6 months and maternal depression during pregnancy, but not postpartum. *Annals of the New York Academy of Sciences, 1032*, 234–236.

Ilett, K. F., Hackett, L. P., Kristensen, J. H., Vaddadi, K. S., Gardiner, S. J., & Begg, E. J. (2004). Transfer of risperidone and 9-hydroxyrisperidone into human milk. *Annals of Pharmacotherapy, 38*(2), 273.

Jacka, F. N., Pasco, J. A., Henry, M. J., Kotowicz, M. A., Dodd, S., Nicholson, G. C., Berk, M. (2005). Depression and bone marrow density in a community sample of perimenopausal women: Geelong Osteoporosis Study. *Menopause, 12*(1), 88–91.

Jager-Roman, E., Deichi, A., Jakob, S., Hartmann, A. M., Koch, S., Rating, D., Steldinger, R., Nau, H., Helge, H. (1986). Fetal growth, major malformations and minor anomalies in infants born to women receiving valproic acid. *Journal of Pediatrics, 108*, 997–1004.

Jones, K. L., Lacro, R., Johnson, K. A., Adams, J. (1989). Pattern of malformations in the children of women treated with carbamazepine during pregnancy. *New England Journal of Medicine, 320*, 1661–1666.

Jovanovic, H., Cerin, A., Karlsson, P., Lundberg, J., Halldin, C., Nordstrom, A. L. (2006). A PET study of 5-HT1A receptors at different phases of the menstrual cycle in women with premenstrual dysphoria. *Psychiatry Research, 148*(2–3), 185–193.

Kelly, L. E., Poon, S., Madadi, P., Koren, G. (2012). Neonatal benzodiazepines exposure during breastfeeding. *Journal of Pediatrics, 161*(3), 448–451.

Kelly, R., Zatzick, D., Anders, T. (2001). The detection and treatment of psychiatric disorders and substance use among pregnant women cared in Obstetrics. *The American Journal of Psychiatry, 158*, 213–219.

Kendell, R. E., Chalmers, J. C., Platz, C. (1987a). Epidemiology of puerperal psychoses. *British Journal of Psychiatry, 150*, 662–673.

Khan, A. Y., Ludvigson, L. Stewart, M., Gorman, J. M., Stewart, M., Gorman, J. M., Stewart, M., Gorman, J. M., Stewart, M., Gorman, J. M.. (2007a). Menopause manifesting as bipolar symptoms. *Journal of Psychiatric Practice, 13*(5), 339–342.

Kieler, H., Artama, M., Engeland, A., Ericsson, O., Furu, K., Gissler, M., Nielsen, R. B., Norgaard, M., Stephansson, O., Valdimarsdottir, U., Zoega, H.. (2012). Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: Population based cohort study from the five Nordic countries. *BMJ, 344*, d8012.

Klatzkin, R. R., Morrow, A. L., Light, K. C., Pedersen, C. A., Girdler, S. S. et al. (2006). History of depression, allopregnanolone responses to stress, and premenstrual symptoms in women. *Biol Psychol, 71*(1), 2–11.

Klinger, G., Stahl, B., Fusar-Poli, P., Merlob, P. (2013). Antipsychotic drugs and breastfeeding. *Pediatr Endocrinol Rev, 10*(3), 308–17.

Koutra, K., Vassilaki, M., Georgiou, V., Koutis, A., Bitsios, P., Chatzi, L., Kogevinas, M. (2014). Antenatal maternal mental health as determinant of postpartum depression in a population based mother-child cohort (Rhea Study) in Crete, Greece. *Social Psychiatry and Psychiatric Epidemiology, 49*(5), 711–721.

Kumar, R. (1994a). Postnatal mental illness: A transcultural perspective. *Social Psychiatry and Psychiatric Epidemiology, 29*(6), 250–264.

Lawrie, T., Hofmeyr, G. J., Jager, M., Berk, M., Paiker, J., Viljoen, E. (1998). A double blind randomized placebo controlled trial of postnatal northisterone enanthate: The effect on postnatal depression and serum hormones. *British Journal of Obstetrics and Gynaecology, 105*, 1082–1090.

Lee, A., Geisbrecht, E., Dunn, E., & Ito, S. (2004). Excretion of quetiapine in breast milk. *The American Journal of Psychiatry, 161*(9), 1715–1716.

Lee, D. T. S., Wong, C. K., Cheung, L. P., Leung, H. C., Haines, C. J., Chung, T. K. (1997). Screening psychiatric morbidity after miscarriage: Application of the 30–item GHQ and EPDS. *Psychosomatic Medicine, 59*, 207–210.

Leib, M., Palm, U., Jacoby, D., Baghai, T.C., Severus, E. (2012). Mirtazapine and hyperemesis gravidarum. *Nervenarzt, 83*(3), 374–376.

M'Bailara, K., Swendsen, J., Glatigny-Dallay, E., Dallay, D., Roux, D., Sutter, A. L., Demotes-Mainard, J., Henry, C. (2005). Baby blues: Characterization and influence of psychosocial factors. *Encephale, 31*(3), 331–336.

Marjoribanks, J., Brown, J., O'Brien, P. M., & Wyatt, K. (2013). Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane Database of Systematic Reviews, 6*, CD001396.

Marzuk, P., Tardiff, D., Leon, A. C., Hirsch, C. S., Portera, L., Hartwell, N., Iqbal, M. I. (1997). Lower risk of suicide during pregnancy. *The American Journal of Psychiatry, 154*, 122–123.

McElhatton, P. (1994). The effects of benzodiazepine use during pregnancy and lactation. *Reproductive Toxicology, 8*(6), 461–475.

Mckenna, K., Koren, G., Tetelbaum, M., Wilton, L., Shakir, S., Diav-Citrin, O., Levinson, A., Zipursky, R. B., Einarson, A. (2005). Pregnancy outcome of women using atypical antipsychotic drugs: A prospective comparative study. *Journal of Clinical Psychiatry, 66*, 444–449.

Mendhekar, D. N. (2007). Possible delayed speech acquisition with clozapine therapy during pregnancy and lactation. *Journal of Neuropsychiatry and Clinical Neurosciences, 19*(2), 196–197.

Menkes, D., Coates, D. C., Fawcett, J. P. et al. (1994). Acute tryptophan depletion aggravates premenstrual syndrome. *Journal of Affective Disorder, 32*(1), 37–44.

Miller, L. (1994). Use of electroconvulsive therapy during pregnancy. *Hospital & Community Psychiatry, 45*(5), 444–450.

Misri, S., Reebye, P., Corral, M., & Milis, L. (2004). The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: A randomized controlled trial. *Journal of Clinical Psychiatry, 65*, 1236–12.

Murray, L. (1992a). The impact of postnatal depression on infant development. *Journal of Child Psychology and Psychiatry, 33*(3), 543–561.

Nager, A., Sundquist, K., Ramirez-Leon, V., Johansson, L. M. (2008a). Obstetric complications and postpartum psychosis: A follow-up study of 1.1 million first-time mothers between 1975 and 2003 in Sweden. *Acta Psychiatrica Scandinavica, 117*(1), 12–19.

Neugebauer, R., Kline, J., Shrout, P., Skodol, A., O'Connor, P., Geller, P. A., Stein, Z., Susser, M.. (1997a). Major depressive disorder in the 6 months after miscarriage. *JAMA, 277*(5), 383–388.

Newport, D. J., Calamaras, M. R., et al. (2007). Atypical antipsychotic administration during late pregnancy: Placental passage and obstetrical outcomes. *The American Journal of Psychiatry, 164*(8), 1214–1220.

Newport, D. J., Pennell, P. B., Calamaras, M. R., Ritchie, J. C., Newman, M., Knight, B., Viguera, A. C., Liporace, J., Stowe, Z. N.. (2008). Lamotrigine in breast milk and nursing infants: Determination of exposure. *Pediatrics, 122*(1), e223.

Nguyen, H. N., & Lalonde, P. (2003). Clozapine and pregnancy. *Encephale, 29*(2), 119–124.

Nulman, I., Koren, G., Rovet, J., Barrera, M., Pulver, A., Streiner, D., Feldman, B. (2012). Neurodevelopment of children following prenatal exposure to venlafaxine, selective serotonin reuptake inhibitors, or untreated maternal depression. *The American Journal of Psychiatry, 169*(11), 1165–1174.

Nulman, I., & Rovet, J. (2002). Child development following exposure to TCA or fluoxetine throughout fetal life: A prospective controlled study. *The American Journal of Psychiatry, 159*, 1889–1895.

Nulman, I., Rovet, J., Stewart, D. E., Wolpin, J., Gardner, H. A., Theis, J. G., Kulin, N., Koren, G. (1997). Neurodevelopment of children exposed in utero to antidepressant drugs. *New England Journal of Medicine, 336*, 258–262.

O'Connor, T. G., Heron, J., Golding, J., Glover, V.. (2003). Maternal antenatal anxiety and behavioral/emotional problems in children: A test of a programming hypothesis. *Journal of Child Psychology and Psychiatry, 44*(7), 1025–1036.

O'Hara, M. (1986). Social support, life events and depression during pregnancy and puerperium. *Archives of General Psychiatry, 43*, 569–573.

O'Hara, M., Schelchte, J., & Lewis, D. (1991). Prospective study of postpartum blues, biologic and psychosocial factors. *Archives of General Psychiatry, 48*, 801–806.

O'Hara, M., Stuart, S., Gorman, L., & Wenzel, A. (2000). Efficacy of Interpersonal psychotherapy for postpartum depression. *Archives of General Psychiatry, 57*, 1039–1045.

Ohman, I., & Vitols, S. (2000). Tomson T Lamotrigine in pregnancy: Pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia, 41*(6), 709.

Parry, B. L. (2010). Optimal management of perimenopausal depression. *International Journal of Women's Health, 2*, 143–151.

Pearlstein, T., & Steiner, M. (2008). Premenstrual dysphoric disorder: Burden of illness and treatment update. *Journal of Psychiatry & Neuroscience, 33*(4), 291–301.

Pederson, L. H., Henriksen T.B., Bech B. H., Licht R. W., Kjaer D., Olsen J. (2013). Prenatal antidepressant exposure and behavioral problems in early childhood-a cohort study. *Acta Psychiatrica Scandinavica, 127*(2), 126–135.

Philip, B. (2003a). Hyperemesis gravidarum: Literature review. *WMJ, 102*(3), 46–51.

Prendergast, J., & Austin, M. P. (2001). Early childhood nurse-delivered cognitive behavioral counseling for post-natal depression. *Australasian Psychiatry, 9*, 255–259.

Quinlan, J., & Hill, A. (2003). Nausea and vomiting of pregnancy. *American Family Physician, 68*(1), 121–128.

Rahman, A., Iqbal, Z., Bunn, J., Lovel, H., & Harrington, R. (2004). Impact of Maternal Depression on Infant Nutritional Status and IllnessA Cohort Study. *Archives of General Psychiatry, 61*(9), 946–952. doi:10.1001/archpsyc.61.9.946.

Rapkin, A. J. (2008a). YAZ in the treatment of premenstrual dysphoric disorder. *Journal of Reproductive Medicine, 53*(9 Suppl), 729–741.

Rapkin, A., & Lewis, E. (2013). Treatment of premenstrual dysphoric disorder. *Women's Health (London, England), 9*(6), 537–556.

Rasgon, N. L., Altshuler, L. L., Fairbanks, L. A., Dunkin, J. J., Davtyan, C., Elman, S., Rapkin, A. J.. (2002a). Estrogen replacement therapy in the treatment of major depressive disorder in perimenopausal women. *Journal of Clinical Psychiatry, 63*(Suppl 7), 45–48.

Robertson, E., Grace, S., Wallington, T., Stewart, D. E.. (2004). Antenatal risk factors for postpartum depression: A synthesis of recent literature. *General Hospital Psychiatry, 26*, 289–295.

Robling, S. A., Paykel, E. S., Dunn, V. J., Abbott, R., Katona, C.. (2000). Long term outcome of severe puerperal psychiatric illness: A 23 year follow up study. *Psychological Medicine, 30*, 1263–1271.

Ross, L. E., Grigoriadis, S., Mamisashvili, L., Vonderporten, E. H., Roerecke, M., Rehm, J., Dennis, C. L., Koren, G., Steiner, M., Mousmanis, P., Cheung, A.. (2013). Selected pregnancy and delivery outcomes afte exposure to antidepressant medication. *JAMA Psychiatry, 70*(No.4), 436–443.

Roy-Byrne, P., Dager, S., Cowley, D. S., Vitaliano, P., Dunner, D. L. (1989). Relapse and rebound following discontinuation of benzo treatment of panic attacks: Alprazolam versus Diazepam. *The American Journal of Psychiatry, 146*(7), 860–865.

Sayegh, R., Schiff, I., Wurtman, J., Spiers, P., McDermott, J., Wurtman, R.. (1995). The effect of a carbohydrate-rich beverage on mood, appetite, and cognitive function in women with premenstrual syndrome. *Obstetrics and Gynecology, 86*, 520–528.

Schmidt, P. J., Haq, N., Rubinow, D. R. (2004a). A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. *The American Journal of Psychiatry, 161*(12), 2238–2244.

Schneider, L. S., Small, G. W., Hamilton, S. H., Bystritsky, A., Nemeroff, C. B., Meyers, B. S.. (1997a). Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. Fluoxetine Collaborative Study Group. *The American Journal of Geriatric Psychiatry, 5*(2), 97–106.

Schou, M. (1976). What happened later to the lithium babies? A follow-up study of children born without malformations. *Acta Psychiatrica Scandinavica, 54*(3), 193–197.

Sharma, V., Smith, A., Khan, M. (2004a). The relationship between duration of labour, time of delivery, and puerperal psychosis. *Journal of Affective Disorders, 83*(2–3), 215–220.

Sherer, D. (1991). D'Amico, et al. Recurrent mild abruption placentae occurring immediately after repeated ECT in pregnancy. *American Journal of Obstetrics and Gynecology, 165*, 652–653.

Silverman, S. L., Shen, W., Minshall, M. E., Xie, S., Moses, K. H.. (2007a). Prevalence of depressive symptoms in postmenopausal women with low bone mineral density and/or prevalent vertebral fracture: Results from the Multiple Outcomes of Raloxifene Evaluation (MORE) study. *Journal of Rheumatology, 34*(1), 140–144.

Spinelli, M. (1997). Interpersonal psychotherapy for depressed antepartum women: A pilot study. *The American Journal of Psychiatry, 154*, 1028–1030.

Spinelli, M. G. (2009a). Postpartum psychosis: Detection of risk and management. *The American Journal of Psychiatry, 166*(4), 405–408.

Stewart, D. E. (1988). Prophylactic lithium in postpartum affective psychosis. *The Journal of Nervous and Mental Disease, 176*(8), 485–489.

Stewart, D. E., & Boydell, K. M. (1993). Psychological distress during menopause: Associations across the reproductive life cycle. *International Journal of Psychiatry in Medicine, 23*(2), 157–162.

Strouse, T. B., Szuba, M. P., Baxter, L. R., Jr. (1992a). Response to sleep deprivation in three women with postpartum psychosis. *Journal of Clinical Psychiatry, 53*(6), 204–206.

Teixeira, J. M., Fisk, N. M., Glover, V.. (1999). Association between maternal anxiety in pregnancy and increased uterine artery resistance index: A cohort study. *British Medical Journal, 318*(7193), 1288–1289.

Thapar, A. K., & Thapar, A. (1992a). Psychological sequelae of miscarriage: A controlled study using the general health questionnaire and the hospital anxiety and depression scale. *British Journal of General Practice, 42*(356), 94–96.

Thisted, E., & Ebbesen, F. (1993). Malformations, withdrawal manifestations and hypoglycemia after exposure to valproate in utero. *Archives of Disease in Childhood, 69*, 288–291.

Toh, S., Mitchell, A. A., Louik, C., Werler, M. M., Chambers, C. D., Hernandez-Diaz, S.. (2009). Selective serotonin reuptake inhibitor use and risk of gestational hypertension. *The American Journal of Psychiatry, 166*(3), 320–328.

Tomson, T., Ohman, I., & Vitols, S. (1997). Lamotrigine in pregnancy and lactation: A case report. *Epilepsia, 38*(9), 1039.

Trogstad, L. I., Stoltenberg, C., Magnus, P., Skjaerven, R., Irgens, L. M.. (2005a). Recurrence risk in hyperemesis gravidarum. *BJOG, 112*(12), 1641–1645.

Usall, J., Pinto-Meza, A., Fernandez, A., de Graaf, R., Demyttenaere, K., Alonso, J., de Girolamo, G., Lepine, J. P., Kovess, V., Haro, J. M.. (2009a). Suicide ideation across reproductive life cycle of women. Results from a European epidemiological study. *Journal of Affective Disorders, 116*(1–2), 144–147.

Van der Lugt, N. M., van de Maat, J. S., van Kamp IL, Knoppert-van der Klein EA, Hovens JG, Walther FJ (2012). Fetal, neonatal and developmental outcomes of lithium-exposed pregnancies. *Early Human Development, 88*(6), 375–378.

Viguera, A. C., Newport, D. J., Ritchie, J., Stowe, Z., Whitfield, T., Mogielnicki, J., Baldessarini, R. J., Zurick, A., Cohen, L. S.. (2007). Cohen LS; Lithium in breast milk and nursing infants: Clinical implications. *The American Journal of Psychiatry, 164*(2), 342.

Viguera, A., & Nonacs, R. (2000). Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. *The American Journal of Psychiatry, 157*, 179–184.

Wassertheil-Smoller, S., Shumaker, S., Ockene, J., Talavera, G. A., Greenland, P., Cochrane, B., Robbins,

J., Aragaki, A., Dunbar-Jacob, J.. (2004a). Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). *Archives of Internal Medicine, 164*(3), 289–298.

Wegrzyniak, L. J., Repke, J. T., & Ural, S. H. (2012). Treatment of Hyperemesis Gravidarum. *Review of Obstetrics & Gynecology, 5*(2), 78–84.

Whalley, L. J., Blain, P. G., & Prime, J. K. (1981). Haloperidol secreted in breast milk. *British Medical Journal (Clinical Research Ed.), 282*(6278), 1746.

Wikner, B. N., Stiller, C. O., Bergman, U., Asker, C., Kallen, B.. (2007). Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: Neonatal outcome and congenital malformations. *Pharmacoepidemiology and Drug Safety, 16*(11), 1203–1210.

Wiles, D. H., Orr, M. W., & Kolakowska, T. (1978). Chlorpromazine levels in plasma and milk of nursing mothers. *British Journal of Clinical Pharmacology, 5*(3), 272.

Wisner, K. L., & Wheeler, S. B. (1994). Prevention of recurrent postpartum major depression. *Hospital & Community Psychiatry, 45*(12), 1191–1196.

Wisner, K. L., Perel, J. M., Peindl, K. S., Hanusa, B. H. (2004a). Timing of depression recurrence in the first year after birth. *Journal of Affective Disorders, 78*(3), 249–252.

Wisner, K. L., Perel, J. M., Peindl, K. S., Hanusa, B. H., et al. (2004b). Prevention of postpartum depression: A pilot randomized clinical trial. *The American Journal of Psychiatry, 161*(7), 1290–1292.

Yonkers, K. A., Lin, H., Howell, H. B., Heath, A. C., & Cohen, L. S. (2008). Pharmacologic treatment of postpartum women with new-onset major depressive disorder: A randomized controlled trial with paroxetine. *Journal of Clinical Psychiatry, 69*(4), 659–665.

Yonkers, K. A., Wisner, K. L., Stewart, D. E., Oberlander, T. F., Dell, D. L., Stotland, N., Ramin, S., Chaudron, L., Lockwood, C.. (2009). The management of depression during pregnancy: A report from the American Psychiatric Association and the American college of Obstetricians and Gynecologists. *General Hospital Psychiatry, 31*(5), 403–413.

Yonkers, K. A., Wisner, K. L., Stowe, Z., Leibenluft, E., Cohen, L., Miller, L., Manber, R., Viguera, A., Suppes, T., Altshuler, L.. (2004). Management of bipolar disorder during pregnancy and the postpartum period. *The American Journal of Psychiatry, 161*(4), 608–620.

Yoshida, K., Smith, B., Kumar, R. (1999a). Psychotropic drugs in mothers' milk: A comprehensive review of assay methods, pharmacokinetics and of safety of breast-feeding. *Journal of Psychopharmacology, 13*(1), 64–80.

Yoshida, K., Smith, B., Craggs, M., Kumar, R., . (1998a). Neuroleptic drugs in breast-milk: A study of pharmacokinetics and of possible adverse effects in breast-fed infants. *Psychological Medicine, 28*(1), 81–91.

Zeskind, P. S., & Stephens, L. (2004). Maternal SSRI use during pregnancy and newborn neurobehavior. *Pediatrics, 113*(2), 368–375.

Zuckerman, B., Amaro, H., Bauchner, H., Cabral, H.. (1989). Depressive symptoms during pregnancy: Relationship to poor health behaviors. *American Journal of Obstetrics and Gynecology, 160*, 1107–1111.

Zuckerman, B., Bauchner, H., Parker, S., Cabral, H. (1990). Maternal depressive symptoms during pregnancy and newborn irritability. *Journal of Developmental and Behavioral Pediatrics, 11*, 190–194.

Recommended Reading

Burt, V. K., Suri, R., et al. (2001). The use of psychotropic medications during breast feeding. *The American Journal of Psychiatry, 158*(7), 1001–1009.

Clayton, A. H., & Ninan, P. T. (2010). Depression or Menopause? Presentation and Management of Major Depressive Disorder in Perimenopausal and Postmenopausal Women. *Primary Care Companion to the Journal of Clinical Psychiatry, 12*(1), PCC.08r00747.

Cohen, L., & Nonacs, R. (2005). *Mood and Anxiety Disorders During Pregnancy and Postpartum*. Washington, DC: American Psychiatric Press.

Einarson, A., & Boskovic, R. (2009). Use and safety of antipsychotic drugs during pregnancy. *Journal of Psychiatric Practice, 15*(3), 183–192.

Ernst, C., & Goldberg, J. (2002). The reproductive safety profile of mood stabilizers, atypical antipsychotics and broad spectrum psychotropics. *Journal of Clinical Psychiatry, 63*(suppl 4), 42–55.

Iqbal, M. M., Aneja, A., Rahman, A., Megna, J., Freemont, W., Shiplo, M., Nihilani, N., & Lee, K. (2005). The potential risks of commonly prescribed antipsychotics: During pregnancy and lactation. *Psychiatry (Edgmont), 2*(8), 36–44.

Llewellyn, A., & Stowe, Z. (1998). Psychotropic medications in lactation. *Journal of Clinical Psychiatry, 59*(suppl 2), 41–52.

Llewellyn, A., Stowe, Z., & Strader, J. (1998). The use of lithium and management of women with bipolar disorder during pregnancy and lactation. *Journal of Clinical Psychiatry, 59*(suppl 6), 57–64.

MGH Center for Women's Mental Health. Pharmacological treatment during pregnancy: Weighing the risk.

MGH Center for Women's Mental Health. Breast feeding and psychiatric medications.

Miller, L. (1999). *Postpartum Mood Disorder*. Washington, DC: American Psychiatric Press.

Miller. L. (2005). Daniels-Brady. Depression during Perimenopause. Menopause management.

Pearlstein, T. (2008). Perinatal depression: Treatment options and dilemmas. *Journal of Psychiatry & Neuroscience, 33*(4), 302–318.

Rapkin, A. (2003). A review of treatment of premenstrual syndrome and premenstrual dysphoric disorder. *Psychoneuroendocrinology, 28*, 39–53.

Schimidt, P., et al. (2004). A longitudinal evaluation of the relationship between reproductive status and mood in perimenupausal women. *American Journal of Psychiatry, 161*, 2238–2244.
Steiner, M., Dunn, E., & Born, L. (2003). Hormones and mood: From menarche to menopause and beyond. *Journal of Affective Disorders, 74*, 67–83.

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www.perinatalweb.org
www.womensmentalhealth.org