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WOMEN'S HEALTH

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Editorial Note:

Dear Doctor,

It's our immense pleasure to inform you that we have published our newsletter, "Women's Health". In this issue we are focusing on the depression during pregnancy and its management. Your comments and suggestions will enrich our upcoming issues. Please participate in quiz competition and win prizes.

Depression during pregnancy:
detection,
comorbidity and
treatment

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WOMEN'S HEALTH

Depression during pregnancy: detection, comorbidity and treatment

Depressive symptoms present in up to 20% of women, commonly occuring during childbearing years. Studies show that 10–16% of pregnant women meet the diagnostic criteria for major depressive disorder (MDD), with greater numbers suffering from subsyndromal illness. However, even when appropriately screened, over 80% of women with antenatal depression do not receive treatment during pregnancy. Frequently cited reasons for undertreatment are concerns regarding stigma, or diagnostic uncertainty among professionals confusing depressive syndromatology with normative pregnancy experiences (poor sleep, fatigue, appetite dysregulation). Effective treatment is also sometimes limited by underdosing of otherwise effective medications because many physicians are unsure how to balance maternal medication with the risk of exposing the growing fetus to pharmacotherapy. Finally, even if treated aggressively, depression during pregnancy may prove treatment-refractory due to secondary maintaining factors including the presence of bipolar depression, anxiety disorders, substance abuse, or the presence of severe psychosocial stressors.

Depression during childbearing presents with the same symptomatology as depressive episodes outside of childbearing. According to the *Diagnostic and Statistical Manual of Mental Disorders, Version 4* (DSM-IV) criteria, a diagnosis of depression must include existence of a depressed mood or inability to experience pleasure; many women who are depressed during the puerperium also note an irritable mood and marked anxiety as key features. Frequently women report worrisome cognitions regarding the infant's health and preoccupations about becoming a competent parent. These preoccupations can take on an obsessional flavor and in a few cases deteriorate to psychotic thinking. Many of the classic symptoms of depression (sleep and appetite dysregulation, poor energy) overlap with the physical and mental changes experienced during pregnancy, often resulting in them being misattributed to the physiologic changes during gestation.

A critical primary risk factor is genetic vulnerability manifesting as previous personal depression or family history of depression. Other common risk factors are a woman's perception of limited social support and presence of social conflict. Other risk factors include: past or present physical, emotional, or sexual abuse; current or past cigarette smoking; alcohol or substance abuse; financial or occupational stressors; medical health concerns; living alone; greater number of children at home; and finally, ambivalence about the pregnancy.

Screening and collaborative care

There are several user-friendly screening tools for depression that can be easily administered during pregnancy. The Edinburgh Postnatal Depression Scale (EPDS) is a brief 3-minute screening tool and the gold-standard instrument used across the peripartum. Two other commonly used depression screening measures for adults in ambulatory care are the Beck Depression Inventory Scale (BDI-II) and the Center for Epidemiologic Studies Depression Scale, Revised (CES-DR), both of which are valid for pregnancy use.

However, when using the BDI-II or the CES-DR clinicians have to consider the possibility of overdiagnosing depression because both instruments include items inquiring somatic complaints of depression which. Similarly, items assessing anhedonia, such as ''I have enjoyed reading a book or watching TV,'' or psychomotor retardation, such as ''I feel I am slowed down,'' are potentially more likely related to body changes due to pregnancy and following childbearing than due to depression. These concerns have lead to the development of the EPDS, a peripartum-specific depression measure. Adaptations made by the EPDS include elimination of misleading or inappropriate items such as questions about weight change, body image change, somatic preoccupation, and work difficulty, and emphasis on more prototypical depression symptoms during the peripartum such as agitation, irritability and anxious preoccupation.

Regardless of the screening method used, it is important to further support patients who manifest depressive symptoms upon screening in their help seeking. Because management of a depressed, pregnant woman may be diagnostically complex and also includes care of her growing fetus, treatment may be optimized by applying an informed, multidisciplinary approach, that is, a collaborative care model, including input from an obstetrician, psychiatrist, pediatrician, and care manager to provide optimal care.

Consequences of antenatal depression

Unidentified and untreated depression can lead to detrimental effects in both the mother and her child. Maternal infanticide and/or suicide are the most catastrophic effects of undertreated depression. In addition, depressed women are more likely to participate in unhealthy practices during pregnancy such as smoking and substance use. They may have poor nutrition, in part due to lack of appetite, leading to poor pregnancy weight gain. Depressed women are less compliant with prenatal care and feel less invested in antenatal care. Women with depression may have increased pain and discomfort during their pregnancies, often complaining of myriad somatic concerns, sometimes leading to medical procedures. Untreated maternal depression during pregnancy has been associated with poor obstetric, fetal, and neonatal outcomes.

Negative birth outcomes are associated most highly with depression symptoms in the second and third trimesters. These infants cry more often and are more difficult to console than babies born to non-depressed mothers. Higher levels of prenatal maternal anxiety and depression predict more infant sleep problems at 18 and 30 months. Other groups also reported on offspring behavioral problems in early and middle childhood, and in teenage years when mothers were depressed/anxious/stressed during pregnancy. If a baby is exposed to a depressed maternal environment during early infancy, and the mother has recurrent depressive episodes, the child shows changes in neuroendocrine functioning and more behavior problems at school entry. As these children grow, perhaps because of early exposure or the continued stressful home environment, they are more likely to have emotional instability and conduct disorders, attempt suicide.

Comorbidity and other factors impacting treatment

Undiagnosed bipolar depression, comorbidity with other mental illness including anxiety disorders, posttraumatic stress disorder (PTSD), substance abuse & co-occurring severe psychosocial stress can contribute to treatment-resistance. Clinicians wanting to prevent treatment refractory states during pregnancy need to consider contributing factors and address them (Table 1).

Bipolar depression

Several factors, such as worsening dysphoria on selective serotonin reuptake inhibitors (SSRIs), agitation and extreme insomnia, and emerging psychosis should alert a clinician to a potential underlying bipolar depression. For patients who present for the first time during pregnancy, a differential diagnosis including infectious, immunologic, electrolyte or endocrine disorders should be considered. Medications which may contribute to affective roughening include steroids, bronchodilators, decongestants, antihypertensives, and immunosuppresants; but ‘‘unopposed’’ antidepressant medication alone can also trigger (hypo)mania and treatment refractoriness.

Exacerbation of bipolar illness may be particularly problematic during pregnancy, as risk-taking behavior, including sexually promiscuous behavior and excessive use of drugs or alcohol, may put a fetus at risk. Because many mood stabilizers may cause an increase in fetal anomalies when used during the first trimester, these medications are often tapered antepartum, leaving women vulnerable to exacerbations within the 2nd - 3rd trimester.

Anxiety disorders

Modest levels of anxiety occur in a majority of women during pregnancy, hence differentiating generalized anxiety disorder (GAD) can be difficult. GAD characterized by the presence of at least 6 months of excessive worry with additional unique somatic symptoms occurs at the rate of 8.5% during the last trimester of pregnancy. Peripartum is a vulnerable period for GAD. Prevalence of panic disorder during pregnancy is 1–2%. Co-occurring anxiety and depressive systems are common in that 50% of women with panic disorders report major depression. This comorbidity may complicate treatment regimens and may necessitate the use of both an antidepressant and an anxiolytic (commonly SSRIs and benzodiazepines). Obsessive worries centering on pregnancy outcomes are very common during pregnancy. However, the prevalence of obsessive-compulsive disorder (OCD) is lower during pregnancy (0.2%) relative to both postpartum prevalence (2.7–3.9%) and lifetime prevalence. One of the most common obsessional themes during pregnancy is the fear of intentionally or accidentally harming the fetus, or that the fetus may have some undetected medical condition. Obsessive thoughts about harming the fetus (e.g., falling down stairs and hurting the unborn) must be differentiated from psychotic delusions present in psychotic depression or bipolar illness (e.g., delusion that fetus is ‘‘eating her up from the inside’’). In general, women with OCD-like thoughts about hurting their child are very distressed, identifying these thoughts as unwanted and unreasonable. In contrast, women with psychotic harmful thoughts towards their child lack insight into their delusions and may be at risk of acting on their delusion (e.g., stabbing the fetus causing major abdominal injuries to herself). In

Table 1. Key points for clinical care of treatment – refractory depression during pregnancy

Bipolar depression	Any woman who experiences significant irritability and a ‘‘roughening’’ course of her depressive illness during pregnancy or postpartum, particularly with psychotic features, should be evaluated for bipolar depression
	A history of mood instability and more specifically the induction of hypomania, rapid cycling or mixed episodes, following treatment with antidepressants may provide a clue about the underlying bipolar nature
	Poor or failed response to antidepressants and severe psychotic features also hint to underlying bipolar illness
	A personal past history of postpartum depression or family history of bipolar illness also may suggest bipolar illness
Anxiety	Anxiety is common during pregnancy, ranging from increased rates of GAD and OCD, to possible exaggeration in panic disorder and PTSD
	Comorbidity with depression is common, and co-occurrence of anxiety and depression complicates treatment hence increasing the risk of treatment-resistance
Substance use disorders	Substance use is frequently comorbid with anxiety and mood disorders, and may contribute to treatment-resistance if unrecognized and untreated
	Patients frequently self-medicate with alcohol or other illicit drugs to alleviate anxiety, depression, or insomnia
	Screening for substance abuse during pregnancy, mainly alcohol consumption, is critical for optimal child outcomes , and several screening tools are available in primary care

GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress syndrome.

such cases, imminent safety measures for the mother and child are warranted and necessitate emergent treatment of the mother. Presence of OCD spectrum disorders, comorbid with antenatal depression, complicates treatment and may require higher levels of medications (SSRIs) or behavioral therapy. Finally, post-traumatic stress disorder (PTSD) can be present during pregnancy, either as new onset or exacerbation of preexisting illness. History of childhood abuse, particularly sexual abuse, is related to higher rates of perinatal PTSD as well, with symptoms sometimes precipitated by the intrusive procedures inherent in the management of pregnancy and delivery. Child hood sexual abuse survivors are also more likely to suffer perinatal depression, confirming the observation that PTSD and depression are commonly comorbid during the perinatal period, again complicating treatment algorithms and increasing the likelihood of treatment resistance.

Substance use disorders

Patients present, with preexisting comorbid substance abuse. Substance abuse during pregnancy has significant adverse effects on the developing fetus.

Severe psychosocial stress

The presence of psychosocial stressors can trigger the onset of depression during pregnancy, or can exaggerate and maintain concurrent depression. Such stressors include exposure to trauma and violence, relationship conflict, and inadequate social support systems. The strain of poverty and resultant food, housing and financial insecurity may be further stressors.

Past physical or sexual abuse is common in women suffering substance use and mental health problems. Domestic violence during pregnancy poses a significant threat to a pregnant woman as well as the fetus. Exposure to violence and abuse can lead to adverse physical and mental health consequences for the affected women, including depressive and anxiety disorders. Screening for domestic violence and trauma is essential to begin to address the challenges faced by these affected women in an empathic and nonjudgmental way, and to create a supportive environment for change.

Pregnancy is a time of role transition for all women. The prospect of delivery and a new infant fundamentally alters a woman's role as a self-reliant individual, professional, and partner in various adult relationships, as well as the balance of power within the relationship. Screening for relationship satisfaction and the quality of the partner relationship are important as they allow providers to evaluate for relationship conflict, which may underpin the depressive illness and contribute to treatment resistance.

Stress related to lack of social support from the spouse, family and the larger community further confound depressive illnesses.

Treatment options for depression during pregnancy.

Pharmacotherapy

Antidepressants

There are few pharmacological standards for treatment of women with depressive disorders during pregnancy, in part because ethical constraints preclude randomized controlled trials using medication during gestation. In a recent publication, both the American Psychiatric Association and American College of Obstetrics and Gynecology suggested that women should consider the use of psychotherapy prior to considering medications, but that those with moderate to severe, recurrent depressive symptoms or suicidal thinking should remain on antidepressants during pregnancy. Many women are reluctant to seek treatment, but for those who do, some physicians are unsure of how to balance maternal medication requirements with risk of exposure to the growing fetus. Since many pregnancies are unplanned or undetected for some time, all women of childbearing age should have their depression managed as if pregnancy is possible. The primary care provider should engage in preconception planning with all women of childbearing age who are at risk of depressive illness. Decisions regarding the use of pharmacotherapy during conception and the first

Table 2. Use of antidepressants during pregnancy

Medication	Use during pregnancy/teratogenicity	Spontaneous abortion	Neonatal adaptation and monitoring at birth
SSRIs	No increased risk of teratogenicity above baseline rate Small risk of septal defects and other anomoalies, Paroxetine controversial	Mixed findings suggesting increased rates of type of antidepressant; findings may be confounded by impact of illnessin	30% of infants exposed have transient Risk for pulmonary hypertension suggested some but not all studies
TCAs	No increased risk of teratogenicity above baseline rate	Mixed findings suggesting increased rates of spontaneous abortion regardless of type of antidepressant; findings may be confounded by impact of illness	Difficulties with neonatal adaptation, and withdrawal symptoms well established
SNRIs and other AD	No increased risk of teratogenicity above baseline rate	Buproprion exposure during pregnancy linked with significant risk for spontaneous abortion	Difficulties with neonatal adaptation, and withdrawal symptoms well established with venlafaxine

SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; SNRIs, serotonin-norepinephrine reuptake inhibitor; AD, antidepressant.

trimester are among the most critical for a woman and her physician. Women diagnosed with depression who have been asymptomatic for over a year may wish to attempt to reduce or discontinue antidepressants prior to conception and throughout the pregnancy. Women should be closely monitored for relapse of symptoms. Women who discontinued their antidepressants during pregnancy experienced more relapsing symptoms (68%), compared with those who continued their medication regimen (26%). If a woman's depression history contains multiple relapses or severe symptoms such as suicide attempts and multiple inpatient psychiatric admissions, some recommend she remain on antidepressants for her own safety, regardless of pregnancy status.

All psychotropic medications cross the placenta and enter the amniotic fluid. General guidelines include some straightforward principles: (a) keep the medication regimen simple using monotherapy when possible; (b) discuss risks and consequences of both pharmacotherapy and untreated depression; and (c) choose agents with demonstrated fetal safety. Use of multiple medications in sequence as well as medication augmentation strategies all increases the exposure of the fetus. The woman's history of prior response to pharmacotherapy should be considered when choosing a medication. Although many factors influence pharmacotherapy during pregnancy, drugs with fewer metabolites, drug–drug interactions, more protein binding (preventing placental passage) and lesser teratogenic risk, if known, should be prioritized when possible.

Spontaneous abortion. Research results are mixed when examining rates of antidepressant use and its relationship to spontaneous abortion, and may be confounded by the effect of the illness itself. One study suggests that women taking antidepressants during pregnancy have a statistically significant higher rate of spontaneous abortion (3.9%) regardless of the type of antidepressant, whereas, other studies show spontaneous abortion rates are elevated by exposure to several different antidepressant classes, but only exposure to bupropion is statistically significant.

Teratogenicity. Research on antidepressant teratogenicity is growing and there is considerable scientific debate about the safety of antidepressants during pregnancy. Although the mainstream media has created controversy regarding the safety of SSRIs, the majority of research to date does not confirm major congenital malformations above the 2–4% baseline rate cited for the general population. A recent meta-analysis confirmed no increased risk of major congenital malformations with in utero exposure to SSRIs. The use of paroxetine continues to be debated among perinatal psychiatrists. Most practitioners choose other agents, except for those women who have demonstrated a past positive preferential response to paroxetine. When paroxetine is used, it is recommended that the fetus is monitored with fetal echocardiography. While a 2007 study found no significant relationship between SSRIs and congenital cardiovascular malformations, the authors of that study suggest an association between SSRIs (especially paroxetine during the first trimester) and infants with anencephaly, craniosynostosis, and omphalocele. These findings were refuted by another recent study finding no increased risk of these anomalies with SSRI use by pregnant women. They did, however, find some significant relationships between sertraline and omphalocele and between paroxetine and right ventricular outflow tract obstruction defects. Although these findings indicate some increased risk of specific rare birth defects with specific drug exposure, the overall absolute risk of birth defects with the use of SSRIs is small.

Neonatal adaptation. Studies show that up to 30% of infants exposed to SSRIs in the third trimester are likely to have symptoms of poor neonatal adaptation. These symptoms include short-term self-limited cardiorespiratory symptoms, hypothermia, hypoglycemia, irritability, hyper and hypotonia, feeding disturbances, and seizures. One author, correcting for these confounding variables, found no increased rate of premature labor or intensive care monitoring for babies exposed to SSRIs or venlafaxine in utero. As in other studies, some infants did exhibit neonatal adaptation syndrome symptoms. While some international literature suggests tapering of SSRIs to avoid the late gestation exposure, most practitioners in the US avoid this, as it predisposes women to a substantially heightened risk of late pregnancy and postpartum morbidity secondary to depression and predisposes the infant to medication withdrawal symptoms in utero.

The bulk of the literature to date does not show increased risk of congenital malformations associated with pregnant women taking tricyclic antidepressants (TCAs). Doses of TCAs may need to be increased as much as 1.6 times the prepregnancy dose in the second half of pregnancy to establish therapeutic levels as a result of increased plasma volumes and metabolism. Case reports have presented babies with TCA exposure as experiencing temporary withdrawal symptoms within the first 12 hours of life, including jitteriness, irritability, urinary retention, bowel obstruction, and occasionally seizures. Nulman et al. found there were no associations between a mother's use of TCAs or fluoxetine during pregnancy and the global IQ, language or behavioral development in preschool children. Much more limited information is available regarding in utero exposure to atypical antidepressants such as bupropion, mirtazapine, nefazodone, trazodone, duloxetine, and venlafaxine; however, data so far indicate a satisfactory safety profile. See Table 2 for an overview of antidepressant use during pregnancy.

Workby Oberlander and colleagues shows that length of prenatal SSRI exposure increases the risks of lower birth weight, neonatal respiratory distress and reduced gestational age even after controlling for maternal illness.

Complex infant gene polymorphism by maternal prenatal medication interactions in explaining potential risk and vulnerability constellations for children exposed to maternal illness and/or prenatal medications.

Mood stabilizers

The challenges in managing women with bipolar disorder center around the potential risk of teratogenicity associated with the major mood stabilizers. Lithium had originally been associated with a substantially increased risk of Ebstein's anomaly. The risk of Ebstein's anomaly following first trimester lithium exposure to be 0.05–0.1%. Use of lithium in later pregnancy has, however, been associated with neonatal withdrawal symptoms in the infants.

Compared with lithium, the anticonvulsant medications may pose a somewhat greater risk of teratogenicity. It is important to recognize, however, that the bulk of information about congenital anomalies with anticonvulsants comes from epilepsy literature, and it is well known that infants born to unmedicated epileptic women present an increased risk of major malformations, thus the relative risk of the anticonvulsants themselves is unknown.

The overall rate of carbamazepine (CBZ) related teratogenicity is approximately 6%, with specific increases in rates of spina bifida ranging from 0.5–1%. In addition, there have been sporadic case reports of coagulopathies, microcephaly, craniofacial anomalies, and growth retardation.

Valproic acid (VPA) or valproate may be an even more serious teratogen, conferring an approximately fivefold increased risk (11%) of major malformations when used within the first trimester. The relative risk of neural tube defects is 50-fold greater than the spontaneous rate, and occurs in 1–2% of all pregnancies exposed to valproate within the first trimester. Prenatal use of folate is essential in this population. Fetal exposure to valproate has been also associated with craniofacial anomalies and cognitive delays.

Based on data from the Lamotrigine Prenancy Registry, the estimated risk of congenital anomalies with lamotrigine monotherapy (2.5%) is similar to the base rate in the general population.

Antipsychotics

Until recently, literature regarding the use of antipsychotics during pregnancy was limited to studies and case reports

Table 3. Use of mood stabilizers during pregnancy

Medication	Pregnancy/teratogenicity	Neonatal adaptation	Monitoring at birth
Lithium	Increased risk of cardiovascular anomalies in the first trimester, but lower than initially stated	Neonatal withdrawal symptoms including respiratory symptoms, hypotonia, and poor neonatal adaptation	May be reinstituted in second trimester to prevent relapse of bipolar illness Dosage should be increased in third trimester to control for increase plasma volume Following delivery dosage should be decreased to prepregnancy levels Fetal survey should be obtained at 18 weeks Infants should be monitored following delivery for respiratory symptoms and tone
Valproic acid	First trimester use contraindicated; associated with high rates (up to 11%) of congenital anomalies, including neural ube defects	Poor neonatal adaptation reported insome infants, with cognitive delays seen longer term	When used in second and third trimester plasma levels should be monitored due to increased plasma volumes Fetal survey essential at 18 weeks, and folate supplementation recommended Compatible with breastfeeding
Lamotrigine	Limited data, but to date, relatively favorable. One study suggesting similar risk of major anomalies to population at large	Limited data	As in nonpregnant state; careful monitoring for rash Monitor maternal LFTs
Antipsychotic agents	The high potency, first generation antipsychotics are best studied (haloperidol) with no clear evidence of increased risk of teratogencity For the atypical agents there is no clear evidence of teratogenic risk at this time, all studies are underpowered to be conclusive	No data	Continued monitoring for extrapyramidal side effects, CBC, LFTs, and EKG necessary in women using antipsychotics during pregnancy

CBC, complete blood count; LFTs, liver function tests; EKG, electrocardiography.

involving the conventional neuroleptics. High-potency typical neuroleptics such as perphenazine and haloperidol have shown relative safety in pregnancy. For overview see Table 1. Studies of newer atypical antipsychotics are ongoing. See Table 3 for an overview of mood stabilizer use during pregnancy.

Benzodiazepines. Early studies reported increased risk of major malformation and oral cleft malformations, especially during first trimester exposure; however, recent studies do not confirm these previous reports. High-dose use late in pregnancy may predispose the infant to neonatal withdrawal symptoms including hypotonia, neonatal apnea, or temperature instability. While some authors conclude that third trimester discontinuation was indicated to avoid these sequelae, most conclude that such discontinuations would unnecessarily predispose women to a relapse of anxiety disorders.

ECT during pregnancy

ECT use during pregnancy is considered effective for treatment-resistant depression, relatively safe without risk of teratogenity, and has a moderate adverse complications. For women in the second and third trimester of pregnancy, it is noteworthy that women should be positioned slightly toward their left side with support under the right hip when receiving ECT to prevent a vena caval compression syndrome.

Psychotherapy

Psychotherapy is recommended as the treatment of choice for mild moderate depression, and should be included in the treatment of all women with treatment-resistant symptoms due to severity of illness and psychosocial issues seen in complicated treatment resistance (TRD). Interpersonal psychotherapy (IPT) and/or cognitive behavioral therapy (CBT) are both evidence-based approaches for treatment of depression outside of pregnancy. CBT was found to be effective. IPT, which focuses on role transitions or role conflicts that may surface in the context of depression, may be particularly relevant for childbearing women since this may be a period of significant role transitions and role disputes with significant others. Studies have demonstrated effectiveness of IPT treatment during pregnancy and postpartum.

Alternative treatments

Light therapy has been studied both during pregnancy and postpartum, and both applications are effective for reducing depressive symptoms. Consumption of two to three seafood meals per week is associated with decreased risk of depression and other mood disorders. Current guidelines recommend EPA and DHA supplementation to support mood stabilization of at least 1 g per day as capsules during or outside of childbearing, or at least two see fish meals per week outside of pregnancy. More recently, there has been interest in researchon mind–body modalities, some of which have been practiced over thousands of years, such as progressive muscle relaxation, yoga, or awareness-enhancing meditation.

Ref:Depression during pregnancy: detection, comorbidity and treatment. Maria Muzik, Sheila Marie Marcus, Heather Flynn & Katherine Lisa Rosenblum. Asia-Pacific Psychiatry 2 (2010) 7–18.

Congratulations !

The Winners of WOMEN'S HEALTH Quiz Competition

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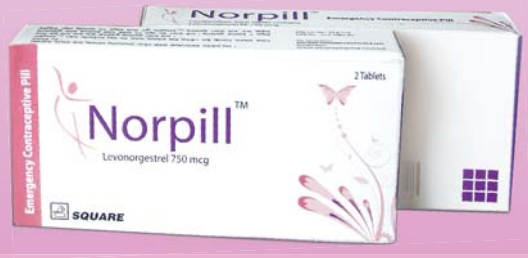

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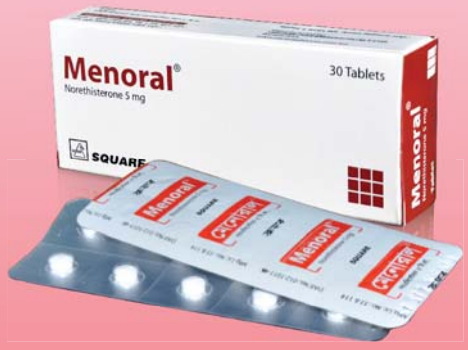

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