Current PSYCHIATRY

Just how safe are SSRIs?

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Ms. K, age 25, is 6 weeks pregnant and is taking medications for generalized anxiety disorder (GAD). When she was diagnosed with GAD at age 19, her symptoms included 6 months of excessive anxiety—insomnia, fatigue, difficulty with concentration, and psychomotor agitation—without mood symptoms. These symptoms interfered greatly with her schoolwork and other daily activities.

For 6 years Ms. K has been taking the selective serotonin reuptake inhibitor (SSRI) paroxetine, 15 mg/d, and the benzodiazepine clonazepam, 0.5 mg as needed, with good symptom control. Now that she is pregnant and her primary care doctor has refused to continue these medications, she is seeking treatment and advice.

Not enough is known about how to safely treat anxiety disorders during pregnancy, and physicians are not sure what to do with patients such as Ms. K. Without evidence-based guidelines, we feel anxious about potential risks to mother and fetus as we try to provide appropriate drug therapy.

To help you and your patients weigh the risks and benefits of perinatal treatments for anxiety disorders, this article briefly summarizes the evidence on:

- anxiety disorders' natural history during pregnancy
- how untreated maternal anxiety affects the fetus

continued

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Offspring of high-anxiety mothers exhibit neurobehavioral differences compared with those of calmer mothers

Table 1

How pregnancy affects the course of 4 anxiety disorders

Disorder	Prevalence	Effect
Generalized anxiety disorder (GAD)	8.5% of women experience GAD during the third trimester, compared with a 5% prevalence in the general population	No studies have reported on the course of GAD in pregnant women with preexisting disorder
Obsessive-compulsive disorder (OCD)	2% to 12% of OCD outpatients of childbearing age report onset during pregnancy	Preexisting OCD usually shows no change during pregnancy but may worsen postpartum
Panic disorder (PD)	1.3% to 2% in pregnant women, compared with 1.5% to 3.5% in the general population	Panic symptoms in women with preexisting PD may improve during pregnancy and worsen postpartum
Posttraumatic stress disorder (PTSD)	2.3% to 7.7% in pregnant women and 0% to 6.9% postpartum, compared with 1% to 14% in the community	No studies have reported on the course of PTSD in pregnant women with preexisting disorder

Source: References 1,2

- nonpharmacologic therapies for anxiety disorders
- a plan to manage fetal risks by staggering SSRI and benzodiazepine use during the first and third trimesters.

Anxiety during pregnancy

Nearly one-third of women experience an anxiety disorder during their lives, with peak onset during childbearing years.[1,2] Compared with research on perinatal depression, far fewer studies have examined anxiety disorders' onset, presentation, prevalence, and treatment.[1]

The literature includes no studies of the course of preexisting GAD or posttraumatic stress disorder (PTSD) and no evidence that symptoms of preexisting obsessive-compulsive disorder (OCD) change during pregnancy. Some studies of panic disorder show symptoms improving during pregnancy, whereas others do not (*Table 1*).[1]

One small study done in late pregnancy found a significant association between the prevalence of an anxiety disorder, maternal primiparity, and comorbid medical conditions. Thus, a woman in her first pregnancy may be at increased risk to develop an anxiety disorder if she has a comorbid medical condition.[3] As in the case of Ms. K, however, continuation of preexisting anxiety appears more likely than onset of a new anxiety disorder during pregnancy.

Fetal risks from maternal anxiety

Fetal risk from severe maternal anxiety is not zero. Offspring born to high-anxiety mothers exhibit neurobehavioral differences compared with offspring of calmer mothers. Changes in high-anxiety mothers' offspring include:

- altered EEG activation and vagal tone
- increased time in deep sleep and less time in active alert states
- lower performance on the Brazelton Neonatal Behavior Assessment Scale.[4]

A cohort study by Teixeira et al[5] found an association between maternal anxiety in pregnancy and uterine artery resistance, suggesting a possible mechanism by which a mother's psychologic state may affect fetal development. High anxiety and self-reported life stress during pregnancy also are associated consistently with abnormal, high-frequency heart rate variability in infants—a finding linked with negative infant behavior and later adult hostility.[6]

Exposure to maternal high anxiety has been associated with mental developmental delays in infants and increased risk for behavioral and emotional problems in young children.[7-10] Anxiety may not directly

Box

Psychotherapy: First choice for anxiety during pregnancy

No studies directly address the efficacy or outcome of any psychotherapy for anxiety in pregnancy. Even so:

- For mild to moderate anxiety, psychotherapy is the first-line treatment for pregnant women.
- Interpersonal psychotherapy (IPT) without medications can reduce depressive symptoms in pregnant women with depression.[14]
- Cognitive-behavioral therapy (CBT) without medications has shown efficacy for anxiety disorders in psychiatric populations.[15,16]

Because no evidence suggests that pregnant women require different psychotherapeutic recommendations than other psychiatric patients, consider a course of CBT that targets anxiety symptoms or IPT for a pregnant patient with an anxiety disorder.

Relaxation therapy also has shown efficacy in treating anxiety disorders. In a randomized controlled trial of 110 pregnant women with high-level anxiety, 7 weeks of applied relaxation training sessions was associated with significant reductions in low-weight births, cesarean sections, and instrumental extractions.[16,17]

Because poor marital relationships are consistent psychosocial predictors of anxiety during pregnancy and postpartum depression,[1] recommend family or marital therapy when appropriate.

cause intrauterine growth retardation and preterm delivery, but it is significantly associated with prenatal tobacco, alcohol, and narcotics use—which predicts these and other negative neonatal outcomes.[11]

Anxiety during pregnancy is a risk factor for postnatal depressive symptoms, independent of depressed mood and family or marital stressors during pregnancy.[12] Mothers with postpartum depression appear less able to respond sensitively and competently to their newborns, and these infants may be at increased risk of behavioral, emotional, and cognitive problems.[7,13]

CASE CONTINUED

'Stay the course'

Ms. K worries that she could not tolerate recurrence of her anxiety symptoms and wishes to continue both medications. Her husband concurs, but they want to minimize potential risks to their baby. You discuss the options for treating anxiety symptoms during pregnancy, including medications, psychotherapy, and behavioral treatments.

Treatment decisions

Ideally you'll begin treating anxiety disorders in women of childbearing age with preconception psychoeducation. Explaining the risks of medications if she were to become pregnant and asking about the contraception she is using are *de rigueur*. Psychotherapy is low risk to the fetus and is considered first choice for treating mild to moderate anxiety in women of childbearing age who plan to become pregnant (*Box*).[1,14-17]

Psychotherapy alone is inadequate, however, for the many patients—such as Ms. K—who present already pregnant with a history of moderate to severe anxiety. Adjunctive psychotropic therapy—along with various nonmedication therapies—is warranted for patients whose social or occupational functioning would be substantially impaired by suboptimal control of anxiety during pregnancy.

Because Ms. K wishes to continue taking paroxetine and clonazepam, what can you tell her about the risks and benefits of SSRIs and benzodiazepines during pregnancy?

SSRIs in pregnancy

Teratogenicity. Compared with benzodiazepines, SSRIs have been considered agents of choice for use during pregnancy because of a lower risk of teratogenic effects.[15] Paroxetine, however, appears to pose a greater risk for teratogenicity than other SSRIs.

An increased risk for fetal ventricular and/or atrial septal defects has been associated with first-trimester exposure to

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Before pregnancy, explain to the patient the risks of medications if she were to become pregnant and ask about contraception

Anxiety in pregnancy

Clinical Point

Paroxetine appears to pose a greater risk for teratogenicity (specifically cardiac malformations) than other SSRIs

paroxetine, but no other SSRI.[18] First trimester exposure to paroxetine at doses averaging 25 mg/d has been associated with statistically significant risks of major congenital anomalies (2-fold increase) and major cardiac anomalies (3-fold increase),[19] although other studies have failed to reproduce this finding. A meta-analysis of 7 studies by Bar-Oz et al[20] found an association between first-trimester paroxetine exposure and a significant increase in risk for cardiac malformations (odds ratio [OR] 1.72; 95% CI,1.22-2.42).

The overall rate of fetal malformations from SSRIs appears to be low, although most studies have examined only fluoxetine or paroxetine. Some studies have reported various malformations with fluoxetine or sertraline, but others have not. In Finland, a population-based study found no increase in rate of major congenital malformations in offspring of 1,782 women who filled prescriptions for SSRIs during pregnancy, compared with the general population rate of 1% to 3%.[21]

Neurobehavioral effects. SSRI exposure during fetal life has shown no long-term neurobehavioral effects. A blinded prospective study by Nulman et al[22] found no differences in global IQ scores, language development, or behavioral development among children age ≤5 who were exposed in utero to fluoxetine (N=40) or a tricyclic antidepressant (N=46), compared with unexposed children of nondepressed mothers (N=36). Similarly, using reports from teachers and clinical measures of internalizing behaviors, Misri et al[10] found no increase in depression, anxiety, or withdrawal in 4-year-olds with prenatal exposure to SSRIs (N=22), compared with nonexposed children (N=14).

Pulmonary hypertension. SSRI exposure in later pregnancy may increase the rate of persistent pulmonary hypertension of the newborn (PPHN), which occurs in 1 to 2 infants per 1,000 live births. PPHN showed a statistically significant association with late prenatal SSRI exposure (OR 6.1) in a study that controlled for maternal smoking, body mass index, and diabetes.[23] PPHN occurred in approximately 1% of infants exposed to SSRIs in late pregnancy. PPHN rates were not affected by maternal depression/anxiety, non-SSRI antidepressant exposure throughout pregnancy, or SSRI exposure during early pregnancy only.

Toxicity and withdrawal syndromes. Infants of women who continue to take SSRIs just before delivery can develop toxicity or withdrawal syndromes. Occurrence of either syndrome depends on SSRI half-life, serum concentration, and the pharmacodynamics of other medications given during pregnancy and labor.[24]

Discontinuation syndromes can occur in SSRI-exposed neonates within a few hours or days after birth and last up to 1 month after delivery, depending on the infant's susceptibility.[25] Nearly two-thirds of suspected SSRI-induced neonatal withdrawal syndromes have been associated with paroxetine, although all SSRIs appear be associated with some risk.[26] Several trials, including a recent prospective study, found prenatal antidepressant use associated with lower gestational age at birth and increased risk of preterm birth.[27]

A prospective study compared the effects of maternal SSRI use on behavioral state, sleep, motor activity, and heart rate variability in 17 exposed vs 17 nonexposed matched neonates. In the first 1 to 2 weeks of life, SSRI-exposed neonates showed:

- greater tremulousness
- less flexible and dampened state regulation
- more time in uninterrupted REM sleep
- more frequent startles or sudden arousals
- greater generalized motor activity
- greater autonomic dysregulation.[28]

In a cohort study of 60 neonates exposed to SSRIs in utero, 30% met diagnostic criteria for neonatal abstinence syndrome. The most common discontinuation symptoms were:

- tremor (37/60)
- GI disturbances (34/60)—including exaggerated sucking, poor feeding, regurgitation, vomiting, and loose stools
- sleep disturbance (21/60).

Other symptoms included irritability, constant crying, shivering, increased tone, convulsions, jitteriness, poor gaze control, vomiting, myoclonus, and lethargy.[25]

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trials: ***Body as a Whole***—asthenia, back pain, accidental injury, chest pain; ***Cardiovascular***—hypertension; ***Digestive***—dry mouth, increased appetite, thirst, constipation; increased salivation; ***Metabolic and Nutritional***—weight gain, peripheral edema, edema; ***Nervous System***—somnolence, tremor, depression, dizziness, speech disorder, amnesia, paresthesia, apathy, confusion, euphoria, incoordination; ***Respiratory***—pharyngitis, dyspnea; ***Skin and Appendages***—sweating, acne, dry skin; ***Special Senses***—amblyopia, abnormal vision; ***Urogenital***—dysmenorrhea, vaginitis.

Adverse Events with an Incidence ≥1% in Intramuscular Trials—The following treatment-emergent adverse events were reported at an incidence of ≥1% with intramuscular olanzapine for injection (2.5-10 mg/injection) and at incidence greater than placebo in short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania: ***Body as a Whole***—asthenia; ***Cardiovascular***—hypotension, postural hypotension; ***Nervous System***—somnolence, dizziness, tremor.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials—Extrapyramidal Symptoms—In an acute-phase controlled clinical trial in schizophrenia, there was no significant difference in ratings scales incidence between any dose of oral olanzapine (5±2.5, 10±2.5, or 15±2.5 mg/d) and placebo for parkinsonism (Simpson-Angus Scale total score >3) or akathisia (Barnes Akathisia global score ≥2). In the same trial, only akathisia events (spontaneously reported COSTART terms akathisia and hyperkinesia) showed a statistically significantly greater adverse events incidence with the 2 higher doses of olanzapine than with placebo. The incidence of patients reporting any extrapyramidal event was significantly greater than placebo only with the highest dose of oral olanzapine (15±2.5 mg/d). In controlled clinical trials of intramuscular olanzapine for injection, there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales incidence or spontaneously reported adverse events.

Other Adverse Events—Dose-relatedness of adverse events was assessed using data from this same clinical trial involving 3 fixed oral dosage ranges (5±2.5, 10±2.5, or 15±2.5 mg/d) compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

In an 8-week, randomized, double-blind study in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder comparing fixed doses of 10, 20, and 40 mg/d, statistically significant differences were seen between doses for the following: baseline to endpoint weight gain, 10 vs 40 mg/d; incidence of treatment-emergent prolactin elevations >24.2 ng/mL (female) or >18.77 ng/mL (male), 10 vs 40 mg/d and 20 vs 40 mg/d; fatigue, 10 vs 40 mg/d and 20 vs 40 mg/d; and dizziness, 20 vs 40 mg/d.

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia; hypotension, and tachycardia in clinical trials (*see* PRECAUTIONS).

Laboratory Changes—Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT and with increases in serum prolactin and CPK (*see* PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine in the premarketing database.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in incidence of potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

Other Adverse Events Observed During Clinical Trials—The following treatment-emergent events were reported with oral olanzapine at multiple doses ≥1 mg/d in clinical trials (8661 patients, 4165 patient-years of exposure). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. *Frequent* events occurred in ≥1/100 patients; *infrequent* events occurred in 1/100 to 1/1000 patients; *rare* events occurred in <1/1000 patients. ***Body as a Whole***—*Frequent:* dental pain, flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; *Rare:* chills and fever, hangover effect, sudden death. ***Cardiovascular***—*Frequent:* hypotension; *Infrequent:* atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, ventricular extrasystoles; *Rare:* arteritis, heart failure, pulmonary embolus. ***Digestive***—*Frequent:* flatulence, increased salivation, thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration. ***Endocrine***—*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis, goiter. ***Hemic and Lymphatic***—*Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; *Rare:* normocytic anemia, thrombocythemia. ***Metabolic and Nutritional***—*Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia; hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, water intoxication. ***Musculoskeletal***—*Frequent:* joint stiffness, twitching; *Infrequent:* arthritis, arthrosis, leg cramps, myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, rheumatoid arthritis. ***Nervous System***—*Frequent:* abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse. ***Respiratory***—*Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, voice alteration; *Rare:* atelectasis, hiccup, hypoventilation, lung edema, stridor. ***Skin and Appendages***—*Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, vesiculobullous rash; *Rare:* hirsutism, pustular rash. ***Special Senses***—*Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, pigment deposits lens. ***Urogenital***—*Frequent:* vaginitis*; *Infrequent:* abnormal ejaculation*, amenorrhea*, breast pain, cystitis, decreased menstruation*, dysuria, female lactation*, glycosuria, gynecomastia, hematuria, impotence*, increased menstruation*, menorrhagia*, metrorrhagia*, polyuria, premenstrual syndrome*, pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged*, vaginal hemorrhage*; *Rare:* albuminuria, breast enlargement, mastitis, oliguria. (*Adjusted for gender.)

The following treatment-emergent events were reported with intramuscular olanzapine for injection at one or more doses ≥2.5 mg/injection in clinical trials (722 patients). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. ***Body as a Whole***—*Frequent:* injection site pain; *Infrequent:* abdominal pain, fever. ***Cardiovascular***—*Infrequent:* AV block, heart block, syncope. ***Digestive***—*Infrequent:* diarrhea, nausea. ***Hemic and Lymphatic***—*Infrequent:* anemia. ***Metabolic and Nutritional***—*Infrequent:* creatine phosphokinase increased, dehydration, hyperkalemia. ***Musculoskeletal***—*Infrequent:* twitching. ***Nervous System***—*Infrequent:* abnormal gait, akathisia, articulation impairment, confusion, emotional lability. ***Skin and Appendages***—*Infrequent:* sweating.

Postintroduction Reports—Reported since market introduction and temporally (not necessarily causally) related to olanzapine therapy: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, neutropenia, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

DRUG ABUSE AND DEPENDENCE: Olanzapine is not a controlled substance.

Literature revised October 1, 2007

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of >1,400 studies by Dolovich et al[30] found a small association between fetal exposure to benzodiazepines and major malformations/cleft palate, but only in pooled data from case-controlled studies. No association was found between fetal exposure to benzodiazepines and malformations/cleft palate in pooled data from cohort studies.

A 32-month, hospital-based surveillance program of 28,565 births found no increase in the rate of major malformations in 43 infants exposed to clonazepam monotherapy—33 (77%) in the first trimester.[31] Thus, the risk of major malformations/cleft palate with the use of benzodiazepines in the first trimester appears to be low.

Toxicity and withdrawal syndromes. Neonatal benzodiazepine toxicity and withdrawal syndromes have been reported in studies and case reports. Although these syndromes occur, they do not affect all infants with late third-trimester benzodiazepine exposure. Prevalence rates have not been calculated.[32]

- Neonatal toxicity ("floppy infant syndrome")—characterized by hypothermia, lethargy, poor respiratory effort, and feeding difficulties—occurs after maternal benzodiazepine use just before delivery.[8]
- Neonatal withdrawal may be caused by very late, third trimester exposure to benzodiazepines. Symptoms—which can persist ≤3 months after delivery—include restlessness, irritability, abnormal sleep patterns, suckling difficulties, growth retardation, hypertonia, hyperreflexia, tremulousness, apnea, diarrhea, and vomiting.[8,29]

Recommendations. When possible, avoid benzodiazepines in the first trimester because of possible teratogenicity and then again late in the third trimester before delivery because of neonatal withdrawal syndromes. To reduce as much as possible the small risk of a benzodiazepine-related fetal malformation/cleft palate, wean the mother from benzodiazepines before conception. After the first trimester, the benzodiazepine can be restarted if necessary.[29]

To minimize neonatal withdrawal, gradually taper the mother's benzodiazepine before delivery.[29] Because the baby's due date is calculated to be ±2 weeks before delivery, begin this taper 3 to 4 weeks

before the due date and discontinue at least 1 week before delivery. Breastfeeding while taking benzodiazepines is not recommended because of the risk of oversedating the infant.

A rational approach

Both benzodiazepines and SSRIs are associated with low but demonstrated risks to the fetus when used during pregnancy (*Table 2, page 45*).[19,20,23,25,30,33] Use these medications to manage a patient's anxiety only if the clinical benefit to the mother justifies the potential risks to the fetus.[29]

A staggered combination of SSRIs during the first 2 trimesters and benzodiazepines during the last 2 trimesters can help balance the risks and benefits of pharmacotherapy of anxiety disorders during pregnancy (*Table 3*).

Frankly discuss with your patient the risks and benefits in the context of her perceived need for symptom control to sustain her level of functioning. You could document this discussion in the progress note as "R, B, A, and pt C," signifying that risks, benefits, and alternatives were discussed, and the patient consented. If possible, include the patient's husband, partner, or parent in this discussion.

CASE CONTINUED

CBT plus medication

Ms. K and her husband are open to adding weekly cognitive-behavioral therapy (CBT) for anxiety as long as she can continue her medications. You discuss the evidence regarding potential neonatal risks with paroxetine and clonazepam treatment. Because Ms. K is 6 weeks pregnant, you outline a plan for a rapid cross-taper off paroxetine and onto fluoxetine, 10 to 30 mg/d, explaining that paroxetine might pose a greater first-trimester risk of major congenital malformations and cardiac malformations. You discuss possible side effects of fluoxetine and explain a plan to taper off fluoxetine during the third trimester to reduce the risk of PPHN, early delivery, and withdrawal in the newborn.

Because Ms. K has been taking clonazepam at only 0.5 mg 1 to 2 times per week, you instruct her to stop taking the benzodiazepine for the next 6 weeks until she is through her first trimester. You also reassure her that she can use clonazepam after the first trimester, if necessary, as long as she agrees to taper off completely 1 to 2 weeks before to her due date.

You refer her to a CBT therapist and emphasize the importance of CBT, relaxation, and sleep hygiene—as well as support from her husband, family, and friends—to reduce her stress and facilitate the medication taper during her third trimester. You plan to see her monthly and co-manage her care with the CBT therapist and Ob/Gyn. You document this discussion in her medical record as evidence of informed consent.

Table 3

Staggered, combination therapy for anxiety disorders during pregnancy

Pregnancy stage	Recommended to manage risks to mother and fetus
First trimester	• SSRI (not paroxetine) • No benzodiazepines • Nondrug therapies*
Second trimester	• SSRI (not paroxetine) • Can use benzodiazepine if needed • Nondrug therapies*
Third trimester	• Taper off SSRI by 1 to 2 months before due date • Can use benzodiazepine until 2 weeks before due date • Nondrug therapies*

SSRI: selective serotonin reuptake inhibitor

* Nondrug therapies can include prenatal exercise, sleep hygiene, relaxation, and psychotherapy (cognitive-behavioral therapy, interpersonal therapy, supportive therapy, family/couples therapy)

Clinical Point

Discuss the risks, benefits, and alternatives with the patient and (if possible) the patient's husband, partner, or parent

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continued

Anxiety in pregnancy

Clinical Point

Benzodiazepines can be restarted in the second trimester, if needed, but taper them off completely 2 weeks before the patient's due date

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Related Resources

- Managing stress and anxiety during pregnancy. Patient information. www.babycenter.com/0_managing-stress-and-anxiety-during-pregnancy_1683.bc.
- Organization of Teratology Information Specialists (OTIS). www.otispregnancy.org.

Drug Brand Names

Clonazepam • Klonopin	Paroxetine • Paxil
Fluoxetine • Prozac	Sertraline • Zoloft

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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Bottom Line

Prenatal anxiety carries risks for mother and fetus, as do the SSRIs and benzodiazepines used to treat anxiety disorders. Carefully plan and discuss the use of SSRIs, benzodiazepines, and nonmedication therapies with the pregnant woman diagnosed with an anxiety disorder. Consider combining SSRI use during the first 2 trimesters with benzodiazepines during the last 2 trimesters to help balance the risks and benefits of pharmacologic therapy.

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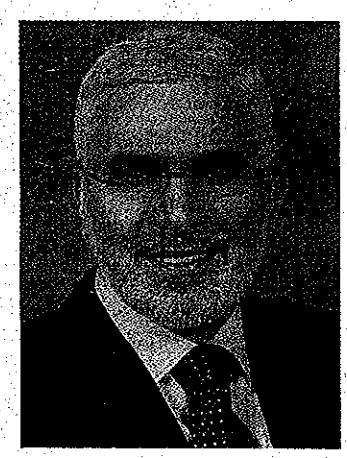

Henry A. Nasrallah, MD
Editor-in-Chief

Pregnant and mentally ill
A labor-intensive clinical challenge

Life in the womb is fraught with hazards. Any deviation from a healthy pregnancy can damage a major organ system (first trimester), impair brain structural/functional development (second trimester), or cause prematurity and low birth weight (third trimester).

So many things can go wrong in the intrauterine environment that it is miraculous most babies are born with no apparent physical malformations. But behavioral teratogenesis is more subtle than physical defects and might not manifest until years later. Numerous studies have linked prenatal and obstetric complications to serious psychiatric disorders later in childhood or adulthood.

No wonder, then, that the pharmacologic management of mentally ill pregnant women is a high-stakes challenge. Consider the article in this issue by Louann Brizendine et al on treating anxiety during pregnancy with selective serotonin reuptake inhibitors vs benzodiazepines (page 38).

FDA rankings of drugs' teratogenic potential are guided by the lowest tier of evidence-based medicine

Risk vs benefit. Psychotropics can have unpredictable, serious effects on fetal growth and development, but fetal repercussions may be equally devastating if we do not stabilize the mentally ill mother and guard her against self-neglect, nonadherence to prenatal care, suicide, or infanticide. Thus, the benefit:risk ratio is sufficiently high to justify pharmacologic intervention during pregnancy—with the requisite caution this treatment deserves.

The greatest risk to the fetus is teratogenicity, which 1 review article[1] defined as "the dysgenesis of fetal organs as evidenced either structurally or functionally (eg, brain functions). The typical manifestations of teratogenesis are restricted growth or death of the fetus, carcinogenesis, and malformations, defined as defects in organ structure or function. These abnormalities vary in severity (eg, hypospadias that is mild and may be missed, or is severe, necessitating several corrective operations). Major malformations may be life-threatening and require major surgery or may have serious cosmetic or functional effects."

continued

To comment on this editorial or other topics of interest, contact Dr. Nasrallah at henry.nasrallah@currentpsychiatry.com or visit CurrentPsychiatry.com and click on the "Contact Us" link.

Table

FDA classification of medications' teratogenic potential

Category	Examples
A: Controlled studies in pregnant women demonstrate no fetal risk	Folic acid, levothyroxine
B: Controlled animal studies have not shown a fetal risk, but there are no studies done on women OR controlled studies in animals have shown a fetal risk that was not reproduced in controlled human studies	Amoxicillin, ceftriaxone
C: Controlled animal studies have demonstrated adverse fetal effects and there are no human studies OR there are no controlled studies in humans or animals	Nifedipine, omeprazole
D: Controlled studies in humans demonstrate adverse fetal effects but the benefits of using the drug may be greater than the risks	Propylthiouracil
X: Controlled studies in animals and humans have demonstrated adverse fetal effects OR there is evidence of fetal risk based on human experience. The risk of using these drugs outweighs any possible benefit. The drug is absolutely contraindicated in pregnancy	Misoprostol, warfarin, isotretinoin

Source: Adapted from Food and Drug Administration. Current categories for drug use in pregnancy (www.fda.gov/fdac/features/2001/301_preg.html)

Because of teratogenicity concerns, pregnant women are excluded from clinical trials of investigational drugs. Thus, new drugs are not approved for use in these patients, and FDA rankings of drugs' teratogenic potential (*Table*) are guided by nonblinded, noncontrolled, naturalistic, after-the-fact observations—the lowest tier of evidence-based medicine.

Proceed with caution. Against this background, I follow these principles when treating pregnant patients:

- **Counsel all mentally ill women** about the potential risks of conceiving while receiving a psychotropic *before* they consider pregnancy. Counseling should include all prescription and nonprescription drugs.
- **Obtain a family history** of psychiatric disorders from all pregnant patients.
- **Make an accurate psychiatric diagnosis** in pregnant patients, and assess the risks of providing vs withholding needed pharmacotherapy.
- **Use nondrug treatments** (if evidence-based) before medications. Options include behavioral therapies, interpersonal therapy, supportive therapy, and somatic treatments such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, and light therapy.
- **When using psychotropics,** select the lowest-risk agents (Category A) first, and use the lowest efficacious dose.
- **Collaborate with** the patient's obstetrician. I coined the term "psychiatric dystocia" to describe the complicating potential of mental illness on pregnancy.
- **Completely avoid drugs** with established teratogenicity, and educate the patient not to take these drugs if another physician prescribes them to her.
- **Prescribe high-dose folate** (4 to 5 mg/d) for psychotic, bipolar, or depressed pregnant patients to protect against neural tube defects and enhance fetal CNS development.
- **Regularly check** the patient's nutrition, sleep hygiene, substance use (smoking, alcohol, coffee, illicit drugs), and use of over-the-counter supplements.
- **Use stress-reduction techniques** to reduce potential deleterious effects of stress-induced hypercortisolemia on the fetus, and involve the patient's partner.
- **See the mentally ill pregnant patient frequently** for check-ups on response and/or side effects.
- **Arrange for a child psychiatrist** to examine the infant of a seriously mentally ill patient shortly after birth. A newborn's irritability, crankiness, or insomnia may be perceived as withdrawal symptoms or behavioral teratogenesis, whereas it could very well be a genetically inherited temperament instability from a mother suffering from anxiety, depression, or psychosis.

Helping the mother without harming the child is like walking a tightrope: it calls upon all our skills, experience, and sound judgment.

Henry A. Nasrallah, MD
Editor-in-Chief

P.S. To help you manage potential medico-legal issues such as prescribing during pregnancy, CURRENT PSYCHIATRY welcomes Douglas Mossman, MD, as editor of *Malpractice Rx* (page 80). This month, Dr. Mossman discusses documentation and invites you to submit questions about liability.

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