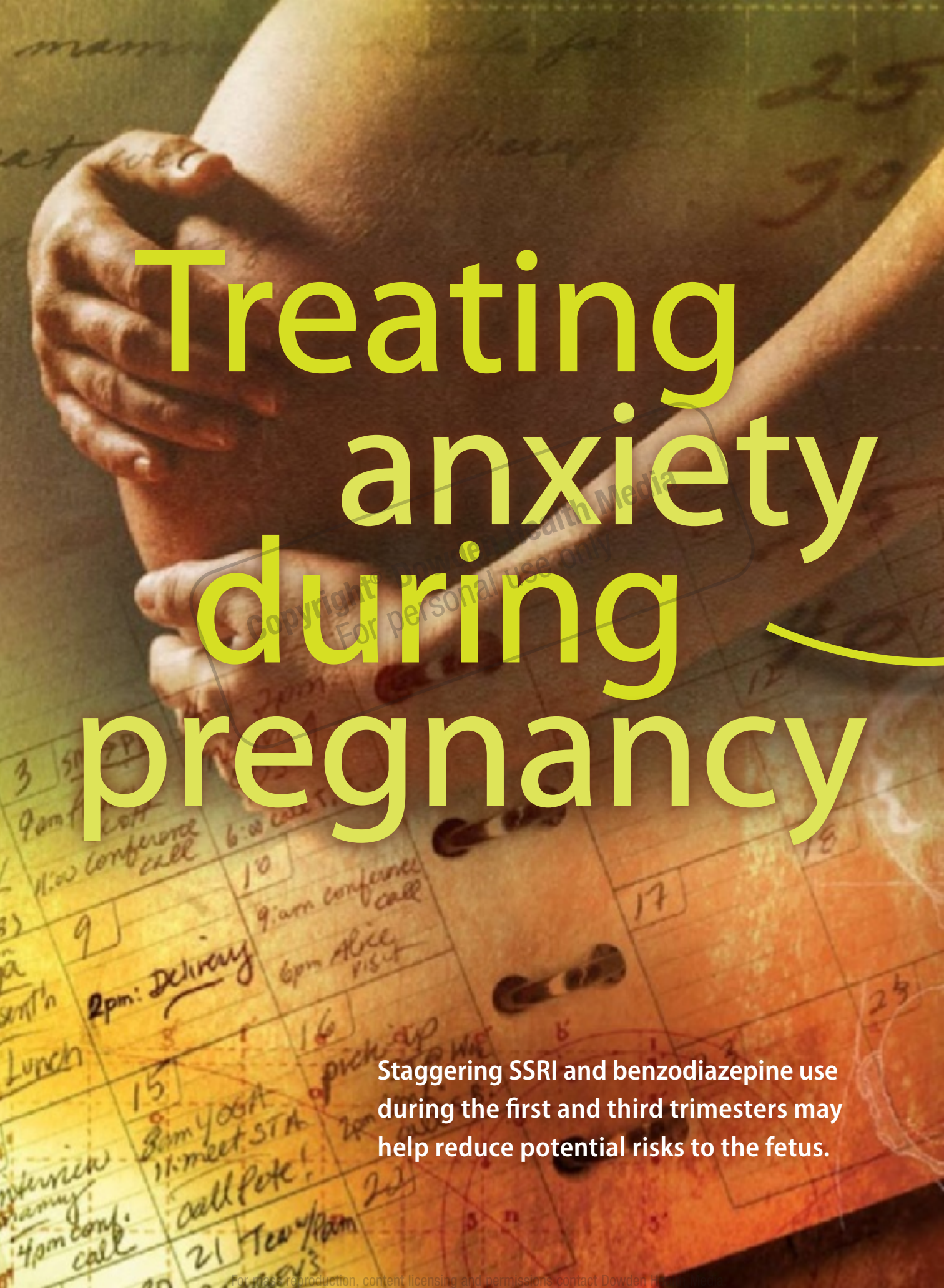

Treating anxiety during pregnancy

Staggering SSRI and benzodiazepine use during the first and third trimesters may help reduce potential risks to the fetus.

Current PSYCHIATRY

Just how safe are SSRIs?

Deborah B. Raphael, MD
Resident

Jessica Ross, MD
Postdoctoral fellow

Louann Brizendine, MD
Clinical professor
Director, Women's Mood and Hormone Clinic

Department of psychiatry
University of California, San Francisco

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

Clinical Point

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

Clinical Point

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

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]

continued on page 45

continued from page 42

Table 2

Risks of SSRIs vs benzodiazepines during pregnancy stages

Pregnancy stage when given	Fetal risk	SSRIs	Benzodiazepines
First trimester*	Teratogenicity	Paroxetine use associated with 2-fold increased risk of major congenital anomalies and 3-fold increased risk of major cardiac anomalies;[19] meta-analysis calculated significant risk of cardiac malformations (odds ratio 1.72; population prevalence = 13.4/1,000 births)[20,33]	Meta-analysis of case control studies showed increased risk of major malformations/ cleft palate (odds ratio 3.01; population prevalence = 10 to 20/1,000 births); no association seen in cohort studies[30]
Third trimester	PPHN	Case control study showed 3.7% of infants with PPHN were exposed to SSRIs vs 0.7% of controls; adjusted odds ratio 6.1, absolute risk to exposed population = 6 to 12/1,000 births)[23]	
Perinatal and long-term effects	Toxicity/ withdrawal syndromes	Cohort study of 60 infants concluded prevalence of discontinuation syndromes is 30% in neonates with third trimester SSRI exposure[25]	Neonatal toxicity ("floppy infant syndrome") and neonatal withdrawal reported with maternal benzodiazepine use in late third trimester; prevalence unknown†
	Preterm birth, serotonin withdrawal syndromes, CNS effects, long-term neurobehavioral effects	Unknown†	Unknown†

PPHN: persistent pulmonary hypertension of the newborn; SSRIs: selective serotonin reuptake inhibitors

* Available data indicate that first-trimester exposure to SSRIs (other than paroxetine) and benzodiazepines may increase the relative risk for congenital anomalies, but the absolute risk of having a child with an anomaly is small.

† Some case reports, but published literature is insufficient to determine prevalence or magnitude of risk.

Recommendations. The perception that SSRIs have low fetal toxicity has guided prescribing practices in recent years. Newer evidence shows, however, that fetal exposure to SSRIs may have some adverse effects, including lower birth weight and early delivery. First-trimester paroxetine use has been associated with increased risk for fetal ventricular and/or atrial septal defects.

Discuss these risks with the patient when you consider starting or continuing SSRI use during pregnancy.[24] If you prescribe an SSRI, use the minimum effective dosage and avoid paroxetine during pregnancy.[18]

To reduce the risk for PPHN, early delivery, and neonatal withdrawal syndromes, taper and discontinue the SSRI during the third trimester. Restarting the SSRI soon after delivery is the most effective way to prevent recurrence of anxiety symptoms or postpartum depression.

Benzodiazepines

Teratogenicity. Like SSRIs, benzodiazepines cross the placenta to the fetus.[29] Benzodiazepine teratogenicity remains controversial.[8] Some—but not all—data show a small but significant increased risk for major malformations/oral cleft malformations with first-trimester benzodiazepine exposure.

A Medline literature search from 1966 to 2000 found not enough information to determine whether potential benefits of benzodiazepines to the mother outweigh risks to the fetus.[29] An ambitious meta-analysis

continued on page 50

Current PSYCHIATRY
CurrentPsychiatry.com

Clinical Point

Taper and discontinue SSRI use during the third trimester, then restart after delivery to prevent anxiety symptom recurrence

continued from page 45

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)

References

1. Ross LE, McLean LM. Anxiety disorders during pregnancy and the postpartum period: a systematic review. *J Clin Psychiatry* 2006;67(8):1285-98.
2. Labad J, Menchon JM, Alonso P, et al. Female reproductive cycle and obsessive-compulsive disorder. *J Clin Psychiatry* 2005;66(4):428-35.
3. Adewuya AO, Ola BA, Aloba OO, Mapayi BM. Anxiety disorders among Nigerian women in late pregnancy: a controlled study. *Arch Womens Ment Health* 2006;9(6):325-8.
4. Field T, Hernandez-Reif M, Diego M, et al. Stability of mood states and biochemistry across pregnancy. *Infant Behav Dev* 2006;29(2):262-7.
5. Teixeira JM, Fisk NM, Glover V. Association between maternal anxiety in pregnancy and increased uterine artery resistance index: cohort based study. *BMJ* 1999;318(7177):153-7.

continued

Current PSYCHIATRY
CurrentPsychiatry.com

Clinical Point

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

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

6. Monk C, Myers MM, Sloan RP, et al. Effects of women's stress-elicited physiological activity and chronic anxiety on fetal heart rate. *J Dev Behav Pediatr* 2003;24(1):32-8.
7. Egliston KA, McMahon C, Austin MP. Stress in pregnancy and infant HPA axis function: conceptual and methodological issues relating to the use of salivary cortisol as an outcome measure. *Psychoneuroendocrinology* 2007;32(1):1-13.
8. Levey L, Ragan K, Hower-Hartley A, et al. Psychiatric disorders in pregnancy. *Neurol Clin* 2004;22(4):863-93.
9. Oberlander TF, Reebye P, Misri S, et al. Externalizing and attentional behaviors in children of depressed mothers treated with a selective serotonin reuptake inhibitor antidepressant during pregnancy. *Arch Pediatr Adolesc Med* 2007;161(1):22-9.
10. Misri S, Reebye P, Kendrick K, et al. Internalizing behaviors in 4-year-old children exposed in utero to psychotropic medications. *Am J Psychiatry* 2006;163(6):1026-32.
11. Copper RL, Goldenberg RL, Das A, et al. The Preterm Prediction Study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. *Am J Obstet Gynecol* 1996;175(5):1286-92.
12. Sutter-Dallay AL, Giaconne-Marcesche V, Glatigny-Dallay E, Verdoux H. Women with anxiety disorders during pregnancy are at increased risk of intense postnatal depressive symptoms: a prospective survey of the MATQUID cohort. *Eur Psychiatry* 2004;19(8):459-63.
13. Nierop A, Bratsikas A, Zimmermann R, Ehlert U. Are stress-induced cortisol changes during pregnancy associated with postpartum depressive symptoms? *Psychosom Med* 2006;68(6):931-7.
14. Weissman MM. Recent non-medication trials of interpersonal psychotherapy for depression. *Int J Neuropsychopharmacology* 2007;10(1):117-22.
15. Ward RK, Zamorski MA. Benefits and risks of psychiatric medications during pregnancy. *Am Fam Physician* 2002; 66(4):629-36.
16. Bastani F, Hidarnia A, Montgomery KS, et al. Does relaxation education in anxious primigravid Iranian women influence adverse pregnancy outcomes? A randomized controlled trial. *J Perinat Neonatal Nurs* 2006;20(2):138-46.
17. Fricchione G. Generalized anxiety disorder. *N Engl J Med* 2004;351(7):675-82.
18. Källén BA, Otterblad Olausson P. Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. *Birth Defects Res A Clin Mol Teratol* 2007;79(4):301-8.
19. Berard A, Ramos E, Rey E, et al. First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. *Birth Defects Res B Dev Reprod Toxicol* 2007;80(1):18-27.
20. Bar-Oz B, Einarson T, Einarson A, et al. Paroxetine and congenital malformations: meta-analysis and consideration of potential confounding factors. *Clin Ther* 2005;29(5):918-26.
21. Malm H, Klaukka T, Neuvonen PJ. Risks associated with selective serotonin reuptake inhibitors in pregnancy. *Obstet Gynecol* 2005;106(6):1289-96.
22. Nulman I, Rovet J, Stewart DE, et al. Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry* 2002;159(11):1889-95.

Related Resources

- Baby Center. 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.

23. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006;354(6):579-87.
24. Haddad PM, Pal BR, Clarke P, et al. Neonatal symptoms following maternal paroxetine treatment: serotonin toxicity or paroxetine discontinuation syndrome? *J Psychopharmacology* 2005;19(5):554-7.
25. Levinson-Castiel R, Merlob P, Linder N, et al. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. *Arch Pediatr Adolesc Med* 2006;160(2):173-6.
26. Sanz EJ, De-las-Cuevas C, Kiuru A, et al. Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. *Lancet* 2005;365(9458):482-7.
27. Suri R, Altshuler L, Hellemann G, et al. Effects of antenatal depression and antidepressant treatment on gestational age at birth and risk of preterm birth. *Am J Psychiatry* 2007;164(8):1206-13.
28. Zeskind PS, Stephens LE. Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. *Pediatrics* 2004;113(2):368-75.
29. Iqbal MM, Sobhan T, Ryals T. Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. *Psychiatr Serv* 2002;53(1):39-49.
30. Dolovich LR, Addis A, Vaillancourt JM, et al. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. *BMJ* 1998;317(7162):839-43.
31. McElhatton PR. The effects of benzodiazepine use during pregnancy. *Reprod Toxicol* 1994;8(6):461-75.
32. Lin AE, Peller AJ, Westgate MN, et al. Clonazepam use in pregnancy and the risk of malformations. *Birth Defects Res A Clin Mol Teratol* 2004;70(8):534-6.
33. Levy M, James MS, Erickson JD, McClearn AB. Prevalence of birth defects. *Birth outcomes.* Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/reproductivehealth/Products&Pubs/DatatoAction/pdf/birout4.pdf. Accessed January 9, 2008.

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.