Panic Disorder During Pregnancy

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KEY WORDS

anxiety disorders, panic disorder, pregnancy, treatments, pharmacology, course, teratogenicity, SSRI, benzodiazepines

ABSTRACT

Panic disorder, which can be complicated by agoraphobia, has a lifetime prevalence of approximately 2% and is the primary diagnosis in approximately 1 out of every 5 to 10 psychiatric patients. Panic disorder primarily affects women, who undergo unique biochemical and physiological changes during the various stages of female life cycle, particularly pregnancy, which seems to have a variable impact on the course of the disorder. Treatment providers should use pregravid symptom severity as a guideline for the treatment of panic disorder during pregnancy, and should routinely evaluate the severity of their gravid panic patients' symptoms. Many effective pharmacological treatments are available for panic disorder, including benzodiazepines and the selective serotonin reuptake inhibitors (SSRIs). Although there is a paucity of data concerning the teratogenicity of the SSRIs, extant research indicates that the absolute risk of teratogenic effects with both SSRIs and benzodiazepines is low. Still, if one of the many pharmacological treatments available for panic disorder is considered, both patients and their practitioners should carefully weigh the risks and benefits of pharmacotherapy. Mental Fitness. *2003;2(4):45-53*

INTRODUCTION

Panic disorder is an anxiety disorder characterized by clearly defined physical and cognitive symptoms. It affects about 2% of the general population and between 10% and 20% of those seeking psychiatric care.[1] Agoraphobia can complicate panic disorder in as many as half of the cases.[2,3] Moreover, it is well known that panic disorder and major depressive disorder are highly comorbid.[4,5]

Like most other mood and anxiety disorders, panic disorder primarily affects women, who are more likely than men to have a chronic course with poor remission and high relapse rates.[6] Thus, it is likely that a patient seeking care for panic disorder will be a woman. Because the bulk of treatment for panic disorder is delivered in both emergency and primary care settings,[7] treatment providers in these settings should be aware that the unique physiological effects of the female life cycle, particularly those of pregnancy, may affect the course and treatment of panic disorder. This article reviews the epidemiology, course, and treatment of panic disorder in the context of pregnancy, from conception to the postpartum period. Biological and psychological effects, as well as current risk-benefit assessments of effective treatments, are discussed. Finally, directives for practitioners are provided.

DIAGNOSIS OF PANIC DISORDER

Essential to a *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (*DSM-IV)* diagnosis of panic disorder is the recurrence of unprecipitated panic attacks, characterized by at least 5 of the 13 possible physical and cognitive symptoms (see Table 1). In addition, a diagnosis of panic disorder stipulates that these attacks lead to persistent concerns about subsequent attacks, or to a change in behavior. The minimum symptomatic period is 1 month.[8] Occasionally referred to as "anxiety attacks," panic attacks have a precipitous onset with a crescendo-like pattern over the course of several minutes. The frequency of panic attacks varies widely among

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DSM-IV PANIC SYMPTOMS

TABLE 1

PHYSICAL SYMPTOMS	COGNITIVE SYMPTOMS
• SHORTNESS OF BREATH • CHOKING SENSATIONS • HEART PALPITATIONS • CHEST PAIN AND/OR DISCOMFORT • TREMULOUSNESS • DIZZINESS AND/OR LIGHTHEADEDNESS • SWEATING • CHILLS AND/OR HOT FLUSHES • NAUSEA AND/OR ABDOMINAL DISCOMFORT	• PARASTHESIAS • DEPERSONALIZATION AND/OR DEREALIZATION • FEAR OF LOSING CONTROL AND/OR GOING CRAZY • FEAR OF DYING

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patients. Similarly, there is considerable variation in the constellation of symptoms for each attack. Often patients experience clusters of symptoms such as cardiovascular symptoms (eg, heart palpitations, chest pain, and parasthesias) or cognitive symptoms (eg, the conviction that a catastrophic event, including death, will imminently occur).[9] Patients who have several panic attacks and suffer from worry or develop a change in behavior typically experience more impairment and thus a more malignant course. Patients often suffer from attacks precipitated by stressors or traumatic events. Technically, these attacks do not qualify for a diagnosis of panic disorder because they are not unexpected. Some patients with panic attacks do not qualify for a diagnosis of panic disorder, but may still experience functional impairment. However, little is know about the prognosis of subthreshold panic.[10-12]

Several general medical conditions commonly occur in conjunction with panic disorder. Both hyperventilation[13] and sleep deprivation[14] can induce or worsen panic attacks. Panic attacks are also frequent in patients who suffer from chest pain that is not associated with coronary artery disease.[12] Historically, many patients with panic disorder have been assigned a diagnosis of mitral valve prolapse,[15] although newer cardiac imaging studies do not show as strong an association.[16] Both hyperthyroidism and hot flashes, medical conditions that are more likely to occur in women, have been associated with panic attacks.[17-19] It has been proposed that physical sensations, such as those caused by medical illnesses that affect the autonomic nervous system, may form somatic triggers that give rise to catastrophic thoughts and the subsequent development of panic.[20,21] In addition, the use of caffeine, alcohol, marijuana, cocaine, and even cold medications can induce or worsen panic attacks.

ILLNESS COURSE IN PREGNANCY

The medical community has long maintained that pregnancy acts as a buffer against psychiatric illnesses,[22,23] including panic disorder.[24] However, some studies suggest that women, especially those with a history of affective instability, may have a heightened susceptibility to panic during pregnancy and the postpartum period.[25-27] Unfortunately, knowledge about the course of panic disorder during pregnancy is limited to small case series and reports. Findings suggest that severe pregravid symptoms tend to stay severe and may worsen, while mild symptoms tend to stay mild and may even remit completely. Moderate symptoms, it seems, may either worsen or improve[25] (see Figure).

There are theoretical reasons to believe that pregnancy may affect the course of panic disorder, although arguments for either improvement or worsening can be made. On one hand, progesterone may have anxiolytic properties, either by itself or by virtue of some of its metabolites[28,29] that function as agonists at the γ–aminobutyric acid

(GABA)-benzodiazepine receptor. On the other hand, respiratory mechanics may change during pregnancy and may increase the propensity to panic. Pregnant women often take smaller breaths with less respiratory excursion. This occurs because progesterone induces mild hyperventilation.[30] In addition, the pelvic and abdominal contents can compress the diaphragm. In the former case, panic attacks could attenuate, whereas mechanical changes in the latter case could increase susceptibility to panic.

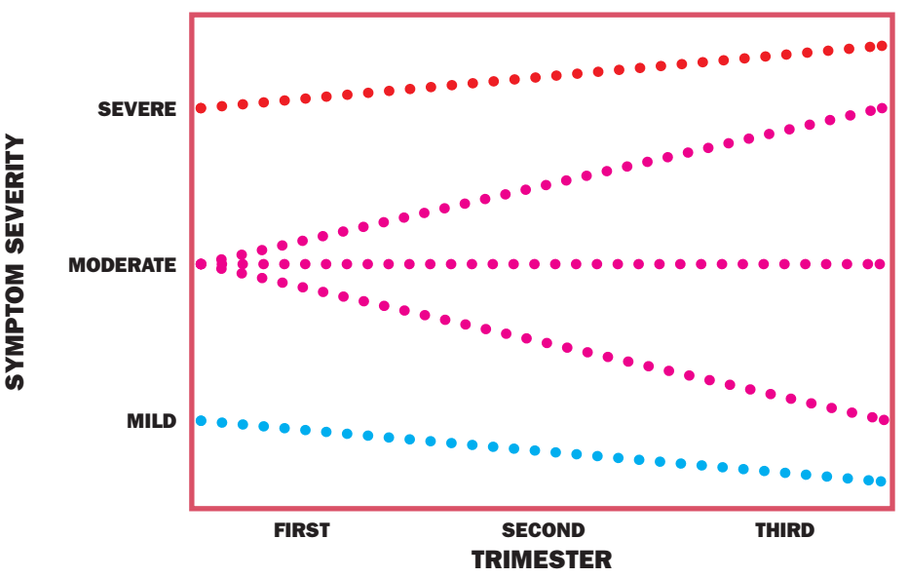
Women may elect to discontinue prophylactic treatment for panic attacks when they become pregnant in order to prevent perinatal complications. The limited evidence available suggests that women with severe pregravid panic symptoms will likely relapse if medication is discontinued. Only women with mild pregravid symptoms seem to successfully discontinue drug treatment.[25] This lends further support to the notion that pregnancy has a variable impact on the course of panic disorder. It further suggests that pregravid symptom severity can predict the gravid course of the disorder and whether or not a woman will be able to remain panic-free during pregnancy, should she elect to discontinue her medication.

PANIC WITH AGORAPHOBIA

Studies estimate that between 7% and 50% of patients who suffer from panic disorder also experience agoraphobia, which is anxiety associated with the fear of being in a place from which escape may be difficult or help unavailable.[2,3] However, it should be noted that agoraphobia can be mistaken for simple or specific phobia, which could account for the wide range in the comorbidity estimates.[31] Moreover, agoraphobia does not only occur alongside panic. In fact, community studies indicate that agoraphobia has a lifetime prevalence of between 3.5% and 6%,[32] which indicates that agoraphobia actually occurs alone far more frequently than with panic disorder. Anecdotally, however, patients presenting with agoraphobia sans panic are far less common in treatment settings. This discrepancy has several plausible explanations. For example, patients suffering from panic with agoraphobia may experience a course that is more functionally impairing than those who have panic disorder alone. Patients with uncomplicated panic disorder may thus seek help more frequently than patients with agoraphobia, who can become housebound and do not enter into treatment at all.

POTENTIAL COURSE OF SYMPTOMS OF PANIC DISORDER DURING PREGNANCY

FIGURE



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Agoraphobia often causes those affected by it to become phobically avoidant of potentially problematic places or situations, or to endure them only with severe distress or discomfort. In extreme cases, patients will not leave the house without a trusted companion, a situation that renders them virtually housebound. Patients who suffer from panic with agoraphobia have a less promising prognosis than those who suffer from uncomplicated panic.[21,33] However, it is not known whether pregnant women are more likely to suffer from panic disorder with agoraphobia than from uncomplicated panic. It remains unclear whether or not the gravid course of panic with agoraphobia differs from the non-gravid course of the disorder.

TREATMENT

In general, panic disorder treated on an outpatient basis rarely requires hospitalization, and panic during pregnancy is no exception. Just as pregravid symptom severity functions as a predictor of the clinical course of the disorder during pregnancy, symptom severity during pregnancy should function as a guideline for prescribed treatment. Treatment providers should consider that panic-free patients are not necessarily recovered patients; the absence of panic attacks during treatment is not indicative of symptom remission and does not indicate that treatment can be discontinued successfully. As previously mentioned, relapse rates are high in panic disorder patients who discontinue pharmacotherapy.[34] Findings from a recent study that examined medications prescribed and the patients' ability to discontinue treatment indicate that pregnancy does not increase the likelihood of successful discontinuation of pharmacological treatment.[35] Therefore, women with more severe panic symptoms may be at risk for symptomatic persistence that warrants maintenance therapy, whether that therapy is nonpharmacological or pharmacological in nature.

Nonpharmacological Treatment

Psychotherapy has been the predominant psychiatric treatment for patients suffering from panic disorder. However, it has proven difficult to define psychotherapeutic aspects clearly; the efficacy of various modalities has been formally evaluated only recently.[9] Several forms of psychotherapy are known to be effective in the treatment of panic disorder, including cognitive and behavioral therapies, as well as cognitive-behavioral therapy (CBT), a combination of the two. On the other hand, treatments such as emotion-based psychotherapy are not successful interventions for panic disorder.[36]

CBT has been well-studied and established as an effective treatment for panic disorder.[9] In fact, several controlled studies have shown CBT to be superior to other nonpharmacological treatments.[37] Typically, treatment lasts between 3 and 6 months, and involves psychoeducation, breathing retraining, cognitive restructuring, exposure to fear cues, and continuous panic monitoring. The patient is educated about her illness and the treatment procedures, while her practitioner carefully monitors her symptoms. Treatment providers guide the exploration of both catastrophic and negative thoughts, as well as fears of various bodily sensations. The patient completes assignments that enable her to identify and correct negative thinking and dysfunctionally avoidant behaviors. She may be instructed to gradually expose herself to places or situations that elicit fear in a process known as "graded exposure". In addition, the patient is taught to control or manage panic attacks by relaxation and deep-breathing exercises; a number of self-help books and tapes that describe these techniques are available at bookstores. Typically, group therapy assumes a cognitive-behavioral framework.

There is little to no risk involved in these particular treatment modalities. However, while some women with mild pregravid symptoms may experience symptomatic relief, others with more severe symptoms may not benefit significantly from CBT or its components alone. Moreover, the effective components and duration of CBT have not been defined clearly for pregnant women with panic. A substantial number of pregnant women, especially those with moderate to severe panic symptoms, often require some intervening treatment with medication, either alone or in conjunction with psychotherapy.[25,37]

Pharmacological Treatment

Two broad classes of medications are effective pharmacological treatments for panic disorder. The first class consists of benzodiazepine anxiolytics, and the second class consists of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and others (see Table 2). Because the most widely prescribed agents for the treatment of panic disorder are benzodiazepines and SSRIs, TCAs and MAOIs will not be addressed.

When prescribing medication for pregnant patients, clinicians need to consider that drug pharmacokinetics

and plasma levels may change.[38] Decreases in gastrointestinal motility and the secretion of gastric acids, the expansion of plasma volume, and changes in cardiac output which increase hepatic and renal blood flow[38] are known to decrease the bioavailability and thus increase the drug dose requirements. Still other processes, such as changes in plasma protein-binding and decreases in plasma protein affinity for the drug, can make more of the free drug available and diminish drug requirements.

The changes in placental structures and uterine circulation during pregnancy are conducive to greater placental passage later in the term. These changes yield 3 potential fetal effects associated with medication use during pregnancy: morphological teratogenicity (organ malformation), neonatal toxicity (perinatal syndrome), and behavioral teratogenicity (postnatal behavioral sequelae) (see Table 3). However, it should be noted when considering these potential effects that the risk of untreated psychiatric disorders may affect feto-placental integrity and central nervous system (CNS) development.[39] A database of information regarding teratogenicity is published and regularly updated by Briggs and colleagues.[40]

Benzodiazepines. Of the women who take psychotropic medications during pregnancy, over 35% take benzodiazepines.[41] These agents are the most widely prescribed and studied drugs, and are common and effective treatments for anxiety disorders,

PHARMACOLOGICAL TREATMENTS FOR PANIC DISORDER

TABLE 2

CLASS	GENERIC NAME	TRADE NAME	STANDARD DOSE (MG/DAY)
BENZODIAZEPINES	ALPRAZOLAM*	XANAX	2-8
	CHLORDIAZEPOXIDE	LIBRIUM	20-80
	CLONAZEPAM	KLONOPIN	1-4
	CLORAZEPATE	TRANXENE	15-60
	DIAZEPAM	VALIUM	10-40
	LORAZEPAM	ATIVAN	2-8
	OXAZEPAM	SERAX	30-70
	PRAZEPAM	CENTRAX	20-80
	TEMAZEPAM	RESTORIL	7.5-30
	TRIAZOLAM	HALCION	0.125-0.5
MAOIs	PHENELZINE	NARDIL	45-90
	TRANCYPROMINE	PARNATE	30-70
OTHER	VENLAFAXINE	EFFEXOR	37.5-225
SSRIs	FLUOXETINE	PROZAC	5-80
	FLUVOXAMINE	LUVOX	50-300
	PAROXETINE*	PAXIL	10-50
	SERTRALINE*	ZOLOFT	50-200
TCAS	AMITRPTYLINE	ELAVIL AND OTHERS	150-300
	CLOMIPRAMINE	ANAFRANIL	100-250
	DESIPRAMINE	NORPRAMIN AND OTHERS	150-300
	DOXEPIN	SINEQUAN AND OTHERS	150-300
	IMIPRAMINE	TOFRANIL	150-300
	NORTRIPTYLINE	PAMELOR AND OTHERS	75-200

*FDA-approved for the treatment of panic disorder

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POTENTIAL TERATOGENIC EFFECTS OF DRUG EXPOSURE DURING THE FIRST AND THIRD TRIMESTERS

TABLE 3

TRIMESTER OF EXPOSURE	GENERAL TERATOGENIC EFFECT TYPE	SPECIFIC POTENTIAL EFFECTS
FIRST	MORPHOLOGICAL TERATOGENICITY	ORAL CLEFT CLEFT LIP CARDIOVASCULAR MALFORMATIONS REDUCED HEAD CIRCUMFERENCE VENTRICULAR SEPTAL DEFECTS CONOTRUNCAL MALFORMATIONS
THIRD	NEONATAL TOXICITY	MILD SEDATION HYPOTONIA RELUCTANCE TO SUCK APNOEIC SPELLS CYANOSIS IMPAIRED METABOLIC RESPONSE TO COLD STRESS
	BEHAVIORAL TERATOGENICITY	IMPAIRED NEUROBEHAVIORAL DEVELOPMENT* REDUCED IQ*

*Studies show these effects diminish by 18 months[58] and resolve completely by 4 years.[46]

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particularly panic disorder, due to their rapid and effective onset of action.[42] Benzodiazepines are lipophilic, undissociated, molecular agents that readily penetrate membranes. Such properties enable these drugs to promote binding to the GABA-benzodiazepine cell membrane receptor complex, which increases its affinity and augments the inhibitory activity of the neurotransmitter GABA. This raises the threshold of neuronal firing and thereby modulates the neurotransmission of serotonin, dopamine, and norepinephrine, a process thought to be the source of the tranquilizing, myorelaxing, and anticonvulsant properties of benzodiazepines.[43]

In addition to their anxiolytic properties, however, benzodiazepines have sedative properties and can cause anterograde amnesia. There is also potential for abuse and dependence in a subgroup of patients, and all patients who remain on benzodiazepines for a substantial period of time experience withdrawal symptoms if treatment is discontinued abruptly. Typically, abrupt withdrawal manifests itself in the re-emergence of anxiety symptoms, but can include other effects such as insomnia and even seizures. Abrupt withdrawal may be an issue with the neonate when born to a mother taking high doses of these agents over time.

Teratogenicity. During pregnancy, benzodiazepines exhibit a rapid placental transfer with significant uptake of the drug during both early and late pregnancy.[44] Thus, both clinicians and patients logically express concern regarding exposure to these agents during pregnancy. However, first trimester exposure to benzodiazepines has been the focus of most research.

It is generally maintained that benzodiazepines are not teratogenic. However, the findings of several studies suggest that there is an increase in congenital anomalies (eg, oral cleft) over the baseline risk. For instance, one study found an increased risk of congenital anomalies in fetuses exposed to maternal benzodiazepine use during the first trimester of pregnancy.[38] Moreover, a recent meta-analysis found that in case-control studies, fetuses exposed to

benzodiazepines are almost 2 times more likely to have oral cleft (risk ratio = 1.79, 95% CI = 1.13 – 2.82). Analyses of the data collected in cohort studies failed to find an association between oral cleft and gestational exposure to benzodiazepines. What probably accounts for the differences between the case-control and cohort findings is the fact that case-control studies are designed to investigate rare events. Results from case-control studies suggest a risk of oral cleft of about 80% over the baseline risk of 6/10,000 births.[45] Still, the absolute risk of congenital anomalies remains low.

One study, a 4-year follow-up of 550 children exposed to benzodiazepines, found that there was no increase in malformation rates or adverse effects on neurobehavioral development and IQ. The same study found that exposure to benzodiazepines during the third trimester and labor resulted in marked withdrawal symptoms in neonates. These symptoms included mild sedation, hypotonia, reluctance to suck, apnoeic spells, cyanosis, and an impaired metabolic response to cold stress.[46]

Selective Serotonin Reuptake Inhibitors. The SSRIs have been found to be effective in the treatment of panic disorder; sertraline and paroxetine have been approved by the Food and Drug Administration (FDA). However, there are relatively few data on the teratogenicity of the drugs in this class. The largest available body of data on teratogenicity exists for fluoxetine, although risks may vary even among drugs in the same class. In addition, the initial treatment response may take as long as 4 weeks, and a full response typically requires 8-12 weeks of treatment. Bearing in mind that individual cases should be evaluated and treated appropriately, physicians should consider these points when prescribing SSRIs to pregnant women with panic disorder.

Teratogenicity. Compared to benzodiazepines, relatively few studies have been published on the teratogenic effects of SSRIs. A recent report examining the results of several studies indicates that exposure to the SSRIs does not increase the risk for intrauterine death or major birth defects, nor does it affect the development of children whose mothers take fluoxetine during gestation.[47] Moreover, several studies have failed to find behavioral teratogenicity with SSRIs. In fact, the biggest risk with SSRIs appears to be preterm labor and low birth weight.[48-51] Most controlled studies find that infants exposed to SSRIs are smaller at birth than controls.[49,50,52] However, the differences are not always significant,[53] and one study failed to find differences between the sizes of SSRI-exposed infants and controls.[54] As with benzodiazepines, direct drug effects and withdrawal syndromes have occurred in some neonates whose mothers were treated with antidepressants near term.[47] (Of the SSRIs, paroxetine has been associated with withdrawal symptoms.)

POSTPARTUM COURSE OF PANIC DISORDER

Little is known about the course of panic disorder during the postpartum period; to date, few studies have focused on the postpartum course of panic, and no studies have examined panic with postpartum onset. However, it is widely known that women have a heightened vulnerability to the development and relapse of mood and anxiety disorders, which is supported by the findings of several studies.[25,55] In light of the dearth of epidemiologic data regarding the postpartum course of panic, treatment providers should closely monitor symptom severity and previous treatment response, which are 2 of the 3 primary considerations of formulating a treatment plan.

Special Considerations for Breastfeeding Mothers

The other major consideration when prescribing treatment to a postpartum woman is whether or not she is breastfeeding. Small amounts of benzodiazepines, of either dietary or endogenous biosynthetic origin, occur naturally in the milk of mothers who do not use benzodiazepine anxiolytics. Both SSRIs and benzodiazepines ingested by nursing mothers appear in human milk, although only high clinical doses might be expected to have an effect on the newborn. Of the SSRIs, only paroxetine is virtually undetectable in infant plasma.[56] In neonates, particularly premature infants, elimination of drugs is less rapid relative to the immaturity of the developing hepatic systems that metabolize pharmacological compounds. In general, therefore, high single doses of benzodiazepines and repeated, prolonged administration of both benzodiazepines and SSRIs should be avoided.[57] As of yet, no psychotropic compounds have been approved by the FDA for use while breastfeeding.

Treatment Directives

Recent research suggests that the variation in the course of panic disorder during pregnancy is predicted by pregravid symptom severity; the latter should be assessed prior to treatment during pregnancy. Treatment providers can outline the risks and benefits

of pharmacological treatment during pregnancy, but the ultimate decision regarding medication treatment of panic disorder during pregnancy is the patient's. Clinicians must closely monitor patients during pregnancy, and should prescribe pharmacotherapy only if the severity of symptoms warrants such measures. With regard to fetal exposure to benzodiazepines, level II ultrasonography should be used to rule out visible forms of oral cleft until more research is reported.[45]

SUMMARY

In summary, pregnancy has a variable impact on the course of panic disorder. As evidenced from epidemiologic data, pregravid symptom severity currently functions as the most accurate predictor of the gravid course of the disorder. Because panic disorder, if left untreated during pregnancy, might be harmful to fetuses and has potentially harmful effects on neonates, practitioners should use gravid symptom severity as a compass to guide treatment during pregnancy. Due to the dearth of literature and data currently available, additional research is required to define more clearly the effects of pregnancy on the disorder, and the effects that the disorder exacts on pregnancy, as well as the safest and most efficacious treatments for the disorder. MF

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