What's the best strategy for bipolar disorder during pregnancy?

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Evidence-based answer

Lithium is the first-line treatment for pregnant patients requiring medication (SOR: **C**, based on expert opinion).

Monotherapy is preferred for women of childbearing age who have bipolar disorder (strength of recommendation [SOR]: **C**, based on expert opinion).

When prescribing lithium or anticonvulsant drugs (eg, valproic acid and carbamazepine), draw blood levels monthly during the first and second trimesters, and then weekly in the third trimester (SOR: **C**, based on expert opinion).

Give all pregnant women taking medications for the prevention of mania a detailed fetal anatomy ultrasound at 18 to 20 weeks (SOR: **C**, based on expert opinion).

Behavior therapy has a role as an adjunct to pharmacologic therapy, but no studies show its benefit alone in preventing mania (SOR: **C**, based on expert opinion).

Electroconvulsive therapy may be beneficial for patients with refractory depressive symptoms, and may be used in pregnancy (SOR: **C**, based on expert opinion).

Clinical commentary

Psychiatric consultation is essential

Unfortunately, the medications used to treat this serious health problem can also have important negative effects on a patient's health. Although the principles outlined here are helpful guidelines, in practice I rarely treat patients with bipolar disorder without psychiatric consultation.

As family physicians, it's critical that we address reliable contraception and the importance of preconception planning with women early in the course of this psychiatric illness.

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Monotherapy is preferred; it generally minimizes risk of congenital anomalies

Evidence summary

Data on the treatment of bipolar disease among fertile women are limited to case-control studies and drug registries because of a lack of RCTs in this population.[1] Onset of bipolar illness often occurs in the teens and twenties, which puts women with bipolar disorder at risk for having episodes requiring treatment during their childbearing years. Treatment might be initiated for a nonpregnant patient, but you must consider potential pregnancy when choosing a medication.

The **TABLE** shows common medications used in bipolar illness, their risk categories for pregnancy and lactation, and monitoring recommendations.[1–5]

CONTINUED

TABLE

Management of bipolar disorder during pregnancy: Drugs, safety categories for pregnancy and lactation, and monitoring recommendations

TREATMENT	PREGNANCY SAFETY CATEGORY*	LACTATION SAFETY CATEGORY†	DOSING AND MONITORING
Lithium	D	L4	More frequent dosing maintains therapeutic levels and avoids peaks; it's unclear if this benefits the fetus Detailed ultrasound in second trimester Monthly levels during 1st and 2nd, weekly during 3rd trimester Decrease dose during delivery, up to 50%
ANTICONVULSANTS			
Carbamazepine (Tegretol)	C/D	L2	Contraindicated in 1st trimester Monthly levels during 2nd trimester, weekly during 3rd trimester
Lamotrigine (Lamictal)	C	L3	Keep daily dose under 200 mg to reduce risk of congenital anomalies
Oxcarbazepine (Trileptal)	C	L3	Decreases level of oral contraceptives
Topiramate (Topamax)	C	L3	Decreases level of oral contraceptives
Valproic acid (Depakene)	D	L2	Once-daily dosing may cause unpredictably high peak levels Contraindicated in 1st trimester Monthly levels during 2nd trimester, weekly during 3rd trimester
ANTIPSYCHOTICS (TYPICAL AND ATYPICAL)			
Haloperidol (Haldol) **Chlorpromazine (Thorazine)**	C C	L2 L3	First-generation agents recommended in 1st trimester to decrease risk of malformations and for recurrence of symptoms during pregnancy among unmedicated patients
Aripiprazole (Abilify)	C	L3	
Clozapine (Clozaril)	C/B	L3	
Olanzapine (Zyprexa)	C	L3	
Quetiapine (Seroquel)	C	L4	
Risperidone (Risperdal)	C	L3	
Ziprasidone (Geodon)	C	L4	Does not decrease effectiveness of oral contraceptives
BENZODIAZEPINES			
Alprazolam	D	L3	
Diazepam	D	L3/L4 for chronic use	Useful for regulating sleep; may prevent postpartum relapse of mania
Lorazepam	D	L3	High potency preferred due to shorter half-life
Clonazepam	C/D	L3	
CARDIOVASCULAR OR ANTIHYPERTENSIVE AGENTS			
Verapamil	C	L2	Efficacy unproven in mania of bipolar disorder Monitor blood pressure, especially if normotensive

***Pregnancy risk categories:**

A Safety demonstrated in human studies.

B Safety presumed based on animal studies.

C Uncertain safety with no human or animal studies showing adverse effects.

D Unsafe; evidence of risk that may be acceptable in certain situations.

X Highly unsafe and/or a teratogen.

† Lactation risk categories from Hale:[4]

L1 Safest

L2 Safer

L3 Moderately safe

L4 Possibly hazardous

L5 Contraindicated

Lithium is first-line treatment

Monotherapy for bipolar illness is preferred; it generally minimizes the risk of congenital anomalies. The use of lithium for long-term management of bipolar disorder is associated with decreased rates of suicide and all-cause mortality.[6]

Is risk of Ebstein's anomaly a factor? Lithium is associated with 10- to 20-fold higher risk of Ebstein's anomaly, a congenital anomaly affecting the tricuspid valve and right ventricle, with varying clinical effects. However, the absolute risk is small: Ebstein's anomaly occurs in 1:20,000 unexposed pregnancies.[2,7,8] Because concerns about this anomaly are less of a problem than once thought, lithium is the first-line treatment for bipolar disorder in pregnancy.[7]

Discontinue with care. The risk of recurrence of mania is 3 times higher with rapid discontinuation of lithium over less than 2 weeks.[2,7] Taper lithium over 2 to 4 weeks when discontinuing the medication.[7]

Women taking lithium may already be pregnant when you see them, and even a slow lithium taper may not minimize exposure to the developing fetus.[2,8]

Thoroughly discuss the risks and benefits of continued treatment and close monitoring compared with discontinuation.

Anticonvulsants and antipsychotics pose their share of risks

Antiseizure medications, including carbamazepine and valproic acid, are considered human teratogens in the first trimester.[9] If a woman has an unplanned pregnancy and presents late in the first trimester or in the second trimester, discontinuation of these medication in stable patients is not recommended. Valproate and carbamazepine are both compatible with breastfeeding.

Although lamotrigine was thought to have fewer risks than other drugs, the FDA issued an alert in September 2006 suggesting a possible increased risk of cleft palate for infants exposed to lamotrigine in the first trimester.[10]

Typical antipsychotics appear to be safe in pregnancy, but they can have side effects for the mother. These side effects include extrapyramidal symptoms, such as tardive dyskinesia and hyperprolactinemia.

Atypical antipsychotics have not been well studied, but there is no conclusive evidence that they cause fetal malformations.[1]

100-fold higher risk of postpartum psychosis

Women with bipolar disorder have a 100-fold higher risk of developing postpartum psychosis.[2]

For this reason, treatment beyond delivery is recommended, along with close monitoring of the infant.

Drug monitoring and dosing

Second and third trimesters. Monitor the levels of lithium and anticonvulsants monthly through the second trimester, then weekly during the third trimester because of blood volume changes.[2]

Medication doses may also need to be increased up to 50% during the second and third trimesters, when creatinine clearance doubles and the plasma volume increases.[8]

Postpartum. Following delivery, you'll need to decrease the dose of lithium to prepregnancy doses, unless there is an acute destabilization of mood.[2]

Verapamil for bipolar disorder?

Wisner et al[11] found verapamil to be effective for mania in a nonrandomized prospective study of bipolar hypomanic/manic and depressed patients.

Verapamil has been used for patients with hypertension during pregnancy, and studies that have looked at outcomes of pregnancies with exposure to verapamil showed no adverse drug related effects.

Cognitive therapy may help

Cognitive behavior therapy—which focuses on adherence to treatment,

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Treat beyond delivery—and monitor the infant closely

minimizing stressors, improving social and occupational function, and minimizing sleep deprivation—may help prevent mania, although there have been no studies specifically on prevention of mania using cognitive behavior therapy.[1,2]

Is ECT teratogenic?

There have been no conclusive reports of teratogenicity with electroconvulsive therapy.[2]

The most common complication, occurring in 1.5% of cases, were fetal arrhythmias. Avoiding atropine, maintaining oxygenation, avoiding excessive hyperventilation, and elevating the right hip can decrease the risk of fetal arrhythmias during electroconvulsive therapy.[5]

Recommendations from others

Educate the mother and family on the impact of mental health and illness on a pregnant woman and the fetus, and the risks of medications during breastfeeding.

APA Practice Guideline. According to the American Psychiatric Association's Practice Guideline for the Treatment of Patients with Bipolar Disorder:[6]

- Women with bipolar disorder should plan their pregnancies.
- Physicians should encourage patients to use contraception and seek preconception counseling.
- Because of genetic risks associated with bipolar disorder, patients may also benefit from genetic counseling.
- High-potency antipsychotics are preferred during pregnancy because they are less likely to have associated anticholinergic, antihistaminergic, or hypotensive effects.

Best Practices and Research in Clinical Obstetrics and Gynaecology from the UK suggests:[12]

- delaying conception until illness is in remission,
- discussing contraception,
- coordinating with psychiatric consultants before pregnancy, and
- reviewing teratogenic effects of medications with the patient. ■

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APA: High-potency antipsychotics are preferable during pregnancy; they're less likely to cause anticholinergic, antihistaminergic, or hypotensive effects

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