

1-MINUTE CONSULT

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**BRIEF ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS**

Q: How should I treat acute agitation in pregnancy?

A: Acute agitation in the pregnant patient should be treated as an obstetric emergency, as it jeopardizes the safety of the patient and fetus, as well as others in the emergency room. Uncontrolled agitation is associated with obstetric complications such as preterm delivery, placental abnormalities, postnatal death, and spontaneous abortion.¹

Current data on the reproductive safety of drugs commonly used to treat acute agitation—benzodiazepines, typical (first-generation) antipsychotics, atypical (second-generation) antipsychotics, and diphenhydramine—suggest no increase in risk beyond the 2% to 3% risk of congenital malformations in the general population when used in the first trimester.^{2,3}

■ FOCUS OF THE EMERGENCY EVALUATION

Agitation is defined as the physical manifestation of internal distress, due to an underlying medical condition such as delirium or to a psychiatric condition such as acute intoxication or withdrawal, psychosis, mania, or personality disorder.⁴

For the agitated pregnant woman who is not belligerent at presentation, triage should start with a basic assessment of airways, breathing, and circulation, as well as vital signs and glucose level.⁵ A thorough medical history and a description of events leading to the presentation, obtained from the patient or the patient's family or friends, are vital for narrowing the diagnosis and deciding treatment.

The initial evaluation should include consideration of delirium, trauma, intracranial hemorrhage, coagulopathy, thrombocytopenia, amniotic and venous thromboembolism, hypoxia and hypercapnia, and signs and

symptoms of intoxication or withdrawal from substances such as alcohol, cocaine, phencyclidine, methamphetamine, and substituted cathinones (“bath salts”). From 20 weeks of gestation to 6 weeks postpartum, eclampsia should also be considered in the differential diagnosis.¹ Ruling out these conditions is important since the management of each differs vastly from the protocol for agitation secondary to psychosis, mania, or delirium.

■ NEW SYSTEM TO DETERMINE RISK DURING PREGNANCY, LACTATION

The US Food and Drug Administration (FDA) has discontinued its pregnancy category labeling system that used the letters A, B, C, D, and X to convey reproductive and lactation safety. The new system, established under the FDA Pregnancy and Lactation Labeling Rule,⁶ provides descriptive, up-to-date explanations of risk, as well as previously absent context regarding baseline risk for major malformations in the general population to help with informed decision-making.⁷ This allows the healthcare provider to interpret the risk for an individual patient.

■ FIRST-GENERATION ANTIPSYCHOTICS SAFE, EFFECTIVE IN PREGNANCY

Reproductive safety of first-generation (ie, typical) neuroleptics such as haloperidol is supported by extensive data accumulated over the past 50 years.^{2,3,8} No significant teratogenic effect has been documented with this drug class,⁷ although a 1996 meta-analysis found a small increase in the relative risk of congenital malformations in offspring exposed to low-potency antipsychotics compared with those exposed to high-potency antipsychotics.²

If restraints are required, use left lateral decubitus position, support the right hip, and monitor frequently

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Initial assessment

- Is patient stable? Vital signs, airway, breathing, circulation, disability, exposure, finger-stick glucose, pulse oximetry
- If patient has emergency medical condition, proceed immediately with medical management with obstetric consultation
- Assess fetal health, with fetal heart rate monitor and ultrasonography
- If no signs or symptoms indicating need for emergency workup, proceed to mild, moderate, or severe agitation



Mild agitation

- Verbal de-escalation
- Consider diphenhydramine
- Reassess; if condition is escalating, treat as moderate or severe agitation



Moderate agitation

- Verbal de-escalation
- If known psychiatric history, consider giving the patient's prescribed psychiatric medications
- If unknown psychiatric history, consider an antipsychotic without benzodiazepine (**Table 1**)
- Reassess; continue management or proceed to severe agitation management



Severe agitation

- Verbal de-escalation
- Consider physical restraints, with patient's right hip positioned 10 to 12 cm off the bed with pillows or blankets
- Haloperidol, benzodiazepine, with or without diphenhydramine (**Table 1**)
- Continuous monitoring of vital signs; physical reassessments
- Consultation with obstetrics and psychiatry services

Figure 1. A stepwise approach to acute agitation in pregnancy.

In general, mid- and high-potency antipsychotics (eg, haloperidol, perphenazine) are often recommended because they are less likely to have associated sedative or hypotensive effects than low-potency antipsychotics (eg, chlorpromazine, perphenazine), which may be a significant consideration for a pregnant patient.^{2,8}

There is a theoretical risk of neonatal extrapyramidal symptoms with exposure to first-generation antipsychotics in the third trimester, but the data to support this are from sparse case reports and small observational cohorts.⁹

NEWER ANTIPSYCHOTICS ALSO SAFE IN PREGNANCY

Newer antipsychotics such as the second-generation antipsychotics, available since the mid-1990s, are increasingly used as primary or adjunctive therapy across a wide range of psychiatric disorders.¹⁰ Recent data from large, prospective cohort studies investigating reproductive safety of these agents are reassuring, with no specific patterns of organ malformation.^{11,12}

DIPHENHYDRAMINE

Recent studies of antihistamines such as diphenhydramine have not reported any risk of major malformations with first-trimester exposure to antihistamines.^{13,14} Dose-dependent anticholinergic adverse effects of antihistamines can induce or exacerbate delirium and agitation, although these effects are classically seen in elderly, nonpregnant patients.¹⁵ Thus, given the paucity of adverse effects and the low risk, diphenhydramine is considered safe to use in pregnancy.¹³

BENZODIAZEPINES

Benzodiazepines are not contraindicated for the treatment of acute agitation in pregnancy.¹⁶ Reproductive safety data from meta-analyses and large population-based cohort studies have found no evidence of increased risk of major malformations in neonates born to mothers on prescription benzodiazepines in the first trimester.^{17,18} While third-trimester exposure to benzodiazepines has been associat-

TABLE 1

Drug therapy options for acute agitation in pregnant women

Drug	Initial dosing	Onset ^a	Major adverse effects ^b
Antihistamines			
Diphenhydramine	25–50 mg PO, IV, or IM every 1–4 hours Maximum 300 mg/day	PO: 15–30 minutes IM, IV: rapid	Sedation, anticholinergic effects
First-generation antipsychotics			
Haloperidol	5–10 mg PO, IV, or IM Maximum 20 mg/day	PO: 2–6 hours IM, IV: 20–30 minutes	Extrapyramidal effect, dystonia, sedation, neuroleptic malignant syndrome, anticholinergic effects
Second-generation antipsychotics			
Olanzapine ^c	5–10 mg PO or IM Maximum 20–30 mg/day	PO: 15 minutes to 4 hours IM: 15–30 minutes	Sedation, orthostatic hypotension, extrapyramidal symptoms
Ziprasidone	20 mg IM Maximum 40 mg/day	IM: 15–30 minutes	Sedation, headache, nausea, extrapyramidal symptoms
Benzodiazepines			
Lorazepam	0.5–2 mg PO, IV, or IM	PO: 15–30 minutes IM, IV: rapid	Sedation, respiratory depression

^aBased on information in Zun LS. Evidence-based review of pharmacotherapy for acute agitation. Part 1: Onset of efficacy. *J Emerg Med* 2018; 54(3):364–374. doi:10.1016/j.jemermed.2017.10.011

^bThe US Food and Drug Administration no longer uses the letter-based risk categories. A synthesis of risks and benefits of medications in this table is available at <https://womensmentalhealth.org/specialty-clinics/psychiatric-disorders-during-pregnancy>.

^cContraindicated in patients taking a benzodiazepine.

IM = intramuscular; IV = intravenous; PO = by mouth

ed with “floppy-baby” syndrome and neonatal withdrawal syndrome,¹⁶ these are more likely to occur in women on long-term prescription benzodiazepine therapy. No study has yet assessed the risk of these outcomes with a 1-time acute exposure in the emergency department; however, the risk is likely minimal given the aforementioned data observed in women on long-term prescription benzodiazepine therapy.

■ STEPWISE MANAGEMENT OF AGITATION IN PREGNANCY

If untreated, agitation in pregnancy is independently associated with outcomes that include premature delivery, low birth weight, growth retardation, postnatal death, and spontaneous abortion.¹ The risk of these outcomes greatly outweighs any potential risk from psychotropic medications during pregnancy.

Nevertheless, intervention should progress

in a stepwise manner, starting with the least restrictive and progressing toward more restrictive interventions, including pharmacotherapy, use of a seclusion room, and physical restraints (**Figure 1**).^{4,19}

Before medications are considered, attempts should be made to engage with and “de-escalate” the patient in a safe, nonstimulating environment.¹⁹ If this approach is not effective, the patient should be offered oral medications to help with her agitation. However, if the patient’s behavior continues to escalate, presenting a danger to herself or staff, the use of emergency medications is clearly indicated. Providers should succinctly inform the patient of the need for immediate intervention.

If the patient has had a good response in the past to one of these medications or is currently taking one as needed, the same medication should be offered. If the patient has never been treated for agitation, it is important to consider the presenting symptoms, differential

diagnosis, and the route and rapidity of administration of medication. If the patient has experienced a fall or other trauma, confirming a viable fetal heart rate between 10 to 22 weeks of gestation with Doppler ultrasonography and obstetric consultation should be considered.

■ DRUG THERAPY RECOMMENDATIONS

Mild to moderate agitation in pregnancy should be managed conservatively with diphenhydramine. Other options include a benzodiazepine, particularly lorazepam, if alcohol withdrawal is suspected. A second-generation antipsychotic such as olanzapine in a rapidly dissolving form or ziprasidone is another option if a rapid response is required.²⁰ **Table 1** provides a summary of pharmacotherapy recommendations.

Severe agitation may require a combination of agents. A commonly used, safe regimen—colloquially called the “B52 bomb”—is haloperidol 5 mg, lorazepam 2 mg, and diphenhydramine 25 to 50 mg for prophylaxis of dystonia.²⁰

The patient’s response should be monitored closely, as dosing may require modification as a result of pregnancy-related changes in drug distribution, metabolism, and clearance.²¹

Although no study to our knowledge has as-

sessed risk associated with 1-time exposure to any of these classes of medications in pregnant women, the aforementioned data on long-term exposure provide reassurance that single exposure in emergency departments likely has little or no effect for the developing fetus.

■ PHYSICAL RESTRAINTS FOR AGITATION IN PREGNANCY

Physical restraints along with emergency medications (ie, chemical restraint) may be indicated when the patient poses a danger to herself or others. In some cases, both types of restraint may be required, whether in the emergency room or an inpatient setting.

However, during the second and third trimesters, physical restraints such as 4-point restraints may predispose the patient to inferior vena cava compression syndrome and compromise placental blood flow.⁴ Therefore, pregnant patients after 20 weeks of gestation should be positioned in the left lateral decubitus position, with the right hip positioned 10 to 12 cm off the bed with pillows or blankets. And when restraints are used in pregnant patients, frequent checking of vital signs and physical assessment is needed to mitigate risks.⁴

■ REFERENCES

- Aftab A, Shah AA. Behavioral emergencies: special considerations in the pregnant patient. *Psychiatr Clin North Am* 2017; 40(3):435–448. doi:10.1016/j.psc.2017.05.017
- Altshuler LL, Cohen L, Szuba MP, Burt VK, Gitlin M, Mintz J. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. *Am J Psychiatry* 1996; 153(5):592–606. doi:10.1176/ajp.153.5.592
- Einerson A. Safety of psychotropic drug use during pregnancy: a review. *MedGenMed* 2005; 7(4):3. PMID:16614625
- Wilson MP, Nordstrom K, Shah AA, Vilke GM. Psychiatric emergencies in pregnant women. *Emerg Med Clin North Am* 2015; 33(4):841–851. doi:10.1016/j.emc.2015.07.010
- Brown HE, Stoklosa J, Freudenreich O. How to stabilize an acutely psychotic patient. *Curr Psychiatry* 2012; 11(12):10–16.
- US Food and Drug Administration. Pregnancy and lactation labeling (drugs) final rule. www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093307.htm. Accessed January 8, 2019.
- Brucker MC, King TL. The 2015 US Food and Drug Administration pregnancy and lactation labeling rule. *J Midwifery Womens Health* 2017; 62(3):308–316. doi:10.1111/jmwh.12611
- Diav-Citrin O, Shechtman S, Ornoy S, et al. Safety of haloperidol and penfluridol in pregnancy: a multicenter, prospective, controlled study. *J Clin Psychiatry* 2005; 66(3):317–322. PMID:15766297
- Galbally M, Snellen M, Power J. Antipsychotic drugs in pregnancy: a review of their maternal and fetal effects. *Ther Adv Drug Saf* 2014; 5(2):100–109. doi:10.1177/2042098614522682
- Kulkarni J, Storch A, Baraniuk A, Gilbert H, Gavrilidis E, Worsley R. Antipsychotic use in pregnancy. *Expert Opin Pharmacother* 2015; 16(9):1335–1345. doi:10.1517/14656566.2015.1041501
- Huybrechts KF, Hernández-Díaz S, Paterno E, et al. Antipsychotic use in pregnancy and the risk for congenital malformations. *JAMA Psychiatry* 2016; 73(9):938–946. doi:10.1001/jamapsychiatry.2016.1520
- Cohen LS, Viguera AC, McInerney KA, et al. Reproductive safety of second-generation antipsychotics: current data from the Massachusetts General Hospital national pregnancy registry for atypical antipsychotics. *Am J Psychiatry* 2016; 173(3):263–270. doi:10.1176/appi.ajp.2015.15040506
- Li Q, Mitchell AA, Werler MM, Yau WP, Hernández-Díaz S. Assessment of antihistamine use in early pregnancy and birth defects. *J Allergy Clin Immunol Pract* 2013; 1(6):666–674.e1. doi:10.1016/j.jaip.2013.07.008
- Gilboa SM, Strickland MJ, Olshan AF, Werler MM, Correa A; National Birth Defects Prevention Study. Use of antihistamine medications during early pregnancy and isolated major malformations. *Birth Defects Res A Clin Mol Teratol* 2009; 85(2):137–150. doi:10.1002/bdra.20513
- Meuleman JR. Association of diphenhydramine use with adverse effects in hospitalized older patients: possible confounders. *Arch Intern Med* 2002; 162(6):720–721. PMID:11911733

16. **Enato E, Moretti M, Koren G.** The fetal safety of benzodiazepines: an updated meta-analysis. *J Obstet Gynaecol Can* 2011; 33(1):46–48. doi:10.1016/S1701-2163(16)34772-7
17. **Dolovich LR, Addis A, Vaillancourt JM, Power JD, Koren G, Einarson TR.** Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. *BMJ* 1998; 317(7162):839–843. pmid:9748174
18. **Bellantuono C, Tofani S, Di Sciascio G, Santone G.** Benzodiazepine exposure in pregnancy and risk of major malformations: a critical overview. *Gen Hosp Psychiatry* 2013; 35(1):3–8. doi:10.1016/j.genhosppsych.2012.09.003
19. **Richmond JS, Berlin JS, Fishkind AB, et al.** Verbal de-escalation of the agitated patient: consensus statement of the American Association for Emergency Psychiatry project BETA De-escalation Workgroup. *West J Emerg Med* 2012; 13(1):17–25. doi:10.5811/westjem.2011.9.6864
20. **Prager LM, Ivkovic A.** Emergency psychiatry. In: Stern TA, Fava M, Wilens TE, Rosenbaum JF, eds. *The Massachusetts General Hospital Comprehensive Clinical Psychiatry*. 2nd ed. London: Elsevier; 2016:937–949.
21. **Feghali M, Venkataramanan R, Caritis S.** Pharmacokinetics of drugs in pregnancy. *Semin Perinatol* 2015; 39(7):512–519. doi:10.1053/j.semperi.2015.08.003

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