



Atypical Antipsychotics *During* Pregnancy

Make decisions based on available evidence,
individualized risk/benefit analysis

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Although clinicians and patients generally are cautious when prescribing or using antipsychotics during pregnancy, inadequately controlled psychiatric illness poses risks to both mother and child. Calculating the risks and benefits of antipsychotic use during pregnancy is limited by an incomplete understanding of the true effectiveness and full spectrum of risks of these medications. Ethical principles prohibit the type of rigorous research that would be needed to achieve clarity on this issue. This article reviews studies that might help guide clinicians who are considering prescribing an atypical antipsychotic to manage psychiatric illness in a pregnant woman.

Antipsychotic efficacy in pregnancy

All atypical antipsychotics available in the United States are FDA-approved for treating schizophrenia; some also have been approved for treating bipolar disorder, unipolar depression, or symptoms associated with autism (see this article at CurrentPsychiatry.com for a *Table* listing the approved indications). Atypical antipsychotics frequently are used off-label for these and other categories of psychiatric illness, including unipolar depression, generalized anxiety disorder, and obsessive-compulsive disorder.

Studies of pharmacotherapy in pregnant women tend to focus more on safety rather than efficacy. Clinical decisions for an individual patient are best made based on knowledge about which medications have been effective for that patient in the past (*Algorithm, page 14*). However, safety



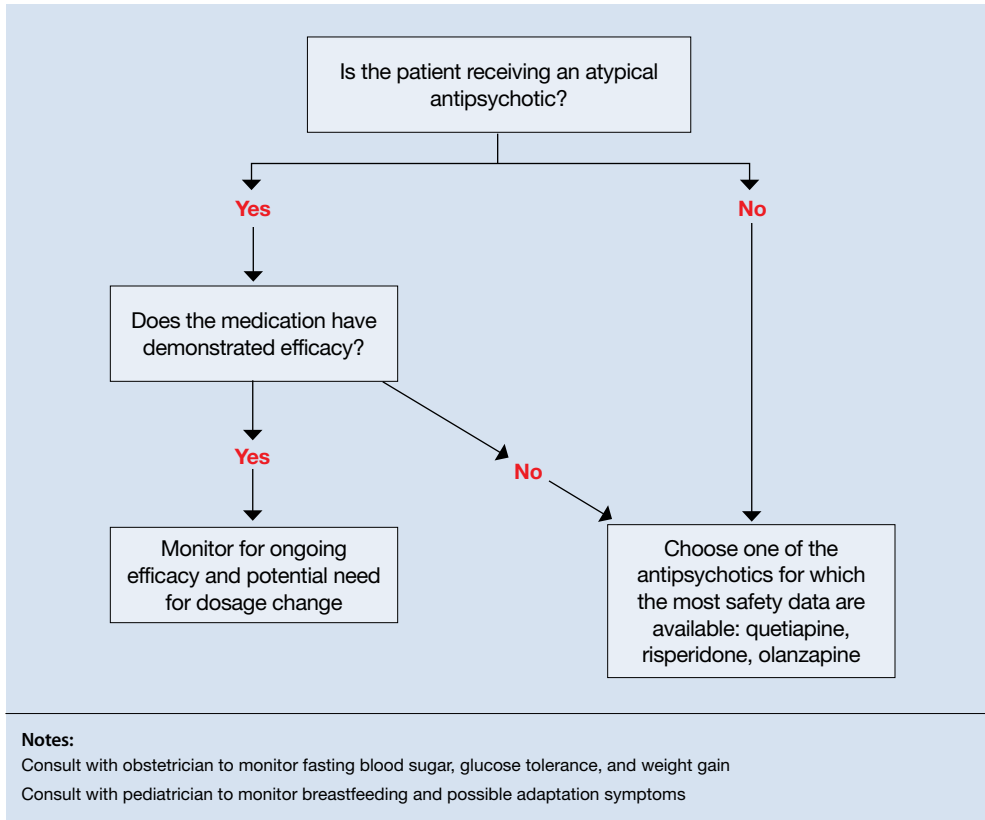
Atypical antipsychotics and pregnancy

Clinical Point

To date, studies of atypical antipsychotics do not support any increased risk for congenital malformations

Algorithm

Guidance for choice of atypical antipsychotics during pregnancy



concerns in pregnancy may require modifying an existing regimen. In other cases, new symptoms arise during pregnancy and necessitate new medications. Additionally, a drug's effectiveness may be affected by physiologic changes of pregnancy that can alter drug metabolism,¹ potentially necessitating dose changes (Box 1).

Risks of treatment vs illness

Complete safety data on the use of any psychotropic medication during pregnancy are not available. To date, studies of atypical antipsychotics do not support any increased risk for congenital malformations large enough to be detected in medium-sized samples,²⁻⁴ although it is possible that there are increases in risk that are below the detection limit of these studies. Data regarding delivery outcomes are conflicting and difficult to interpret.

Several studies²⁻⁴ have yielded inconsistent results, including:

- risks for increased birth weight and large for gestational age³
- risks for low birth weight and small for gestational age²
- no significant differences from controls.⁴

Atypical antipsychotics increase the risk of gestational diabetes, whereas typical antipsychotics do not appear to increase this risk.⁴

Until recently, research has been limited by difficulties in separating the effects of treatment from the effects of psychiatric illness, which include intrauterine growth retardation, prematurity, preterm birth, low Apgar scores, and congenital defects.⁵ In addition, most studies address early and easily measurable outcomes such as preterm labor, birth weight, and congenital malformations. Researchers are just beginning to investigate more subtle and long-term potential behavioral effects.

Several recent studies have explored outcomes associated with antipsychotic use during pregnancy while attempting to



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Antipsychotic metabolism during pregnancy

Pregnancy is associated with an increased volume of distribution, decreased concentration of plasma proteins, increased hepatic function, and hormone-induced changes in metabolic enzymes that may alter medications' efficacy.^a Although no studies have focused on changes in antipsychotic metabolism and dose adjustments in pregnancy, it is likely that antipsychotics' effectiveness is affected by pregnancy.

The activity of the cytochrome P450 (CYP) isozymes CYP2A6,^b 2D6,^c and 2C9,^d and uridine 5'-diphosphate glucuronosyltransferase^e are increased during pregnancy, whereas the activities of CYP1A2^f and 2C19^g are decreased. Changes in liver metabolism with pregnancy

might contribute to decreased serum levels of risperidone, aripiprazole, and iloperidone, which are metabolized by CYP2D6, and to increased serum levels of clozapine and olanzapine, which are principally metabolized by CYP1A2.^h Studies of changes in CYP3A4—the major metabolizing enzyme for quetiapine and lurasidone—in pregnancy have yielded variable results but suggest possible increases in drug clearance during the third trimester.^{i,j}

Increased hepatic blood flow and volume of distribution and decreased concentrations of plasma binding proteins act nonspecifically: the former 2 decrease serum concentrations of blood-borne substances, and the latter increases them.

Source: For reference citations, see this article at CurrentPsychiatry.com

separate the effects of treatment from those of disease (*Box 2, page 16*).

Data on atypicals

Aripiprazole. Case reports of aripiprazole use during pregnancy have reported difficulties including transient unexplained fetal tachycardia that required emergent caesarean section⁶ and transient respiratory distress.⁷ Several small case series were not powered to detect risks related to aripiprazole.^{8,9}

Animal data suggest teratogenic potential at dosages 3 and 10 times the maximum recommended human dose.^{10,11} Two studies^{7,12} that measured placental transfer of aripiprazole found cord-to-maternal serum concentration ratios ranging from 0.47 to 0.63, which is similar to the ratios for quetiapine and risperidone and lower than those for olanzapine and haloperidol.¹³

There are insufficient data to identify risks related to aripiprazole compared with other drugs in its class, and fewer reports are available than for other atypical antipsychotics such as quetiapine and olanzapine. Placental transfer appears to be on the lower end of the spectrum for drugs in this class. Aripiprazole would be an acceptable choice for a woman who had a history of response to aripiprazole but likely would not be a first choice for a woman requiring a new medication during pregnancy.

Clozapine. In case reports, adverse effects associated with clozapine exposure during pregnancy include major malformations, gestational metabolic complications, poor pregnancy outcome, and perinatal adverse reactions. In one case, neonatal plasma clozapine concentrations were found to be twice that found in maternal plasma.¹⁴ Animal data have shown no evidence of increased teratogenicity at 2 to 4 times the maximum recommended human dosages.¹⁵ Boden et al⁸ found an increased risk for gestational diabetes and macrocephaly with clozapine (11 exposures). Four other series^{2-4,16} were underpowered to detect concerns related specifically to clozapine.

There are insufficient data to identify risks related specifically to clozapine use during pregnancy. However, the rare but severe adverse effects associated with clozapine in other patient populations—including agranulocytosis and severe constipation¹⁷—could be devastating in a pregnant patient, which suggests this medication would not be a first-line treatment.

Olanzapine. In postmarketing surveillance studies and case reports, there have been anecdotal cases of fetal malformations related to olanzapine use during pregnancy. Several larger studies^{2-4,8,16} did not find higher rates of congenital malformations or any pattern of malformation

Clinical Point

Physiological changes during pregnancy may necessitate dosage adjustments of atypical antipsychotics

See this article at
CurrentPsychiatry.com 
for a table of approved
indications for atypical
antipsychotics



Atypical antipsychotics and pregnancy

Clinical Point

Infants of women with schizophrenia who did not take antipsychotics were at higher risk of low birth weight or large for gestational age

Box 2

Psychiatric illness during pregnancy: Risks of antipsychotics vs risk of no treatment

In several studies, researchers have attempted to compare the risks of antipsychotic use during pregnancy with the risk of untreated psychiatric illness. Lin et al⁸ examined registry data of 696 mothers with schizophrenia and 3,480 matched controls. The infants of 454 women with schizophrenia who did not take antipsychotics had an elevated risk for low birth weight and small for gestational age, but not for preterm birth or large for gestational age compared with infants of women without schizophrenia. Women with schizophrenia who were treated with atypical antipsychotics ($n = 48$) did not separate on any measure from untreated women with schizophrenia, although 95% confidence intervals were large and overlapped with those of the control group.

Women treated with typical antipsychotics ($n = 194$) had a significantly elevated rate of preterm birth compared with untreated women with schizophrenia. This finding was the study's only reliable outcome; it was insufficiently powered to detect differences between treated, untreated, and non-schizophrenic women for other outcomes. Furthermore, researchers did not control for maternal smoking, alcohol and other substance use, pre-pregnancy body mass index, or nutritional status, and medication adherence was not evaluated. This study highlights the potential morbidity associated with untreated mental illness in pregnancy, and supports a reduction in gestational age at birth with the use of first-generation—but not second-generation—antipsychotics.

Boden et al⁹ examined registry data of 169 women taking olanzapine and/or clozapine, 338

women taking other antipsychotics (218 taking atypicals and 120 taking typicals), and 357,696 women taking no antipsychotics during pregnancy. Both groups of women taking antipsychotics had nearly doubled odds of gestational diabetes. However, the only outcome that showed a significant post-adjustment difference was macrocephaly, for which the olanzapine/clozapine group showed an odds ratio of 3.2 while the other antipsychotics group showed no significant difference from controls. This study also found an increase in preterm births for the other antipsychotics group.

In an investigation of neuromotor outcomes, researchers compared 212 mother-infant pairs with in utero exposure to antipsychotics ($n = 22$) or antidepressants ($n = 202$) to pairs receiving no psychotropics ($n = 85$).⁶ They found a reduction in mean scores at age 6 months on the Infant Neurological International Battery (INFANIB) (mean 63.86, standard deviation [SD] 1.78 for the antipsychotic group and mean 70.12, SD 1.03 for controls) after controlling for multiple factors, including maternal psychiatric history. However, the study was small and, despite the difference in the means, the scatter plot showed similar score ranges for the antipsychotic-treated and control groups. Because there are no normative data available for the INFANIB, the clinical significance of these results is difficult to assess. This study highlights the need for further investigations with larger sample sizes but is reassuring in that the neurological battery score ranges for antipsychotic-exposed and control infants were substantially similar.

Source: For reference citations, see this article at CurrentPsychiatry.com

types, although none were designed or powered to examine rare events. Animal data show no evidence of teratogenicity.¹⁸ A study comparing rates of placental passage of antipsychotics¹³ found higher rates for olanzapine than for quetiapine and risperidone, as well as higher prevalence of low birth weight and perinatal complications. A neonatal withdrawal syndrome has also been reported.¹⁹ Boden et al⁸ found an increased risk for gestational diabetes and macrocephaly with olanzapine.

Data suggest that olanzapine may be associated with somewhat higher rates of the adverse effects attributable to atypical antipsychotics (gestational diabetes and possibly macrocephaly), which could be re-

lated to olanzapine's relatively higher rate of placental passage. Olanzapine could be a reasonable choice in a woman who had a history of good response to this medication, but would be lower priority than quetiapine when a new drug is indicated during pregnancy.

Quetiapine. In clinical trials, quetiapine had lower rates of placental passage compared with risperidone and olanzapine.¹³ One case report found only small changes in quetiapine serum levels during pregnancy.²⁰ Prospective studies (90 exposures,⁸ 36 exposures,² 7 exposures,¹⁶ 4 exposures,³ and 4 exposures⁴) show no increase in fetal malformations or adverse neonatal health

outcomes related to quetiapine, and manufacturer safety data reveal no teratogenic effect, although delays in fetal skeletal ossification were seen in rats and rabbits at doses comparable to the recommended human range.²¹

Quetiapine is a reasonable first choice when a new atypical antipsychotic is indicated for a pregnant patient.

Risperidone. Rates of placental passage of risperidone are higher compared with quetiapine.¹³ Postmarketing surveillance data (265 exposures²² and 10 exposures²³) and prospective studies (including 72 exposures,⁸ 49 exposures,² 51 exposures,⁴ 16 exposures,¹⁶ and 5 exposures³) suggest risperidone has no major teratogenic effect. When malformations were present, they were similar to expected rates and types of malformations, and no specific malformation type was overrepresented. However, in some cases, researchers noted a withdrawal-emergent syndrome that included various combinations of tremors, irritability, poor feeding, and somnolence.²² Animal data are similarly reassuring, although increases in early fetal mortality and (potentially related) changes in maternal behavior have been observed in rats.^{24,25} A major caveat with risperidone is its propensity to cause hyperprolactinemia, which is detrimental to efforts to conceive and maintain a pregnancy.^{26,27}

Risperidone is not associated with higher rates of adverse events in pregnancy than other atypical antipsychotics. It would not be a first choice for a woman trying to conceive or in the early stages of pregnancy, but would be a reasonable choice for a woman already well into pregnancy.

Ziprasidone. Available reports are few and generally do not report findings on ziprasidone separately.^{8,28} Manufacturer data includes 5 spontaneous abortions, one malformation, and one stillbirth among 57 exposures,⁴ and available animal data suggest significant developmental toxicity and impaired fertility.²⁹ In pregnant rats, ziprasidone dosed as low as 0.5 times the maximum human recommended dose resulted in delayed fetal skeletal ossifica-

tion, increased stillbirths, and decreased fetal weight and postnatal survival, and ziprasidone dosed as low as 0.2 times the maximum recommended human dose resulted in developmental delays and neurobehavioral impairments in offspring. In pregnant rabbits, ziprasidone dosed at 3 times the maximum recommended human dose resulted in cardiac and renal malformations.²⁹

Although available data are too sparse to draw reliable conclusions, the small amount of human data plus animal data suggest that ziprasidone should be less preferred than other atypical antipsychotics during pregnancy.

Lurasidone. No data addressing lurasidone use in humans during pregnancy are available. Material submitted to the FDA includes no evidence of teratogenicity or embryo-fetal toxicity in rat and rabbit studies using 3 and 12 times the maximum recommended human dose (80 mg) based on a body surface area comparison.³⁰

Asenapine. No data specifically addressing asenapine use in humans during pregnancy are available. Studies in rats and rabbits found no increase in teratogenicity, but did find increases in postimplantation loss and decreases in pup survival and weight gain with maternal doses equivalent to less than the maximum recommended human dose.³¹

Iloperidone. No data specifically addressing iloperidone use in humans during pregnancy are available. Animal studies of iloperidone found multiple developmental toxicities when iloperidone was administered during gestation.³² In one study, pregnant rats were given up to 26 times the maximum recommended human dose of 24 mg/d during the period of organogenesis. The highest dose caused increased early intrauterine deaths, decreased fetal weight and length, decreased fetal skeletal ossification, and increased minor fetal skeletal anomalies and variations. In a similar study using pregnant rabbits, the highest dose caused increased early intrauterine deaths and decreased fetal viability at term.

Clinical Point

In clinical trials, quetiapine had lower rates of placental passage compared with risperidone and olanzapine

See this article at
[CurrentPsychiatry.com](https://www.currentpsychiatry.com)
for a box that discusses
diabetes, antipsychotics,
and pregnancy



Atypical antipsychotics and pregnancy

Clinical Point

Atypicals could trigger or worsen glucose intolerance, which can have significant negative consequences in a pregnant patient

See this article at

CurrentPsychiatry.com

for a table outlining monitoring recommendations for patients receiving atypicals

Related Resources

- Gentile S. Antipsychotic therapy during early and late pregnancy. A systematic review. *Schizophr Bull.* 2010;36(3):518-544. www.ncbi.nlm.nih.gov/pmc/articles/PMC2879689.
- Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. www.womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry.

Drug Brand Names

| | |
|------------------------|-------------------------|
| Aripiprazole • Abilify | Olanzapine • Zyprexa |
| Asenapine • Saphris | Paliperidone • Invega |
| Clozapine • Clozaril | Quetiapine • Seroquel |
| Haloperidol • Haldol | Risperidone • Risperdal |
| lloperidone • Fanapt | Ziprasidone • Geodon |
| Lurasidone • Latuda | |

Disclosure

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

Paliperidone. In animal studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated with up to 8 times the maximum recommended human dose of paliperidone during the period of organogenesis.³³

A single case report³⁴ measured levels of risperidone and its 9-hydroxy metabolite, paliperidone, in the breast milk of a mother who had taken risperidone during pregnancy and in the serum of her child. 9-OH-risperidone dose in breast milk was calculated as 4.7% of the weight-adjusted maternal dose, and serum levels in the infant were undetectable. No ill effects on the child were observed.

It is not possible to draw solid conclusions about atypical antipsychotics' potential effects on human development from animal studies. Because of the lack of human data for the newer atypical antipsychotics—asenapine, iloperidone, lurasidone, paliperidone—in general these agents would not be advisable as first-line medications for treating pregnant women.

A few caveats

All atypical antipsychotics share the propensity to trigger or worsen glucose intolerance, which can have significant negative consequences in a pregnant patient. When deciding to use an atypical antipsychotic during pregnancy, blood glucose should be monitored carefully and regularly. For a

Box that discusses diabetes, antipsychotics, and pregnancy and a **Table** outlining monitoring recommendations, see this article at CurrentPsychiatry.com.

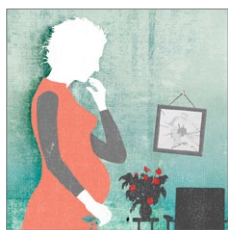
Because all atypical antipsychotics (except clozapine) are FDA pregnancy class C—indicating that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks—the decision to use these medications must be based on an individualized assessment of risks and benefits. Patients and their providers together should make a fully informed decision.

There is an urgent need for larger and better-designed investigations that will be sufficiently powered to detect differences in outcomes—particularly major malformations, preterm delivery, adverse events in labor and delivery, metabolic and anthropometric effects on the newborn, and neurodevelopmental and psychiatric outcomes for individuals exposed in utero—between women without mental illness, untreated women with mental illness, and women receiving atypical antipsychotics during pregnancy. Further research into the pharmacokinetics and clinical efficacy of antipsychotics in pregnant women also would be useful. Clinicians can assist with these efforts by submitting their patient data to a pregnancy registry maintained by the Massachusetts General Hospital (see *Related Resources*).

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Atypical antipsychotics and pregnancy

Clinical Point

Use of atypical antipsychotics during pregnancy must be based on individualized assessment of risks and benefits

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Bottom Line

Treatment with atypical antipsychotics during pregnancy may increase the risk of adverse birth outcomes, but inadequately controlled mental illness also carries some degree of risk. The decision to use any atypical antipsychotic during pregnancy must be based on an individualized assessment of risks and benefits and made by the pregnant patient and her provider.

Table 1

FDA-approved indications for atypical antipsychotics

| Medication | Indication(s) | Approved age group(s) |
|--------------|--|--|
| Aripiprazole | Schizophrenia | Adults and adolescents (age 13 to 17) |
| | Bipolar disorder (manic/mixed) monotherapy or adjunctive to lithium or valproate | Adults and adolescents (age 10 to 17) |
| | Adjunctive treatment of major depressive disorder acute treatment of agitation | Adults |
| | Irritability associated with autistic disorder | Children (age 6 to 17) |
| Asenapine | Acute schizophrenia Bipolar I disorder (manic/mixed) | Adults |
| Clozapine | Treatment-resistant schizophrenia Reduce the risk of suicidal behavior in younger patients with schizophrenia | Adults |
| Iloperidone | Acute schizophrenia | Adults |
| Olanzapine | Schizophrenia, bipolar disorder (manic/mixed) | Adults and adolescents (age 13 to 17) |
| | Bipolar disorder, treatment-resistant depression, agitation associated with schizophrenia and bipolar I mania | Adults |
| Paliperidone | Schizophrenia, schizoaffective disorder | Adults |
| Quetiapine | Schizophrenia | Adults and adolescents (age 13 to 17) |
| | Bipolar disorder (acute manic) | Adults, children, and adolescents (age 10 to 17) |
| | Adjunctive therapy for major depressive disorder | Adults |
| Risperidone | Schizophrenia | Adults and adolescents (age 13 to 17) |
| | Bipolar disorder (manic/mixed) | Adults and adolescents (age 10 to 17) |
| | Irritability associated with autism | Children (age 5 to 16) |
| Ziprasidone | Schizophrenia | Adults |
| | Bipolar disorder (manic/mixed) | |
| | Bipolar disorder (maintenance) | |
| | Acute agitation in patients with schizophrenia | |

Source: Christian R, Saavedra L, Gaynes BN, et al. Future research needs for first- and second-generation antipsychotics for children and young adults. Future Research Needs Papers, No. 13. Rockville, MD: Agency for Healthcare Research and Quality; 2012. <http://www.ncbi.nlm.nih.gov/books/NBK84660>

Table 2

ADA consensus monitoring protocol for patients receiving atypical antipsychotics

| | Baseline | 4 weeks | 8 weeks | 12 weeks | Quarterly | Annually | 5 years |
|-------------------------|----------|---------|---------|----------|-----------|----------|---------|
| Personal/family history | X | | | | | X | |
| Weight (BMI) | X | X | X | X | X | | |
| Waist circumference | X | | | | | X | |
| Blood pressure | X | | | X | | X | |
| Fasting plasma glucose | X | | | X | | X | |
| Fasting lipid profile | X | | | X | | | X |

ADA: American Diabetes Association; BMI: body mass index

Source: American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. J Clin Psychiatry. 2004;65(2):267-272



Atypical antipsychotics and pregnancy

Box

Monitoring for diabetes during pregnancy: Earlier might be better

The American College of Obstetricians and Gynecologists recommends that all pregnant women be screened for gestational diabetes mellitus, whether by patient history, clinical risk factors, or a 50-g, 1-hour glucose challenge test at 24 to 28 weeks of gestation.^a A diagnosis of gestational diabetes can be made based on the result of the 100-g, 3-hour oral glucose tolerance test, for which there is evidence that treatment improves outcome.^a

However, 24 weeks may be later than appropriate for women taking atypical antipsychotics. The American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity recommend baseline assessments of body mass index, waist circumference, blood pressure, fasting glucose, lipid profile, and personal and family history of obesity and diabetes for all patients initiating atypical antipsychotics (**Table 2**).^b Follow-up weights are recommended at 4 and 8 weeks

after initiation, and repeat measures of glucose, lipids, and blood pressure 12 weeks after initiation and annually thereafter for the duration of antipsychotic treatment.^{b,c}

Although no consensus guidelines are available for monitoring pregnant women receiving atypical antipsychotics, we recommend that you maintain vigilance for adverse metabolic consequences of treatment with atypical antipsychotics in pregnant women as you would for all patients.

When caring for a pregnant patient, early liaison and ongoing communication with the obstetrician are crucial. Although regular assessments of weight, fundal height, and blood pressure are a standard component of prenatal care, women using atypical antipsychotics may benefit from earlier and more frequent blood glucose monitoring than is implied by the 24 to 28 week standard, as well as from lipid profile measurements. If a patient taking an atypical antipsychotic develops borderline or frank diabetes during pregnancy, approach her management collaboratively.

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Box 1

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Box 2

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