Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes

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INTRODUCTION

Depressive disorders and anxiety disorders occur in approximately 10 to 15 percent of pregnant women, and can have short- and long-term deleterious effects upon the mother, child, and family [1-4]. Although patients with mild to moderate illness may respond to psychotherapy, patients with severe (eg, suicidality or psychosis), chronic, or recurrent syndromes often require pharmacotherapy.

The decision to prescribe antidepressants for pregnant patients requires clinicians to weigh the negative impact of untreated mood and anxiety disorders against the adverse effects of antidepressants. Although the risks to infants from antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) appear to be small, the potential risks are uncertain due to the lack of high-quality data on the impact of these drugs. The complexity of managing pregnant women with mood and anxiety disorders requires coordinated efforts among psychiatrists, primary care clinicians, obstetricians, and pediatricians.

Maternal use of SSRIs and SNRIs during pregnancy is estimated at approximately 8 percent [5]. SSRIs and SNRIs are first- and second-line medications for unipolar depressive disorders and anxiety disorders, as well as other disorders such as obsessive-compulsive disorder and

posttraumatic stress disorder. In addition, these antidepressants are often combined with second-generation antipsychotics for treating bipolar and unipolar major depression in pregnant women.

This topic reviews the association between antenatal exposure to SSRIs and SNRIs and neonatal outcomes. Antenatal exposure to SSRIs and SNRIs and the risk of abnormalities in growth, motor skills, and cognition in the offspring, as well as the risk of psychopathology, are discussed separately. The antenatal use of antidepressants and risk of teratogenicity and adverse pregnancy outcomes are also discussed separately, as are the clinical features and choice of treatment for antenatal depression, and the risks of exposure to antenatal depression:

- (See "Infants and children with antenatal exposure to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors: Risk of abnormalities in growth, motor skills, and cognition".)
- (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Risk of psychopathology in the offspring".)
- (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors".)
- (See "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors".)
- (See "Unipolar major depression during pregnancy: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Mild to moderate episodes of antenatal unipolar major depression: Choosing treatment".)
- (See "Severe antenatal unipolar major depression: Choosing treatment".)
- (See "Antenatal depression: Pregnancy and neonatal outcomes".)
- (See "Antenatal depression: Risks of abnormal infant and child development".)
- (See "Antenatal depression: Risks of cognitive impairment and psychopathology in the offspring".)

INTERPRETING THE EVIDENCE

Study design — Evidence about the presentation of infants exposed in utero to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) is limited because no randomized trials of antenatal antidepressant exposure have been conducted. Rather, the literature consists of observational studies that have compared pregnant women who chose to use antidepressants with pregnant women who chose not to use antidepressants, and there may be important prognostic differences between these two

groups. Most postnatal adverse events possibly related to antenatal SSRI or SNRI exposure occur in less than 1 percent of infants. Thus, a sufficient number of exposures is required to detect an association, and large observational studies are preferable to case reports and series. In addition, the timing of exposure and dose during pregnancy varies between studies.

In designing observational studies to examine the adverse effects of antenatal exposure to antidepressants, it is preferable to prospectively measure exposures, covariates, and outcomes. However, neonatal outcomes are often examined with retrospective, population based registry studies that were not designed expressly to examine the effects of antenatal exposure. Registry studies have the advantage of high generalizability, large sample size to detect the small risks associated with SSRI and/or SNRI exposure, and outcomes that include clinical disorders rather than scores on rating scales. Limitations include difficulty in determining exactly when exposure occurred during the pregnancy, medication dose, and/or whether infants were truly exposed (as opposed to mothers filling prescriptions, but not taking the medication). Ascertainment bias can also be a problem because patients and clinicians may be more likely to report and document adverse events in neonates after a drug exposure, compared with infants with no antenatal drug exposure.

Another type of observational study is the case control study, in which infants experiencing the outcome under study (cases) are matched to infants not experiencing the outcome (controls), to look for differential odds of in utero exposure to antidepressants. Limitations of these studies can include inflated risk estimates due to the study design itself and recall bias (one is more likely to recall an exposure if one experiences an adverse event).

General information about study designs is discussed separately. (See "Glossary of common biostatistical and epidemiological terms", section on 'Study designs'.)

Confounding factors — Associations between antidepressant exposures and adverse outcomes that are found in observational studies do not prove that the exposures caused the outcomes. One variable that may explain at least part of the association is the severity of the maternal psychiatric illness, which is difficult to quantify without clinical interviews. Pregnant patients with more severe psychiatric illness are more likely to receive antidepressants.

Other variables that could explain associations between antenatal use of SSRIs and SNRIs and infant outcomes include the gestational age at exposure; antidepressant dose; comorbid general medical disorders (including obesity); comorbid psychiatric disorders; exposure to tobacco, alcohol, and illicit drugs; exposure to prescription and nonprescription medications; poor nutrition; inadequate antenatal care; and delivery complications. It is often not possible to

account for these factors using the registry data that comprise much of the evidence; eg, comorbidity is difficult to quantify without clinical interviews.

Differences among antidepressants — It is not clear whether the risk of neonatal complications following antenatal exposure to antidepressants differs between SSRIs and SNRIs; it is also not clear whether differences exist among individual drugs. Adverse effects may differ among drugs because of differences in potency, receptor selectivity, and pharmacokinetic properties (such as half-life and the presence of active and nonactive metabolites). However, most studies analyze pooled data from mothers treated with a variety of SSRIs and SNRIs. In studies that have performed subgroup analyses with specific drug classes or individual antidepressants, confidence intervals around the effect sizes of different classes/drugs typically overlap, which suggests that any observed adverse effects are likely attributable to all of the drug classes, or all of the drugs within a class.

TERATOGENICITY

The teratogenicity of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors is discussed separately. (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors" and "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors".)

PREGNANCY OUTCOMES

The effects of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors on pregnancy outcomes, including spontaneous abortion, stillbirth, length of gestation, fetal growth, and neonatal mortality are discussed separately. (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors" and "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors".)

NEONATAL EFFECTS

Exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) during pregnancy is associated with the poor neonatal adaptation syndrome. Exposure to SSRIs may possibly be related to impaired pulmonary function as well.

Neonatal intensive care unit admission — Antenatal use of SSRIs appears to increase the risk of neonatal morbidity that necessitates admission to the neonatal intensive care unit (NICU) [6]. In addition, the risk of NICU admissions seems to be greater with third trimester exposure to SSRIs and SNRIs, compared with first trimester exposure [7].

Across multiple studies, antenatal exposure to SSRIs and SNRIs increases the probability of a NICU admission by 50 to 70 percent:

- A systematic review included a meta-analysis of 13 observational studies (total n >800,000 newborns), which found NICU admissions were more likely to occur in newborns exposed to antidepressants in utero (n >22,000) than unexposed newborns (odds ratio 1.7, 95% CI 1.4 to 2.1) [8]. In the same review, a second meta-analysis of seven studies showed that NICU admission was also more likely to occur in newborns exposed in utero to antidepressants (n = 286), compared with newborns exposed to maternal depression but not antidepressant medication (n = 293).

  - The largest single investigation in the review was a national registry study that included infants with antenatal exposure to SSRIs (n >17,000) [9]. After adjusting for potential confounding maternal factors (eg, antenatal use of other psychotropic drugs) and fetal factors (eg, gestational age), the analyses found that admission to the NICU occurred in more babies with antenatal exposure to SSRIs than controls (14 versus 8 percent). Compared with controls, SSRI-exposed neonates were more likely to manifest:

    - Hypoglycemia
    - Central nervous system related symptoms such as altered muscle tone
    - Respiratory distress, including persistent pulmonary hypertension of the newborn (see 'Persistent pulmonary hypertension of the newborn' below)

    Among infants with antenatal exposure, admission to the NICU occurred more often with late pregnancy exposure than early pregnancy exposure (17 versus 11 percent). Hypoglycemia, altered muscle tone, and respiratory distress are considered symptoms of poor neonatal adaptation. (See 'Poor neonatal adaptation' below.)

- A national registry study not included in the meta-analysis identified mothers who used antidepressants prior to pregnancy, and compared babies whose mothers either continued (n >21,000) or discontinued (n >23,000) the antidepressant in pregnancy [10]. After adjusting for potential confounding maternal factors (eg, age at delivery and other

psychotropic drugs during pregnancy), the analyses showed that the risk of NICU admission was elevated in babies with in utero exposure (odds ratio 1.5, 95% CI 1.4 to 1.6).

The association of SSRIs and SNRIs with NICU admission may perhaps vary among specific drugs. In a retrospective study of pregnant women who filled at least one antidepressant prescription (n >3600), duloxetine and escitalopram appeared to be associated with the highest rates of NICU admission for their infants, whereas sertraline (and bupropion) had the lowest rates [7].

The relationship between maternal antenatal depression and risk of admission to a NICU is discussed separately. (See "Antenatal depression: Pregnancy and neonatal outcomes", section on 'Neonatal intensive care unit admission'.)

Poor neonatal adaptation — Neonatal complications associated with in utero exposure to SSRIs and SNRIs during the third trimester include the poor neonatal adaptation syndrome (or neonatal behavioral syndrome); although definitions for the syndrome vary, it is thought that symptoms include [4,11-15]:

- Agitation and restlessness
- Irritability and continuous crying
- Insomnia or somnolence
- Poor feeding, vomiting, and diarrhea
- Hypoglycemia
- Hypothermia
- Respiratory distress
- Altered muscle tone, hyperreflexia, jitteriness, shivering, and tremors
- Seizures (rarely)

The symptoms are usually mild and managed with observation, but severe cases may require general medical interventions.

The reported incidence of poor neonatal adaptation among infants exposed to SSRIs and SNRIs during pregnancy ranges from 5 to 85 percent; the variability is probably due to differences in defining the syndrome [11]. Premature babies are more vulnerable to the syndrome and more likely to develop severe symptoms. In addition, concomitant medications (eg, benzodiazepines) during pregnancy may exacerbate symptoms [12].

The poor neonatal adaptation syndrome typically emerges within the first 72 hours of birth [4]. The syndrome is often short lived, with most symptoms resolving by two weeks of age [16]. However, symptoms may persist for at least one month [12,17].

Multiple studies suggest that antenatal exposure to SSRIs or SNRIs increases the probability of poor neonatal adaptation syndrome [18], by as much as three- to five-fold:

- A meta-analysis of eight observational studies (total n = 959 infants) reported that the syndrome was more likely to occur in newborns who were exposed to antidepressants (n = 270) than newborns who were not (odds ratio 5, 95% CI 3-8) [11].

- A subsequent national registry study identified mothers who used antidepressants prior to pregnancy, and compared babies whose mothers either continued (n >21,000) or discontinued (n >23,000) the antidepressant in pregnancy [10]. After adjusting for potential confounding maternal factors (eg, age at delivery and other psychotropic drugs during pregnancy), the analyses showed that the risk of poor neonatal adaptation was elevated in babies with in utero exposure (odds ratio 3, 95% CI 2 to 4).

In addition, multiple observational studies have found that in utero exposure to SSRIs and other antidepressants are associated with specific symptoms of poor neonatal adaptation [19]. A systematic review of 33 observational studies (total n >1.4 million infants) included a series of meta-analyses that found use of antidepressants during pregnancy (total n>22,000 exposures) increased the risk of neonatal convulsions, hypoglycemia, respiratory problems, temperature dysregulation, and feeding problems [8]. In addition, studies not included in the review have found that in utero exposure to SSRIs is associated with neonatal convulsions [20] and respiratory distress [19].

The association of SSRIs and SNRIs with poor neonatal adaptation may vary among specific drugs. A retrospective study of pregnant women who filled at least one antidepressant prescription (n >3600) suggests that duloxetine and escitalopram may be associated with the highest rates of poor neonatal adaptation syndrome for infants, whereas sertraline (and bupropion) may have the lowest rates [7]. In addition, venlafaxine was associated with the highest rate of transient tachypnea of the newborn.

Although the cause of poor neonatal adaptation is not known, several possible explanations have been suggested:

- Abrupt antidepressant withdrawal following parturition – The poor neonatal adaptation syndrome resembles the discontinuation syndrome that is observed in adults when they abruptly stop SSRIs and SNRIs [4]. The adult discontinuation syndrome is thought to arise from decreased serotonin concentrations at neuronal synapses, which produces cholinergic overactivity characterized by anxiety, hyperactivity, insomnia, irritability, dizziness, diarrhea, nausea, vomiting, chills, fatigue, and myalgias. (See "Discontinuing antidepressant medications in adults", section on 'Discontinuation syndrome'.)

- Antidepressant side effects and toxicity – The symptoms of poor neonatal adaptation resemble the side effects (table 1) and toxicity of SSRIs and SNRIs seen in adults [4]. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Overview'.)

- Disruption of the neonatal serotonergic system – In a prospective observational study of 44 infants who were exposed in utero to SSRIs, venlafaxine, or mirtazapine for at least the last two weeks of fetal life and were admitted for observation, poor neonatal adaptation was diagnosed in 20 [21]. Urinary levels of 5-hydroxyindoleacetid, the primary serotonin metabolite, were greater in infants with poor neonatal adaptation than infants without the syndrome.

- Preterm birth – Prematurity may be a risk factor for poor neonatal adaptation [17].

- Genetic factors – Poor neonatal adaptation may be associated with specific genetic polymorphisms [22].

Infants who are exposed in utero to SSRIs and then develop poor neonatal adaptation may perhaps be at increased risk of developing childhood psychiatric symptoms. A small prospective study enrolled mothers who were treated with SSRIs during pregnancy, along with their infants who were screened for poor neonatal adaptation syndrome; there were 30 infants with the syndrome and 52 without the syndrome [23]. The children were then assessed with neurodevelopmental tests at age two to six years. Although cognitive and developmental scores were similar between the two groups of children, abnormal scores on the social behavior component of the test battery were more likely to occur in children who had experienced neonatal abstinence syndrome than children who had not (47 versus 19 percent). However, this may have been a spurious finding due to the number of tests applied, and lack of information about maternal psychopathology and the impact of the postnatal environment. Additional information about the potential association between gestational exposure to SSRIs and childhood psychiatric symptoms is discussed separately. (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Risk of psychopathology in the offspring", section on 'Emotional and behavioral dysfunction'.)

The symptoms of poor neonatal adaptation resemble those observed in neonates exposed in utero to other psychotropic drugs, including opioids [14]. (See "Prenatal substance exposure and neonatal abstinence syndrome (NAS): Clinical features and diagnosis", section on 'Clinical manifestations of NAS'.)

Patient management — We do not recommend lowering the dose or discontinuing antidepressants before delivery to reduce the risk of poor neonatal adjustment, because several

studies suggest that these interventions are not beneficial [24-26]. As an example, a prospective observational study compared infants who were exposed in utero to SSRIs during the last month of pregnancy with infants exposed earlier in pregnancy but not during the last month; among the eight neurobehavioral variables assessed during the first postnatal month, only attention was worse in the infants exposed to SSRIs during the last month [12]. In addition, the highest risk for relapse of psychiatric disorders is in the immediate postpartum period (eg, the first two to three weeks) [27]. Thus, curtailing antidepressants prior to delivery is inconsistent with good clinical practice.

Although the poor neonatal adaptation syndrome is transient and self-limiting, women taking antidepressants should deliver in a hospital with pediatric support to monitor babies' cardio-respiratory functioning and temperature for at least 48 hours [28,29]. Supportive measures such as maternal reassurance, frequent infant feeding, and encouragement of skin-to-skin contact between mother and infant are usually sufficient to manage poor neonatal adaptation. Observation and supportive care for the infant should continue until the syndrome has resolved [4].

Breastfeeding of infants with the poor neonatal adaptation syndrome is not contraindicated; although the impact of breastfeeding upon the syndrome is not clear, some evidence suggests that the incidence of the syndrome may be lower in breastfed babies. In a prospective observational study that examined infants (n = 247) exposed to antidepressants (largely SSRIs) during the third trimester, the incidence of poor neonatal adaptation was lower among infants who were breastfed or fed both breast milk and formula, compared with infants exclusively fed formula (odds ratio 0.3, 95% CI 0.1-0.7) [26].

Persistent pulmonary hypertension of the newborn — Multiple observational studies have found that using SSRIs during late pregnancy (eg, third trimester) is associated with a small absolute increase of persistent pulmonary hypertension of the newborn, a potentially fatal condition that occurs in approximately 2 per 1000 live births in the general population [30]. However, different studies have yielded conflicting results that may reflect differences in methods; for example, some studies do not control for confounding by indication (the possible association between maternal depression and persistent pulmonary hypertension of the newborn). In addition, the risk of persistent pulmonary hypertension of the newborn with SSRI exposure needs to be balanced against the risks of antenatal depression [31].

- A systematic review conducted multiple meta-analyses examining the association between antenatal exposure to SSRIs and persistent pulmonary hypertension of the newborn [32]. In one meta-analysis of five observational studies (sample size not reported), exposure to SSRIs in late pregnancy was associated with an increased risk of persistent pulmonary

hypertension of the newborn (odds ratio 2.5, 95% CI 1.3-4.7). However, heterogeneity across studies was moderate. A second meta-analysis of three observational studies found no association between early pregnancy (eg, first trimester) SSRI exposure and persistent pulmonary hypertension of the newborn (odds ratio 1.2, 95% CI 0.6-2.6).

The low incidence of persistent pulmonary hypertension of the newborn in the general population means that the absolute increase due to late pregnancy SSRI exposure is also low [32]. The meta-analysis estimated that the absolute risk difference between late pregnancy SSRI exposure and no exposure was approximately 3 per 1000 infants, and that approximately 350 women would have to be treated with SSRIs in late pregnancy to cause one additional case of persistent pulmonary hypertension of the newborn.

A subsequent meta-analysis (sample size not reported) included the five observational studies of late pregnancy SSRI exposure plus a later observational study [33]. The investigators found that the risk of persistent pulmonary hypertension of the newborn was greater in the group with late pregnancy exposure to SSRIs (odds ratio 2.0, 95% CI 1.1-3.5). However, heterogeneity across studies was substantial, indicating that the variability of the results across the six studies was high.

- A meta-analysis of 11 observational studies included offspring who were either exposed to SSRI/SNRIs during any pregnancy trimester (n >150,000) or not exposed during pregnancy (n >6 million) [34]. The primary findings included the following:

  - The incidence of persistent pulmonary hypertension of the newborn in exposed and unexposed infants was 2.9/1000 and 1.8/1000. The number needed to harm was 1000, meaning that SSRIs/SNRIs were associated with one additional case of persistent pulmonary hypertension of the newborn for every 1000 infants exposed to SSRIs/SNRIs and 1000 infants not exposed.

  - The risk of persistent pulmonary hypertension of the newborn was greater in the offspring exposed to SSRIs/SNRIs during any trimester than offspring not exposed during pregnancy (odds ratio 1.8, 95% CI 1.3-2.5). However, heterogeneity across studies was moderate to large.

  - In the subgroup of infants exposed to SSRIs/SNRIs at week 20 or later (late pregnancy), persistent pulmonary hypertension of the newborn was more likely to occur in the offspring who were exposed than those not exposed (odds ratio 2.1, 95% CI 1.4-3.0). However, heterogeneity across studies was moderate to large.

- A meta-analysis of eight observational studies with over 7 million pregnancies found that the risk of persistent pulmonary hypertension of the newborn was greater among infants exposed to SSRIs than unexposed infants (odds ratio 1.52, 95% CI 1.04-2.00) [31]. However, the absolute increase in risk was small (0.6 per 1000 live births), with a corresponding number needed to harm of 1615 infants.

The risk of persistent pulmonary hypertension of the newborn may vary among specific SSRIs. A network meta-analysis (11 observational studies, n >6 million participants) ranked each SSRI according to the probability of an association with persistent pulmonary hypertension of the newborn, by using results from direct, head-to-head comparisons between the drugs, as well as indirectly comparing drugs through their relative effect with a common comparator (eg, no exposure) [34]. The rank order, from highest to lowest risk, was fluoxetine, citalopram, paroxetine, escitalopram, and sertraline.

The observed association between late pregnancy exposure to SSRIs and persistent pulmonary hypertension of the newborn may be due to confounding by indication. As an example, a study analyzed an administrative claims database that included depressed, pregnant women who took SSRIs during the third trimester (n >65,000) and depressed, pregnant women who did not (n >650,000); this helped to control for the possible association between maternal depression and persistent pulmonary hypertension of the newborn (confounding by indication) [33]. In addition, the analyses included propensity score matching to balance the exposed and unexposed groups with regard to potential confounders such as maternal age, chronic general medical illnesses (eg, hypertension, diabetes, and asthma), and other medications (eg, other psychotropic drugs, nonsteroidal anti-inflammatory drugs, and antidiabetic drugs). The risk of persistent pulmonary hypertension of the newborn was comparable in exposed and unexposed infants (odds ratio 1.1, 95% CI 0.9-1.3).

It is possible that the respiratory distress observed in the poor neonatal adaptation syndrome represents a subclinical form of persistent pulmonary hypertension of the newborn [4]. (See 'Poor neonatal adaptation' above.)

Additional information about persistent pulmonary hypertension of the newborn is discussed separately. (See "Persistent pulmonary hypertension of the newborn (PPHN): Clinical features and diagnosis".)

ABNORMALITIES IN GROWTH, MOTOR SKILLS, AND COGNITION

Antenatal exposure to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors and the risk of abnormalities in growth, motor skills, and cognition are discussed separately. (See "Infants and children with antenatal exposure to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors: Risk of abnormalities in growth, motor skills, and cognition".)

PSYCHOPATHOLOGY

Antenatal exposure to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors and the risk of psychopathology in the offspring is discussed separately. (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Risk of psychopathology in the offspring".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

SUMMARY

- For neonatal infants who are exposed in utero to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), the risks of adverse outcomes are not clear due to the lack of high-quality studies. (See 'Introduction' above and 'Interpreting the evidence' above.)

- Antenatal use of SSRIs may be associated with neonatal morbidity that necessitates admission to the neonatal intensive care unit. (See 'Neonatal intensive care unit admission' above.)

- Neonatal complications associated with in utero exposure to SSRIs and SNRIs during the third trimester include the poor neonatal adaptation syndrome, which includes agitation and restlessness, irritability and continuous crying, insomnia or somnolence, poor feeding, vomiting, diarrhea, hypoglycemia, hypothermia, respiratory distress, altered muscle tone, hyperreflexia, jitteriness, shivering, tremors, and very rarely, seizures. Symptoms of poor neonatal adaptation syndrome are generally mild, self-limited, and rarely last longer than two weeks. (See 'Poor neonatal adaptation' above.)

- SSRI exposure in late pregnancy appears to be associated with a small increased risk of persistent pulmonary hypertension in the newborn. (See 'Persistent pulmonary hypertension of the newborn' above.)

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