Antenatal depression: Risks of abnormal infant and child development

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INTRODUCTION

Antenatal maternal depression is associated with adverse effects upon infant and child development [1-3]. In addition, prenatal depression is associated with adverse effects upon pregnancy and neonatal outcomes as well as cognitive impairment and psychopathology in the offspring.

This topic reviews the association between antenatal depression and abnormal infant and child development. The association of antenatal depression with adverse pregnancy and neonatal outcomes, as well as cognitive impairment and psychopathology in the offspring, are discussed separately, as are the risks of prenatal antidepressants, and the clinical features, assessment, diagnosis, and treatment of antenatal depression:

- (See "Antenatal depression: Pregnancy and neonatal outcomes".)
- (See "Antenatal depression: Risks of cognitive impairment and 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 "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes".)

- (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".)

QUALITY OF EVIDENCE

Information about the association between antenatal depression and adverse pregnancy outcomes and adverse outcomes in the offspring comes from low to moderate quality studies [4-10]. The evidence is based upon observational studies that can yield associations confounded by measured and residual (unmeasured) factors. These studies include retrospective case-control studies that carry the risk of recall bias, as well as population based registry studies, which may misclassify exposure. Other methodologic problems include incomplete assessment of maternal mental health, identifying depressed patients with screening questionnaires rather than structured clinical interviews, not assessing depression severity, not precisely defining outcomes, and grouping together different types of outcomes across a range of severity from mild to severe. Many studies use the mother's report for both the independent variable (prenatal depression) and dependent variable (child outcome), and depressed mothers may perceive their children in a more negative light than other informants (reporting bias). In addition, some studies fail to use appropriate control (comparison) groups, and some observed associations between exposure and outcome are based upon a small number of exposed and affected infants.

Associations between fetal exposure to antenatal depression and adverse outcomes that are found in observational studies may be confounded by many maternal factors [1-4,11]:

- Duration of depressive syndrome (eg, the antenatal depressive episode may have started prior to conception).
- Poor adherence with prenatal care.
- Comorbid general medical illnesses (eg, obesity).
- Comorbid psychiatric illnesses (eg, anxiety disorders, personality disorders, and substance use disorders).
- Prescribed medications, including psychotropics (eg, antidepressants, antipsychotics, and/or benzodiazepines).

- Demographic and environmental factors, such as age, poor education, financial difficulties, social isolation, and intimate partner violence.
- Postnatal factors (eg, postpartum depression).

The lack of knowledge about the effects of depression upon pregnancy outcomes and outcomes in the offspring complicates our ability to understand the effects of antidepressants upon pregnancy. As an example, an association between selective serotonin reuptake inhibitor (SSRI) use and an adverse outcome (eg, preterm birth) may be observed, because depression is associated with the outcome [7,8,12,13], and pregnant patients who are severely depressed may be more likely to receive SSRIs than patients who are less depressed or not depressed.

POTENTIAL MECHANISMS

Possible direct and indirect mechanisms by which antenatal maternal depression may adversely affect perinatal and longer term child outcomes include the following [2,10,14-17]:

- Shared genetic factors.
- Epigenetic changes (eg, DNA methylation) of genes in the placenta and umbilical cord blood.
- Alterations in maternal and fetal central nervous system serotonergic functioning.
- Dysregulation of maternal hypothalamic-pituitary-adrenal axis hormones (eg, corticotropin-releasing hormone) and increased fetal exposure to cortisol (this is an example of fetal programming).
- Compromised functioning of the maternal immune system.
- Poor adherence with prenatal care, prescribed medications, and vitamins.
- Poor nutrition.
- Lack of exercise.
- Substance use disorders.
- Persistence of antenatal depression into the postpartum period.

One review concluded that although genetic factors and postnatal care clearly affect the risk for adverse outcomes (eg, emotional problems and impaired cognitive development) in children, 10

to 15 percent of the risk may be attributable to prenatal depression and anxiety [18].

INFANT AND CHILD DEVELOPMENT

Antenatal depression is associated with developmental disturbances in infants and children; most of the effects appear to be small to moderate [14].

Sudden infant death syndrome — Depression during pregnancy may be related to sudden infant death syndrome [3]. A study of an administrative heath care database included pregnant women with a live birth and subsequent sudden infant death syndrome fatality (n = 169 cases), and pregnant women with a live birth and infant survival (n = 662 controls) [19]. The analyses controlled for potential confounding factors (smoking status and infant sex), and found that antenatal depression was observed in more cases than controls (9 versus 2 percent).

Other risk factors for sudden infant death syndrome are discussed separately. (See "Sudden infant death syndrome: Risk factors and risk reduction strategies", section on 'Risk factors'.)

Physical health — Multiple prospective studies suggest that children of women with antenatal maternal depression are at increased risk of physical health problems such as diabetes and diarrhea [20,21]:

- One study enrolled pregnant women and followed the mother-child dyads (n >800) for up to five years after birth [22]. The results suggested that antenatal maternal depressive symptoms were associated with offspring physical health problems (eg, asthma, colic, diabetes, and/or diarrhea), independent of postnatal maternal depressive symptoms. However, maternal use of antenatal antidepressants was not reported.

- A study in a low-income country enrolled pregnant women with depressive disorders (n = 160, use of antidepressants was not reported) and pregnant women without depression (n = 160); the infants of all women were assessed at age 12 months [23]. The women were all physically healthy, and the analyses controlled for potential confounding factors (eg, infant birth weight and sex, socioeconomic status, and duration of exclusive breastfeeding). The risk of diarrhea was two times greater in the infants of depressed women. In addition, infants of depressed women had a small, increased risk of not receiving a full set of immunizations (relative risk 1.3). However, the analyses did not control for postpartum depression, which was observed in most of the women with antenatal depression.

However, the association between antenatal depression and other health problems, such as wheezing and rhinitis, is not clear due to contradictory results across studies:

- A prospective study of pregnant women with depression (n = 292) or without depression (n = 1308) followed their offspring for up to five years [24]. After adjusting for potential confounding factors (eg, infant birthweight and sex, maternal age, and prepregnancy maternal smoking and body mass index [BMI]), the analyses found that allergic rhinoconjunctivitis was more likely to occur in the offspring of depressed women than nondepressed women (odds ratio 1.9, 95% CI 1.3-2.6). However, antenatal depression was not associated with wheezing in the children.

- Another prospective study included pregnant women (n = 1152) and followed their infants for the first year of life [25]. After adjusting for potential confounding factors (eg, maternal age, antenatal smoking, and prepregnancy BMI), the analyses found that wheezing was more likely to occur in the offspring of depressed women than nondepressed women (odds ratio 2.1, 95% CI 1.1-4.2). However, antenatal depression was not associated with rhinitis.

Growth — The effect of antenatal depression upon infant physical growth is not clear. A study from a high-income country found that antenatal depression was not associated with infant growth, whereas a study from a low-income country found that antenatal depression predicted poorer growth:

- A prospective study from the United States included infants (n = 31) of women with antenatal depression who were not treated with antidepressants, and infants (n = 97) of women who did not have antenatal depression or exposure to antidepressants [26]. The analyses controlled for potential confounding factors (eg, infant sex, preterm birth, and postpartum depression). During follow-up lasting one-year postpartum, growth in infant weight, length, and head circumference were each comparable in the two groups.

- A prospective study in Pakistan enrolled pregnant women with depressive disorders (n = 160, use of antidepressants was not reported) and pregnant women without depression (n = 160); the infants of all women were assessed at age 12 months [23]. The women were all physically healthy, and the analyses controlled for potential confounds (eg, infant birth weight and sex, socioeconomic status, and duration of exclusive breastfeeding). The risk of stunting (length for age) and being underweight were each three times greater in the infants of depressed women than controls. However, the analyses did not control for postpartum depression, which was observed in most of the women with antenatal depression.

Prenatal maternal depression may be associated with the offspring's physical growth and weight during early childhood. In a prospective study conducted in the United States,

depressive symptoms were assessed in pregnant women (n >800), and anthropometric indices of the children were measured at age three years [27]. After controlling for potential confounds (eg, maternal age, prepregnancy BMI, and postpartum depressive symptoms), the analyses found that antenatal depressive symptoms were associated with a reduced BMI and increased central adiposity in the children.

Brain structure — It is not clear if prenatal maternal depression is associated with changes in brain structure in the offspring, due to inconsistent results across studies.

Evidence that antenatal depression is associated with changes in brain structure, such as decreased integrity of brain fiber organization and decreased cortical thickness, includes the following:

- A prospective study assessed pregnant women (n = 157) for depressive symptoms and used a type of magnetic resonance imaging (MRI) called diffusion tensor imaging to study white matter microstructures in the amygdala of neonates 6 to 14 days after birth [28]. The analyses controlled for potential confounding factors (eg, birth weight, infant age at time of imaging, and maternal age), and found that axial diffusivity (an indication of axonal integrity) and fractional anisotropy (coherence of brain fiber organization) were each lower in the neonates of women with depressive symptoms, compared with neonates of women without depressive symptoms.

- In another prospective study, women (n = 52, including one woman treated with an antidepressant during pregnancy) were assessed for depressive symptoms both during pregnancy and the postpartum period, and the children from these pregnancies underwent structural MRI of the brain; the mean age of the children at the time of scanning was approximately 3.5 years [29]. After adjusting for potential confounds (eg, child's age and birth weight and maternal postpartum depressive symptoms), increased prenatal depressive symptoms were associated with decreased cortical thickness in the children. The findings suggest premature brain development and reduced plasticity in the children of women with antenatal depression.

Associations between prenatal maternal depression and changes in brain structure may be sex-specific. One prospective study assessed women (n = 235) for depressive symptoms during pregnancy and again after delivery, and the offspring underwent structural MRI of the brain at approximately age 4.5 years [30]. After adjusting for potential confounding factors (eg, maternal age and ethnicity, and child's age at MRI), the analyses found that among girls (n = 122), antenatal depressive symptoms were associated with larger right amygdala volume,

independent of postnatal depressive symptoms. In boys, antenatal depressive symptoms were not associated with amygdala volume.

However, other studies suggest that antenatal depression is not associated with changes in brain structure. As an example, a prospective study included neonates (n = 41) of mothers with antenatal depression that was not treated with antidepressants, and neonates (n = 82) of women with no history of depression and no history of using antidepressants [31]. Propensity scoring was used to match the two groups of neonates with regard to potential confounders observed at baseline (eg, maternal age, neonatal sex, and neonatal gestational age at birth and MRI). Global and regional gray matter and white matter brain volumes were comparable for the two groups, as were white matter microstructures.

Brain functioning — Prenatal maternal depression may be associated with altered brain functioning in the offspring, including changes in the amygdala. As an example, a prospective study performed functional MRI in children of mothers with antenatal depression (n = 19), and children of nondepressed mothers (controls, n = 20) [32]. The children were imaged at age six to nine years, during a task in which they were presented with negative emotional faces. Amygdala responses were greater in the children of mothers with antenatal depression than controls. In addition, postnatal maternal depression was not correlated with amygdala hyperresponsiveness.

However, some of the findings regarding the association between antenatal depression and brain functioning in the offspring are inconsistent. As an example, it is not clear whether functional connectivity between the amygdala and other brain structures is increased or decreased, and whether connectivity is sex-specific:

- A prospective study assessed women (n = 24) for depressive symptoms during pregnancy and again after delivery; in addition, the offspring underwent functional MRI of the brain at age six months [33]. After controlling for potential confounding factors (eg, birth weight, household income, and postpartum depressive symptoms), the analyses showed that prenatal depressive symptoms were associated with increased functional connectivity between the left amygdala and other brain structures (eg, left and right anterior cingulate cortex).

- Another prospective study assessed women (n = 128) for depressive symptoms during pregnancy and again after delivery; in addition, the offspring underwent functional MRI of the brain at approximately age 4.5 years [34]. After adjusting for potential confounding factors (eg, maternal age and ethnicity, and child's age at MRI), the analyses found that among girls (n = 71), antenatal depressive symptoms were associated with decreased

functional connectivity between the left amygdala and cortico-striatal circuitry, independent of postnatal depressive symptoms. In addition, functional connectivity between the right amygdala and cortico-striatal circuitry was also decreased. In boys, antenatal depressive symptoms were not associated with amygdala functional networks.

Neonatal functioning — Multiple prospective observational studies indicate that antenatal depression is associated with impaired neurobehavioral functioning in neonates. These studies have examined newborns of mothers with prenatal depressive disorders or symptoms and newborns of mothers with no prenatal depression or exposure to antidepressants; assessments were performed during the first postnatal month. The results show that multiple domains of neurobehavioral functioning are diminished in neonates of mothers with prenatal depression, compared with controls. Aspects of functioning that were impaired include:

- Habituation, which is defined as progressive decreases in response to repeated auditory and visual stimuli while the neonate is asleep [35-37]
- Arousal and activity [36,37]
- Attention (orientation) – Ability to track auditory and visual stimuli [36,38,39]
- Reflexes [38]
- Excitability – High levels of reactivity [38]
- Hypotonia – Decreased muscle tone in limbs and/or trunk [35]
- Regulation of state when confronted with stimulation [36,40]
- Motor performance [36]
- Signs of stress (eg, startle, tremor, and back arching) [36]

Sleep — Prospective studies by the same group of investigators suggest that prenatal depression is associated with disturbed/disorganized sleep and other impaired sleep patterns in newborns:

- A study included neonates (n = 83) of women with antenatal major depression or persistent depressive disorder (dysthymia) who were not treated with antidepressants, and neonates of women who were not depressed (controls, n = 170) [41]. Sleep in the neonates was assessed at approximately day 1 postpartum. Compared with controls, the newborns of depressed mothers spent more time in disturbed/disorganized sleep, and less time in deep sleep.

- Another study included neonates of women with depressive symptoms who were not treated with pharmacotherapy (n = 80) and neonates of nondepressed women (n = 40); newborns were examined on the first afternoon after birth [36]. Disturbed/disorganized sleep patterns were more likely to occur in neonates of women with antenatal depression than nondepressed women.

- In addition, a study enrolled pregnant women with antenatal depressive symptoms but no postpartum symptoms (n = 20), and pregnant women without antenatal or postnatal depressive symptoms (n = 20); neonates were assessed within two weeks of birth [42]. Compared with infants of mothers who were not depressed, infants of depressed mothers spent more time in disturbed/disorganized sleep.

Temperament — Prospective studies from the same research group suggest that antenatal depression is associated with difficult temperament in neonates:

- One study enrolled pregnant women with antenatal depressive symptoms but no postpartum symptoms (n = 20; use of antidepressants not reported), and pregnant women without antenatal or postnatal depressive symptoms (n = 20); neonates were assessed within two weeks of birth [42]. Compared with infants of mothers who were not depressed, infants of depressed mothers exhibited more stress behaviors, and spent more time fussing and crying, and less time awake and alert.

- A second study included neonates (n = 83) of women with antenatal major depression or dysthymia (persistent depressive disorder) who were not treated with antidepressants, and neonates of women who were not depressed (controls, n = 170) [41]. Neonates were assessed at approximately day 1 postpartum. Compared with controls, the newborns of depressed mothers spent more time fussing and crying.

Attention and arousal — Antenatal depression does not appear to be associated with alterations in attention and arousal in the offspring. A prospective study included infants (n = 27) of women with antenatal major depression who were not treated with antidepressants, and infants (n = 98) of women with neither antenatal depression nor exposure to antidepressants; infants were assessed 12 weeks after birth [43]. Attention and arousal of the offspring was comparable in the two groups.

Crying — Antenatal depression may be associated with excessive infant crying. A prospective study included pregnant women with a high level of antenatal depressive symptoms (n >400) and pregnant women with a low level of symptoms (n >2600) [44]. Their babies were assessed at age three to six months for excessive crying, which was defined as crying for an average of three or more hours per day in the past week. The analyses controlled for potential

confounding factors (eg, maternal age, parity, and exclusive breastfeeding), and found that excessive crying was more likely in the babies of mothers with a high level of depressive symptoms, compared with mothers with a low level (odds ratio 1.9, 95% CI 1.2-3.1). However, the analyses did not control for postnatal depressive symptoms or antenatal use of antidepressants.

Motor functioning — It is not clear if antenatal depression is associated with motor functioning in the offspring, due to inconsistent results across studies:

- One prospective study included children of women who screened positive for antenatal depression but not postnatal depression (use of antidepressant drugs not specified; n >1500), and children of women who screened negative for antenatal and postnatal symptoms (n >8000). The children were screened for developmental delays, including gross and fine motor skills, at age 18 months [45]. Developmental delays were more likely to be observed in the offspring of mothers with antenatal depressive symptoms than controls (odds ratio 1.5, 95% CI 1.2-2.0).

- A second prospective study included offspring (n = 27) of women with antenatal major depression who were not treated with antidepressants, and offspring (n = 98) of women without antenatal depression or exposure to antidepressants [43]. During follow-up lasting one and a half years postpartum, infant and child gross and fine motor coordination and control in the two groups was comparable.

Sleep problems — Prenatal depression may be related to early childhood sleep problems, but the effect appears to be modest [11]. A prospective study enrolled pregnant women (n >10,000), who were asked about sleep problems in their children at age 30 months [46]. Sleep disturbances included refusing to go to bed, difficulty going to sleep, and nightmares. After controlling for potential confounding factors (eg, birth weight, prenatal maternal smoking and use of alcohol, and postnatal maternal depression and anxiety symptoms), the analyses found that sleep problems were more likely in the children of women with antenatal depressive symptoms than the children of women who were not depressed (odds ratio 1.4, 95% CI 1.2-1.8). However, prenatal exposure to antidepressants was not reported.

Attachment — Antenatal depression does not appear to be associated with alterations in attachment behavior (the bond between the child and caregiver). One prospective study of pregnant women (n = 586) assessed attachment behaviors in their offspring at age 14 months, and found that prenatal depressive symptoms were not associated with attachment insecurity or with attachment disorganization [47]. Although another prospective study of pregnant women (n = 79) found that antenatal depressive symptoms were associated with disorganized

(insecure) attachment behaviors in infants at age 12 months, the effect was moderated by suboptimal postpartum maternal parenting [48].

Social interactions — It is not clear if prenatal depression is associated with alterations in social behavior in the children, due to discordant results across studies:

- A prospective study included offspring (n = 27) of women with antenatal major depression who were not treated with antidepressants, and offspring (n = 98) of women did not have antenatal depression and did not use antidepressants during pregnancy [43]. During follow-up lasting one and a half years postpartum, infant and child social behavior/engagement in the two groups was comparable.

- A second prospective study included children (n = 98) of women with prenatal depressive symptoms who were not treated with antidepressants, and children (n = 723) of women who did not have depressive symptoms and were not treated with antidepressants; the children were assessed at age four or five years [49]. After adjusting for potential confounding factors (eg, maternal age, smoking, and use of alcohol), the analyses found that problems with social behavior were greater in the children exposed to prenatal depressive symptoms.

PREGNANCY AND NEONATAL OUTCOMES

Antenatal depression may be associated with adverse pregnancy and neonatal outcomes. (See "Antenatal depression: Pregnancy and neonatal outcomes".)

COGNITIVE PROBLEMS AND PSYCHOPATHOLOGY

Antenatal depression may be associated with cognitive problems and psychopathology in the offspring. (See "Antenatal depression: Risks of cognitive impairment and psychopathology in the offspring".)

TREATING ANTENATAL DEPRESSION

Several options are available for treating antenatal depression. (See "Mild to moderate episodes of antenatal unipolar major depression: Choosing treatment" and "Severe antenatal unipolar major depression: Choosing treatment".)

RISKS OF ANTIDEPRESSANTS

The risks of prenatal antidepressants with regard to fetal and infant/child development 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" and "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes".)

POSTPARTUM DEPRESSION

Antenatal depression is a risk factor for postpartum depression, which in turn is associated with abnormal child development as well as cognitive problems and psychopathology in the children. (See "Postpartum depression: Adverse consequences in mothers and their children".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Depression in adults (The Basics)")
- Beyond the Basics topics (see "Patient education: Depression in adults (Beyond the Basics)")

SUMMARY

- Depression during pregnancy may be associated with sudden infant death syndrome and physical health problems in the children, but study results are often inconsistent. (See 'Sudden infant death syndrome' above and 'Physical health' above.)
- Antenatal depression is associated with impaired neonatal neurobehavioral functioning, including habituation, arousal and activity, attention, reflexes, excitability, and motor performance. In addition, prenatal depression is associated with disturbed/disorganized sleep and difficult temperament in neonates. (See 'Neonatal functioning' above.)
- Prenatal depression may also be associated with excessive infant crying and early childhood sleep problems. (See 'Crying' above and 'Sleep problems' above.)
- Several options are available for treating antenatal depression. (See "Mild to moderate episodes of antenatal unipolar major depression: Choosing treatment" and "Severe antenatal unipolar major depression: Choosing treatment".)

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