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Antenatal depression and offspring health outcomes

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Abstract

Background: Depression is the most common mental disorder during pregnancy, with prevalence rates between 4% and 20%. The objective of this review was to synthesize the literature on the association between antenatal depression and offspring birth outcomes, as well as developmental, behavioral, and psychiatric outcomes.

Methods: A search of PubMed, Cochrane, and Medline databases was conducted for articles published until December 2017. Articles focusing on the effects of antenatal depression on the offspring were selected to be reviewed. Reference lists of all studies were examined for any missed articles. A total of 32 articles were included in this review.

Results: Antenatal depression is associated with preterm birth, excessive infant crying, and offspring mental health problems. Untreated antenatal depression is strongly associated with adverse effects on the infant nervous system.

Conclusion: Antenatal depression increases the likelihood of poor offspring health outcomes. Research should investigate whether medication use confounds this relationship.

Keywords

High-risk pregnancy, neonatal medicine, perinatal medicine, stress, maternal–fetal medicine

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Background

Depression is the most common mental disorder during pregnancy,[1] and is characterized by having symptoms, which include but are not limited to feelings of sadness, changes in sleeping patterns, loss of energy, loss of interest, thoughts of suicide, most of the day, nearly every day, for at least two consecutive weeks.[2] Common risk factors for antenatal depression include low socioeconomic status, young maternal age, anxiety, childhood abuse, domestic violence, and single parenthood.[3] The prevalence of depression during pregnancy ranges from 4% to 20%.[1]

There has been limited research investigating how antenatal depression influences fetal development; however, one proposed mechanism is through increased levels of the maternal hypothalamic–pituitary–adrenal (HPA) axis neurohormones, specifically the glucocorticoid hormone, cortisol.[4] HPA system is activated in response to stress and increased HPA activity, and consequently high cortisol levels are commonly observed in depressed women.[4] Although glucocorticoids are essential for normal fetal development of the central nervous system, overexposure can lead to retardation of fetal growth, as well as detrimental development of the brain structure and function, leading to increases in fear behaviors and emotional problems later in life.[5,6] Under normal conditions, placental enzyme, 11 β-hydroxysteroid-dehydrogenase type 2, protects the fetus from high maternal cortisol levels by converting cortisol into its inactive state, cortisone.[7] However, evidence mainly from animal studies suggest that antenatal stressors, including depression, can affect the function of this enzyme, leading to cortisol overexposure in the fetus.[8,9] In addition to negatively impacting fetal brain development, cortisol stimulates placental production of corticotropin-releasing hormone (CRH), which at a certain threshold is critical for the onset of spontaneous labor.[10] Thus, high levels of cortisol associated with antenatal depression may lead to early increases in CRH levels, resulting in preterm birth (PTB); however, this hypothesis requires further exploration.

Not all studies, however, show a clear association between maternal stress and maternal cortisol levels during pregnancy. In a large cohort of women (n = 3039) from the Amsterdam Born Children and

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their Development-study cohort, maternal cortisol during pregnancy was mostly affected by biological and lifestyle factors, and not psychosocial factors.[11] In a recent systematic review, Orta et al.[12] found that most articles (17/29; 59%) reported no correlation between maternal cortisol and antenatal depression, and 12/29 studies (41%) reported that second- and third-trimester cortisol assessments most consistently reported an association. The authors acknowledged, however, that some studies were underpowered to detect statistically significant associations between maternal cortisol and depression. In contrast, a new systematic review and meta-analysis found a consistent negative correlation between maternal antenatal salivary cortisol and infant birth weight, although substantial heterogeneity of effects and publication bias was plausible.[13]

Fetal programming occurs during the critical period of embryonic and fetal development. The concept of fetal programming is that in utero, important physiological characteristics can be affected by environmental factors such as the mother's nutritional and mental health, which can lead to permanent structural, physiologic, and metabolic changes.[14–17] Several studies have shown, for example, that antenatal depression is associated with a higher risk for PTB,[18–21] low birth weight (LBW), and intrauterine growth restriction.[21] However, these findings are not always conclusive, as the correlation between antenatal depression and adverse birth outcomes is more common in developing countries and countries with great health disparities,[21] likely due to women's limited access to adequate health care.[22]

It is also possible that associations between antenatal depression and adverse birth outcomes and developmental outcomes may be due to side effects of antidepressants and other psychotropic medications used during pregnancy. In a cohort study of 98 infants, antenatal selective serotonin reuptake inhibitor-exposed (SSRI) infants had significant gray matter volume expansion in the amygdala and insula, and an increase in white matter structural connectivity between these same regions when compared to infants exposed to untreated antenatal depression and healthy controls.[23] An important limitation of this study, however, was that it was not possible to capture differences in severity of depression between women who received SSRIs and those with untreated antenatal depression.

The objective of this review was to synthesize the existing literature on what is known about the association between antenatal depression and offspring birth outcomes, as well as developmental, behavioral, and psychiatric outcomes.

Methods

A search of PubMed, Cochrane, and Medline databases was conducted for articles published in English through December 2017, and there were no restrictions on geographic location or publication date. These databases, along with a complete search of the literature using specific search strategies for each database, were chosen with the assistance of a librarian search expert, as more than two databases should be used when reviewing the literature in any type of systematic fashion.[24] The following key search terms were used: antenatal, maternal depression, depressive disorder, offspring outcomes, and offspring development. The search was limited to human studies. Titles, key words, and abstracts were reviewed to determine relevance. Only articles which focused on the effects of antenatal depression on the offspring were selected to be reviewed. Reference lists of all retrieved studies were also examined for any missed articles.

One author (AS) determined whether an article met the inclusion criteria and extracted data from the articles. Eligibility criteria included any cross-sectional, cohort, clinical, epidemiological, quasi-experimental or intervention study design, as well as systematic reviews or meta-analyses, which examined the effects of antenatal depression on offspring health outcomes. Narrative reviews were excluded. Grey literature (e.g. conference proceedings, unpublished theses/dissertations, government documents, blogs) was not searched, so we cannot rule out the possibility of publication bias, since negative studies are less likely to be published.[25] See Figure 1 for a flow diagram on the article selection process.

A total of 32 articles were included in this review after excluding articles based on the following criteria: articles focusing on the mechanism between antenatal maternal depression and offspring outcomes only; those focusing on postnatal or perinatal depression; and articles focusing on the effects of antidepressants on the offspring only. Systematic reviews have already been published on offspring antenatal exposure to antidepressants[26–28] and the association between postnatal depression and offspring outcomes,[29] so this review was specific to antenatal depression and offspring outcomes. See Supplementary Table 1 for a summary of the studies reviewed.

Results

Birth and infant outcomes

Birth outcomes. Antenatal depression is associated with adverse birth outcomes, including fetal growth restriction, PTB, and LBW.[21,30,31] Fetal growth restriction is in turn associated with poor neurodevelopmental outcomes in childhood, such as delays in motor, cognitive, social, and behavioral development.[30] LBW effects 17% of births worldwide, with 96.5% of LBW infants born in developing counties; it is also associated with higher rates of morbidity in adulthood.[32] PTB accounts for close to 14% of births in the US, and is the leading cause of infant morbidity and mortality.[30] A study from France reported that after adjusting for potential confounding factors, such as a previous PTB, age, education, and smoking habits, spontaneous PTB was significantly higher in women who were depressed (9.7%) than women who were not (4%) (adjusted OR: 3.3; 95% CI (1.2–9.2)).[18] Similar results were found in a prospective cohort study of 791 pregnant women in Northern California, where PTB was almost twice as likely among women who were clinically depressed than women without depressive symptoms.[19] There was no distinction, however, between spontaneous and iatrogenic PTB, and depressive symptoms were only measured once early in pregnancy. Antenatal depression, when combined with symptoms of anxiety, has

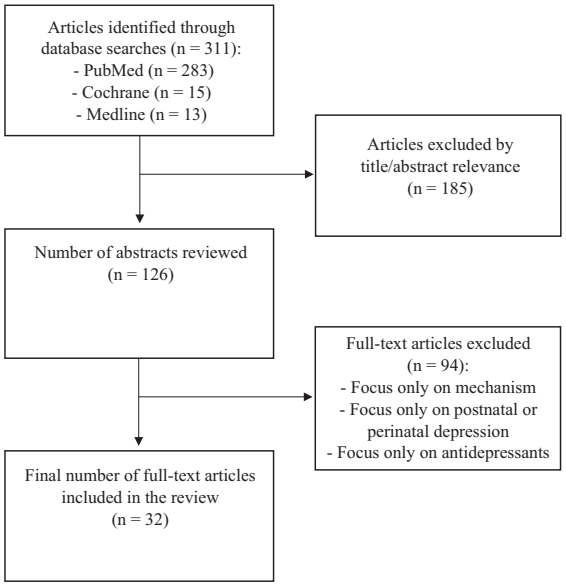

Figure 1. Flow diagram of literature review process.

been shown to more than double the risk of spontaneous PTB (OR: 2.46; 95% CI (1.22–4.94)); however, this study did not report whether mothers were on medication, which may confound the results.[20] Indeed, a systematic review found that exposure to antidepressants may induce epigenetic changes and interfere with physiological fetal behavior, although the clinical relevance of antidepressant exposure on placental functioning was unclear.[26]

There is also a widely held view that pharmacological and non-pharmacological treatments can help mitigate the influence of antenatal mental health disorders on offspring outcomes. However, a recent meta-analysis of 16 non-pharmacological randomized controlled trials found that these treatments had no significant impact on improving birth weight, Apgar scores, or gestational age.[33] It is also noteworthy that no randomized controlled trials examining the association between pharmacological treatments and birth outcomes were found, the quality of most non-pharmacological studies was low, and the studies were largely heterogeneous.

Interestingly, spontaneous PTB has been shown to be particularly high in depressed mothers with a pre-pregnancy body mass index (BMI) less than 19[34] and in women with posttraumatic stress disorder (PTSD).[35] In a cohort study of 634 pregnant women with singleton pregnancies, women with major depression and who were underweight were 6.9 times more likely (95% CI:1.8, 26.2) to have a spontaneous PTB, controlling for sociodemographic and biomedical factors.[34] Another cohort study found that women with PTSD and major depression were at a four-fold increase for spontaneous PTB (odds ratio (OR), 4.08 (95% CI, 1.27–13.15)), and that the risk was both independent of, and greater than the risk of antidepressant and benzodiazepine use.[35] A meta-analysis of 29 studies reported that antenatal depression increased the risk for PTB (39% increase), fetal growth restriction (45% increase), and LBW (49% increase). However, the effect size varied depending on how depression was measured, country location, and socioeconomic status.[21] In contrast, a systematic review and meta-analysis of 30 studies reported that only premature delivery was significantly associated with maternal depression (OR: 1.37; 95% CI (1.04 to 1.81)), and that LBW and gestational age were not associated with antenatal depression.[31] An important caveat from this review was that 12/15 and 8/15 studies did not adjust for alcohol and tobacco use, respectively, both of which have been shown to be associated with PTB.[36] In a recent Canadian retrospective cohort study examining the impact of alcohol outlet accessibility on adverse birth outcomes (n = 25,734), Seabrook et al.[37] found that depression during pregnancy was not associated with LBW or PTB, controlling for sociodemographic, socioeconomic, medical history, and risk-taking factors including alcohol and tobacco use during pregnancy. Findings from the Canadian study largely coincide with those from an Australian longitudinal study, where antenatal depressive and/or anxiety symptoms were not associated with LBW or PTB, although the authors acknowledge that their small sample size (n = 285) likely impacted their statistical power to detect modest associations.[38]

Chang et al.[39] investigated whether gestational age and birth weight was associated with antenatal depression. The authors found that, after adjusting for gestational age, there was no association between offspring of antenatally depressed women and LBW. There was, however, an association between antenatal depression and lower gestational age (OR: 0.66; 95% CI (0.47–0.93)). Conversely, another study found that antenatal depression was associated with both lower gestational age and birth weight.[40] Overall, results on the association between antenatal depression and birth outcomes are mixed, with antenatal depression appearing to have the greatest impact on PTB.

Infant neurodevelopmental outcomes. Antenatal depression is associated with decreased vagal tone and greater frontal electroencephalogram (EEG) activation in newborns, which are associated with lower attentiveness and greater withdrawal behaviors, respectively.[30] Also, dysfunctions of the HPA axis and amygdala (brain region associated with regulation of emotion) have been observed in newborns of antenatally depressed mothers, further suggesting that antenatal depression may negatively influence offspring's ability to respond to both physical and behavioral stressors.[3] Developmental complications such as inflammatory and gastrointestinal diseases, major congenital anomalies, and poor physical health are also associated with antenatal depression.[41–44] Furthermore, offspring of antenatally depressed mothers spend more time crying as infants,[45] have more sleep problems at 18 and 30 months,[46] and experience more anxiety, depression, and withdrawn behavior during childhood than children whose mothers were not depressed during pregnancy.[47] Lastly, psychiatric disorders, including depression and anxiety, have been found in offspring of antenatally depressed mothers.[48–50] Some of these studies adjusted for environmental and genetic factors by comparing the associations between maternal and paternal antenatal depression, and found that maternal depression, but not paternal depression, was associated with offspring anxiety and depression.[49,50] This is important because the fetal programming hypothesis proposes that the association between antenatal stress exposure and offspring health outcomes should be stronger in mothers than fathers if there is a direct biological effect of maternal depression on fetal development.[49] Conversely, if these studies would have found that paternal mental health was more important or equivalent to maternal mental health with respect to offspring depression and anxiety, this could be suggestive of genetic or other environmental mechanisms. Taken together, this suggests that these outcomes are at least partially due to fetal programming and the intrauterine environment.

Offspring developmental outcomes

The impact of antenatal depression on offspring development, including inflammatory and gastrointestinal diseases and major congenital anomalies is another emerging area of research. Krause et al.[41] examined whether anxiety and depressive disorders prior to and during pregnancy affected the incidence of infant inflammatory diseases, gastrointestinal complaints, and corresponding drug administration, as reported by mothers. After adjustment for confounders, severe psychopathological symptoms during pregnancy were associated with inflammatory diseases (i.e. conjunctivitis, mycosis) and anti-infective medication, and anxiety and depressive disorders were related to gastrointestinal complaints (i.e. diarrhea, colic complaints) and medication for gastrointestinal complaints in infants. No information was provided, however, on maternal medication use, which could potentially confound these results. In addition, it is unclear whether these findings were due to fetal programming per se or if it was the result of depression itself. It has been hypothesized, for example, that depressed mothers are less likely to participate in risk-reduction decontamination activities (e.g. hand washing), thus potentially causing their child to become ill.[41] Ban et al.[42] found that offspring of antenatally depressed mothers did not have a higher risk for major congenital anomalies compared to offspring of non-depressed mothers, although the antidepressant paroxetine was associated with increased heart anomalies, indicating that caution should be used if treating antenatal depression with antidepressants.

Antenatal depression has also been associated with offspring weight and adiposity. A prospective cohort study of 838 mothers/offspring in the greater Boston area found that children whose mothers experienced antenatal depression weighed less for a given height at three years of age, and had greater central adiposity compared to offspring of mothers who did not experience antenatal depression.[43] Another cohort study from Australia found that antenatal depression

was associated with worse physical health during early childhood, although this effect was partially explained by ongoing maternal depression in the child's life.[44] At the child's follow-up at age 20, poor physical health during childhood was correlated with higher health-related stress and poor social functioning. These results suggest a potential pathway by which maternal depression can have long-term effects on offspring mental health.

Offspring behavioral outcomes

Offspring temperament and sleep disturbances. A variety of behavioral outcomes have been observed in offspring of antenatally depressed women. Diego et al.[45] found that newborns of antenatally depressed mothers spent more time crying than newborns of non-depressed mothers or newborns of postnatally depressed mothers. Van der Wal et al.[51] found that antenatal depression, anxiety, and stress were both univariately and multivariately associated with excessive infant crying in three to six-month-old infants (adjusted ORs between 1.69 and 2.23). Similarly, Huot et al.[52] found that maternal depression during pregnancy was associated with negative affectivity (i.e. distress, sadness, fear, shyness, frustration) at two and six months of age, and that postpartum depression was not associated with infant temperament. A longitudinal study from Britain also found a significant association between antenatal depression and infant anger and use of force.[53]

Sleep problems affect 20–30% of children, with an increased risk observed in offspring of antenatally depressed women.[30] These sleep problems are associated with negative behavioral and psychological problems, including depression. O'Connor et al.[46] measured total sleep time, night-time awakenings, and sleep problems at 6, 18, and 30 months in children. Antenatal anxiety and depression resulted in more sleep problems in offspring at 18 and 30 months, independent of postnatal depression. Furthermore, infants of antenatally depressed women have more disorganized sleep and less time in deep sleep.[54] Netsi et al. found that improvements in depression during pregnancy was associated with better temperament (i.e. less fussy/difficult) and shorter nocturnal sleep duration in infants.[55] Although the causal mechanisms behind these occurrences were unknown, the authors speculate that improved depressive symptoms could interrupt fetal exposure to adverse physical consequences of programming on neurocognitive processes, and that lower exposure to antenatal depression is less likely to have a harmful cumulative programming effect than is persistent exposure.

Offspring social behavior. Two papers assessed infant behavior using the Brazelton scale and found that infants of depressed mothers showed less responsiveness to faces and voices, and poor habituation and orientation.[56,57] Another study showed that antenatal maternal depression is associated with infant disorganized attachment at 12 months.[58] However, in a large population-based Dutch cohort study, neither antenatal nor postnatal maternal depression was associated with infant–mother attachment insecurity or disorganization, suggesting that more research on this relationship is needed.[59]

Externalizing and internalizing behavior problems have been reported in offspring of antenatally depressed mothers. Externalizing behavior problems are directed outwards (e.g. bullying) and are more common in boys, whereas internalizing behavior problems are directed inwards (e.g. social withdrawal) and are more common in girls.[60,61] Children of depressed parents also have more problems with defiance and cognitive skills[62] and are comparable to children whose parents have schizophrenia.[63] A longitudinal study found that antenatal depression in the first trimester was associated with internalizing behavior problems for male offspring between 14 and 54 months old, whereas antenatal depression in the third trimester was associated with internalizing and externalizing behavior problems in only female offspring between 14 and 54 months of age.[47] In contrast, another longitudinal study on 147 mother–child dyads in Finland found that third-trimester antenatal depression was associated with externalizing behavior problems in both males and females eight to nine years old (OR: 3.1; 95% CI (1.1–8.9)), but antenatal depression was not associated with internalizing behavior problems.[64] These mixed results suggest that more longitudinal studies are needed to assess the impact of antenatal depression on offspring social behavior.

In one of the only studies to explicitly model genetic transmission as a potential pathway for the association between antenatal depression and offspring internalizing and externalizing behavior problems, Hannigan et al.[65] found that shared genetic factors accounted for most of the associations between maternal antenatal depression and offspring behavioral outcomes in early childhood. This is an important finding because it suggests that future research investigating the impact of antenatal depression on offspring mental health should consider the role of genetics as a confounding variable.

Offspring psychiatric outcomes

Many studies have shown that antenatal depression is associated with offspring mental health problems later in life, including depression and anxiety. Pawlby et al.[48] investigated the relationship between antenatal depression and offspring depression at age 16 and found that the risk of depression was 4.7 times greater (CI 1.60–13.86) when exposed to antenatal depression than for offspring not exposed, although this relationship attenuated to non-significance once the chronic nature of the mother's depression was considered. In other words, it was not maternal depression during pregnancy per se which predicted adolescent depression, but rather the number of depressive time periods throughout the child's life. Other studies have explored the extent to which poor offspring mental health is due to a maternal biological impact on fetal development.[49,50] This has been done by controlling for shared environmental and genetic factors by comparing the associations between maternal and paternal depression during pregnancy. Capron et al. found that, after adjusting for parental postnatal depression and anxiety at eight weeks postpartum, children of antenatally depressed mothers had an increased risk of anxiety disorders at age 18 (adjusted OR 1.75; 95% CI (1.19–2.58)),[49] whereas no associations were found between paternal antenatal depression or anxiety and offspring depression or anxiety. Pearson et al.[50] measured offspring depression in over 2000 18 year olds and found that paternal antenatal depression was not associated with offspring depression, while offspring of antenatally depressed mothers were 1.28 times (95% CI [1.08–1.51]) more likely to have depression at age 18, independent of postnatal maternal depression. These differences observed between maternal and paternal depression and offspring outcomes support the fetal programming hypothesis, and that adolescent depression does not arise through antenatal depression continuing into the postnatal period.[50] On the other hand, one study from Germany ($n = 307$) found that antenatal depression was actually associated with lower self-reported levels of depression in young adults.[66] This association was particularly pronounced when antenatal depression was present during the first trimester of pregnancy and when maternal depression was present pre- as well as postnatally. Results of this study should be interpreted with caution, however, since antenatal depressed mood was only assessed shortly after childbirth, and not during pregnancy.

Another emerging area of research is whether biological sex moderates the association between antenatal depression and offspring outcomes.[67,68] Quarini et al.[68] found that gender did not moderate the relationship between antenatal and offspring depression at age 12, that antenatal depression increased the risk of depression in 18-year-old girls compared to boys, and that postnatal depression

was associated with a higher risk of depression in 18-year-old boys compared to girls. Similarly, other research has also found that gender does not moderate the relationship between antenatal depression and offspring depression at age 12 and that a larger proportion of the variance in adolescent depression is attributable to heritability at age 12 compared to age 18.[69] One explanation for why gender differences only emerge in late adolescence is that different biological processes are involved in brain development at age 18 (myelination and synaptic pruning), which can be influenced by early fetal programming. Gerardin et al.[67] assessed the effects of antenatal depression on one year olds and found that males had higher anxiety and sleep problems than females. This early gender difference observed may be important to understanding the different prevalence of mental health disorders between male and female children.[67]

Conclusion

There is a growing body of literature suggesting that antenatal depression can increase the risk of adverse health outcomes in offspring. As this review demonstrates, antenatal depression is associated with an increased risk for adverse birth outcomes, in particular, PTB.[18–21] Antenatal depression is also associated with developmental complications including decreased vagal tone and greater frontal EEG activation in newborns,[3,30,70] and poor physical health in children.[43,44] Furthermore, behavioral and psychiatric disorders such as antisocial behavior, depression, and anxiety have been found in offspring of antenatally depressed mothers.[47–50]

An important consideration in our review is that most studies examining the impact of antenatal depression on offspring health outcomes have not adjusted for maternal medication use, and it is possible that this may be a confounding factor in the apparent association. Similarly, future research should consider statistical adjustment for genetic confounding since shared genes appear to be linked to the association between antenatal depression and offspring health outcomes. More randomized controlled trials, with adequate statistical power, are also needed to assess the impact of complementary and alternative therapy (e.g. omega 3-fatty acids, folate, St. John's Wort, bright light therapy, massage, exercise) for treating antenatal depression. Future studies should also consider the timing and severity of depression and other mental health disorders during pregnancy.

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