

REVIEWS

Evaluating the Impact of Perinatal Depression on Fetal and Childhood Development

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Keywords: perinatal depression, major depression, pregnancy

<https://doi.org/10.52504/001c.34629>

Georgetown Medical Review

Vol. 6, Issue 1, 2022

Perinatal maternal depression leads to a variety of biochemical and behavioral changes in utero. These alterations are linked to impaired fetal development and may also be detrimental to future neonatal, pediatric, and adolescent health. There is a marked rise in the incidence of atopic triad conditions, such as dermatitis and asthmatic wheezing, in children of pregnant mothers with antepartum depression, possibly due to an aberrant TH2 immunologic response and increased fetal oxidative stress. Maternal antepartum depression may also contribute to small-for-gestational age birth status, anomalous fetal neurotransmitter levels, and depression throughout infancy and adolescence. Cortisol has been implicated as a common causative factor responsible for many of these negative offspring outcomes. Minimal research on untreated major depression in pregnancy has been conducted. However, current studies emphasize the importance of holistically evaluating the risks associated with untreated major depression in pregnancy in order to minimize harmful effects on children.

Introduction

Untreated depression around the time of pregnancy is a significant worldwide issue, affecting 15% to 25% of mothers globally and costing a yearly burden of \$5.7 billion.¹ The condition can be subdivided into 3 distinct categories: antepartum depression (APD), postpartum depression (PPD), and perinatal depression (PD). APD refers to depression that occurs during pregnancy, PPD refers to depression that occurs after childbirth, and PD encompasses both APD and PPD. Each category has different risk factors and downstream consequences for mother and child. In this review article, we specifically examine the risks of untreated antepartum maternal depression and untreated perinatal maternal depression on offspring development.

An interesting intersection among the varied downstream consequences of maternal depression points to the role of cortisol. It has been well-established that depression is associated with elevated levels of cortisol in the brain, and during PD the elevated cortisol levels reach the fetus via uteroplacental circulation. Given that cortisol is the body's primary stress hormone and is

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known to have physiologic effects, such as immune suppression and bone growth inhibition, it seems plausible that cortisol could mediate short-term and long-term delayed developmental effects in children of mothers affected by PD in pregnancy.

The rates of APD in pregnant women have also been linked to social determinants of health such as access to maternal health care, mental health screenings, and safe living environments.² Similarly, the likelihood of PD in pregnant women has been linked to individuals who lack social support, have a medical history of depression, and are fearful of childbirth.³ When APD and PD are left untreated, both conditions have a wide range of debilitating consequences on offspring health, ranging from immunological, physical growth, neurologic, and psychological disorders.

Antepartum Depression and Immunology

The Role of Elevated Cortisol and Increased Fetal Oxidative Stress in Atopic Dermatitis

Antepartum maternal depression is thought to contribute to childhood atopic dermatitis by impairing fetal immune development. The specific link between APD and childhood atopic dermatitis is thought to arise from (1) elevated maternal cortisol levels triggering a response in the fetus and (2) increased fetal oxidative stress as measured by lower glutathione to glutathione disulfide ratios.

The enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) is expressed in the placenta and typically helps inactivate the primary stress hormone cortisol at physiologic states. However, stress associated with APD has been found to inhibit 11 β -HSD2 activity in mothers.⁴ With lower 11 β -HSD2 enzymatic function, maternal cortisol levels become elevated, and this maternal cortisol crosses the placenta to significantly impact the in utero environment. Interestingly, fetal cortisol concentrations have been demonstrated to be directly proportional to maternal cortisol concentrations.⁵ Elevated cortisol levels have also been associated with an increase in cytokine IL-4 and IL-13 levels, which are factors that facilitate the proliferation of T_H2 cells and promote elevations in IgE antibody production, respectively. These imbalances in the T_H1/T_H2 ratio and serologic levels of IgE antibody are hallmarks of atopic dermatitis.⁶ In fact, it has been found that children of mothers who have both APD and atopic dermatitis have significantly higher serum IgE levels than children of mothers with atopic dermatitis alone.⁷ Thus, current literature suggests that increased maternal cortisol levels found in APD may promote the development of atopic dermatitis.

Furthermore, it is thought that APD may cause increased fetal oxidative stress because children of mothers with APD who develop atopic dermatitis have been found to have lower placental glutathione to glutathione disulfide ratios as compared with children of mothers without APD.⁷ Normally, the placenta

helps carry out reactive oxygen species detoxification by using the antioxidant glutathione to detoxify electrophiles and forming glutathione disulfide as a byproduct; this reaction eliminates harmful agents that promote oxidative damage. A low placental glutathione to glutathione disulfide ratio, therefore, indicates that there is a large amount of fetal reactive oxygen species detoxification occurring at baseline. Thus, the physiologic condition of antepartum depression may expose a fetus to high levels of oxidative stress, and this environment seems to promote the development of dermatitis.⁸

Increased Incidence of Wheezing in Children of Mothers With Antepartum Depression

A study from 2014 used a questionnaire to assess incidence of wheezing in 4900 children aged between 1 and 4 years. Mothers with APD during the second trimester of pregnancy were associated with increased odds of wheezing in offspring during the first 6 years of life.⁹ Although this study included a large sample size and adjusted for maternal and paternal stress following delivery, childhood wheezing determination could have been evaluated through more robust measures. However, given that both wheezing and atopic dermatitis are mediated by T_H2 cells/IgE elevation, and given that children with eczema are more likely to develop asthma than are children without eczema, it is possible that children of mothers with APD may be at risk for both atopic dermatitis and asthma.

Stress as a General Mechanism for Increased Incidence of Fetal Asthma and Atopic Dermatitis

Interestingly, there has also been a substantial increase in asthma and atopic dermatitis among children in many industrialized, developed nations. This phenomenon may be related to the increasing pace and speed with which work is done in industrialized countries, also known as “time pressure.” Complaints of burnout have become more prevalent, and many women cite workplace stress as a contributor to stress-related symptoms such as shoulder pain.¹⁰ Thus, perhaps APD is one of many contributors to asthma and atopic dermatitis, with the common denominators in asthma and atopic dermatitis etiology being any developmental condition that increases fetal stress.

Perinatal Depression and Small-for-Gestational Age Status

Influence of Socioeconomic Class on Perinatal Depression and Occurrence of Small-for-Gestational Age Infants

Another embryologic consequence of perinatal depression is a condition known as small for gestational age (SGA), in which a developing fetus is in the bottom 10th percentile of weight during prenatal check-ups.¹¹

A 1992 study found that mothers who scored above 21 on the Beck Depression Inventory, which is the threshold for clinical depression, had a 3.02-fold increased risk of delivering an SGA newborn. Concurrently, initial findings from this study seemed to indicate that mothers with lower socioeconomic

status and depression had an even greater likelihood of birthing babies who were SGA.¹² Further studies should investigate the links between socioeconomic status, rates of perinatal depression screenings, access to therapy, and SGA.

The Role of Increased Adrenocorticotrophic Hormone and Elevated Cortisol in SGA

Underlying mechanisms that drive SGA may be linked to fetal cortisol elevations. One study found that SGA infants were exposed to significantly higher levels of adrenocorticotrophic hormone (ACTH) in the umbilical cord than non-SGA infants. Given the role of ACTH in the hypothalamic-pituitary-adrenal axis, increased ACTH levels could lead to greater levels of the stress hormone cortisol in utero. Because cortisol prevents bone growth, this could explain the mechanism behind the delayed growth of SGA fetuses and subsequent newborns.²

Association Between Lack of Regular Maternal Sleep Cycles in PD and SGA

Beyond the role of elevated cortisol in possibly inhibiting bone growth in SGA infants, the irregular sleep cycles of perinatally depressed mothers may also be linked to the development of SGA. One study found that in mothers with depression, the sleep cycles of infants were highly irregular. Thus, irregular maternal sleep cycles might explain the irregular sleep cycles of SGA infants and contribute to the delayed growth of SGA babies.² Future research should focus on whether any metabolic or physiologic associations exist between lack of sleep and impaired fetal growth.

Antenatal Depression and Neurodevelopment

APD and Decreased Infant Behavioral Development

Initial studies that discovered that APD is associated with altered fetal neurotransmitter levels were conducted at the University of Miami School of Medicine.^{13,14} It had been previously established that hypothalamic-pituitary and norepinephrine systems are perturbed in individuals with depression, and researchers wanted to determine whether neuroendocrine and sympathetic systems are also altered in infants of mothers with APD.¹³ Results showed that infants of mothers with depression had lower levels of urinary dopamine and norepinephrine as compared with infants of mothers without depression. A few days after birth, infants from depressed mothers also demonstrated less excitability, increased withdrawal, and abnormal reflexes as compared with infants from mothers without depression as per the Brazelton Neonatal Behavioral Assessment.^{13,14} Both the altered biochemical levels and abnormal behavioral results suggested that maternal depression seriously impacted neurocognitive and behavioral development during infancy.

One major drawback of pioneer studies by Lundy et al¹³ and Field et al¹⁴ was their method of measuring urinary levels of implicated factors. Urinary levels are not consistently reliable markers of dopamine and norepinephrine because these factors can be peripherally metabolized. Furthermore, although these initial studies examined early stages of child development, they failed to conduct prospective analyses to determine whether in utero conditions of APD also had far-reaching negative consequences.

Deleterious Impact of APD on Neurodevelopment is Linked to Altered Fetal Nerve Growth Factor and Brain-Derived Neurotrophic Factor Signaling

Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are neurotransmitters that pass through the placenta. While NGF helps regulate the survival and integrity of sensory and sympathetic neurons in utero, BDNF modulates neuroplasticity and hippocampal long-term potentiation.^{15, 16}

Recent studies have examined how maternal depression is associated with fetal neurotransmitter levels of NGF and BDNF through sampling fetal cord blood from the umbilical vein.¹⁷ This method of using cord blood as a proxy for fetal neurotransmitter levels was validated in 2009 when Kodomari et al¹⁶ found that maternal BDNF penetrated the utero-placental barrier to enter the fetal brain. In particular, NGF and BDNF are neurotransmitters of interest because they are crucial for coordinated neural development.^{15,16}

When NGF is absent, it produces a lethal phenotype that impairs development of sensory and sympathetic neurons, particularly impacting function of the brain, spleen, and skeletal muscles.¹⁸ Furthermore, when BDNF is absent, it triggers depressive behaviors, neuronal atrophy, and decreased maturation of cortical neurons.¹⁹ It is evident that any perturbation in NGF and BDNF levels could have a detrimental effect on fetal development.

Within the last decade, there has been growing interest in characterizing fetal NGF and BDNF levels and determining whether these are altered in pregnant mothers with major depression. One study suggested that women experiencing depression in pregnancy had lower placental levels of NGF,¹⁵ while other research suggested that APD is associated with lower levels of fetal cord blood BDNF.¹⁹ Given the extensive literature that highlighted the critical role of NGF and BDNF in fetal brain development, these recent studies conveyed that decreased uteroplacental levels of NGF and BDNF may place infants of mothers with depression at higher risk for behavioral, cognitive, and emotional developmental delays.^{15,19} These data further support the notion that mothers experiencing APD should receive psychiatric care. Pharmacologic treatment for APD is associated with maternal and fetal risks; although further research

comparing examining health outcomes of women who receive psychiatric medication for APD in pregnancy is necessary, the risks of medical therapy must be considered alongside the maternal and fetal benefits.

Association Between High Cortisol Levels in Maternal APD and Fetal Mood Disorders

It is well-established in psychopathology research that women who experience APD have high cortisol levels, and that these elevated levels pass to the fetus in utero.¹⁴ Although research elucidating the link between cortisol and fetal psychiatric health has not been extensively performed, emerging literature indicates that high cortisol levels can place offspring at increased risk for mood disorders.²⁰ However, it is important to note that this study has only taken place in animal models thus far. Further research must be conducted to better understand the human implications of high cortisol levels in utero on the risk of future psychiatric events.

Evaluating the Impact of APD on Long-term Psychosocial Risks for Offspring

Potential Link Between High Cortisol Levels in Maternal APD and Fetal Mood Disorders

In a study that examined the link between APD and infant behavior, 22 low-risk pregnant mother-infant pairs were recruited from a University of California, Irvine, obstetrics clinic.²¹ The mothers reported their psychological state at the third-trimester and postpartum phases using the State-Trait Anxiety Inventory and the Center for Epidemiologic Studies Depression Scale. The Harvard Infant Behavioral Reactivity Protocol was then used to evaluate infant behavioral reactivity to novel stimuli; this battery serves as a proxy for predicting future shy or inhibited temperament in psychology literature. As per this protocol, 4-month-old infants were presented with novel stimuli, such as balloon popping, and their corresponding behavior was recorded. A linear regression model demonstrated that 27% of the variance in infant negative behavioral reactivity was accounted for by APD. Therefore, negative behavioral reactivity, such as recurrent motor activity and crying, was found to be correlated with increased risk for future behavioral inhibition and shyness.²¹ This research suggested that APD not only has negative impacts on infant behavior, but also has far-reaching consequences on the future psychosocial relationships of offspring.

Link Between APD and Delayed Development in 18-Month-Old Infants

A prospective cohort study was conducted to determine the impact of APD on infant development.²² Postal questionnaires and the self-reporting Edinburgh Postnatal Depression Scale validated during pregnancy were sent to all pregnant women in Avon, England, with delivery dates from 1991 through 1992. At the 18-month postpartum mark, the Denver Developmental Screening Test was sent to the mothers regarding their children's

developmental process and present health. A post hoc analysis compared Edinburgh Postnatal Depression Scale intensity and persistence to examine the importance of maternal depression timing. There was a 50% increase in the odds of a child having a developmental delay if the mother had persistent APD. When postnatal depression was adjusted for its effects, there was a statistically significant 34% increase, demonstrating a strong relationship between APD and delayed childhood development. These data build on studies that have suggested that APD-associated neurotransmitter alterations and molecular impacts in utero impact neurocognitive offspring outcomes.^{15,19}

Link Between APD and Depression in Adolescence

The results of a longitudinal study by Pawlby et al²³ determined that out of 17 adolescents aged 16 years with diagnosed depression, 11 (68.7%) had been exposed to APD, while the remaining 6 (31.3%) were exposed to maternal depression later in life. This supported the theory that timing of maternal depression can have negative psychiatric outcomes on offspring. Beyond just the timing of maternal depression, logistic regression also indicates that the incidence of maternal depression episodes throughout a child's life strongly contributes to depression outcomes as well. This supported current research demonstrating that untreated APD has persistent effects on offspring development.

In contrast to the above research, a recent study by Glasheen et al²⁴ that analyzed data from both the Maternal Health Practices and Child Development Project and the Childhood Abuse as a Predictor of Adolescent Alcohol Project had different results. Recruited pregnant women attending a hospital-based prenatal clinic were interviewed 11 times at time points ranging between the first trimester and 16 years postpartum. Logistic regressions demonstrated no statistical evidence that pre- and postnatal maternal depression or anxiety symptom exposure increased the chances of depression diagnosis in offspring at age 16 years. Nevertheless, pre- and postnatal anxiety correlated with male offspring being 5.6-times more likely to meet Conduct Disorder criteria at age 16 years than those with mothers fitting low-anxiety profiles. Although many studies have discussed the close relationship of anxiety and depression, to our knowledge, Glasheen et al²⁴ study was the first to statistically explore the association.

The variation in results of Pawlby et al²³ compared with those of Glasheen et al²⁴ may be attributed to the usage of different study interventions. While the former used a specific diagnostic tool, the latter used the broad Center for Epidemiologic Studies Depression Scale inventory and, therefore, may not have been able to detect clinically diagnosed depression and anxiety.

Link Between APD and Emotional Disorders in Adolescence

APD is a well-known predictor of PPD. PPD is a common disorder affecting 1 in 9 mothers after giving birth.²⁵ It is known that mothers with PPD are at higher risk for major depression later in life. One study tested 2 hypotheses to determine whether APD effects contribute to PPD, and if negative effects from perinatal depression could be explained by repeated exposure of maternal depression on offspring.²⁶ A total of 150 antenatal women were assessed for APD and PPD through questionnaires, clinical interviews, and home visits. Of those, 27.3% of offspring fit the criteria of *DSM-IV* emotional disorders, with the most prevalent disorders being separation anxiety disorder at 11 years of age and depressive illness at 16 years of age. All offspring had mothers diagnosed with APD. χ^2 analysis demonstrated a significant association for APD and emotional disorders in girls. A logistical regression model undermined this relationship, determining that reexposure to maternal depression was the predicting factor in emotional disorders in adolescence. This study demonstrated that maternal depression has long-term impacts on adolescent psychological development.

As discussed above, APD has been linked to long-term psychosocial risks for offspring, and is associated with high cortisol levels and fetal mood disorders, delayed development in 18-month-old infants, depression in adolescence, and emotional disorders in adolescence. However, it is important to acknowledge that referencing studies for these associations are correlative and not causative in nature. It is plausible that aside from the fetal experience of being exposed to a mother with depression, individuals with a biologic propensity for depression may pass down genetics that increase the rates of adolescent emotive disorders.

Conclusions

Perinatal depression has been shown to have deleterious, long-term consequences on both mother and child, ranging from biochemical alterations to psychological deficits. Perinatal depression significantly impairs the immunological health, physical growth, neurologic health, and psychosocial development of children starting at in utero condition, with lasting effects throughout adolescence and beyond. Affected children demonstrate increased susceptibility to TH2/IgE-mediated atopic triad immune hypersensitivity disorders, low birth weight status as SGA babies, impaired neurocognitive development, and mood disorders.

In the present review, we have shown how cortisol hormone may influence the immunologic, physical growth, neurologic, and psychosocial disorders that affect offspring. Prior review articles have not been able to concisely pinpoint the role of cortisol in having these widespread effects on the offspring of mothers who experience PD. However, further research is needed to confirm this association. An exhaustive study that specifically measures fetal cord levels of cortisol in infants of mothers affected by APD/PD as compared with control, and then follows up these infants through adolescence, would better

legitimate whether cortisol is an important factor in the altered developmental effects seen in affected offspring. A simultaneous research study that upregulates cortisol in pregnant animal models to mimic perinatal depression, and then examines whether offspring have similar developmental impairments as those seen in human offspring, would help confirm the role of cortisol as a potentially causative factor in mediating the negative developmental effects of APD/PD on offspring.

Ultimately, this review article outlined notable risks associated with perinatal depression and posed the question of whether the risks are significant enough to merit pharmacologic treatment. Although it is tempting to argue that the dangers associated with maternal depression in terms of immunological, physical, neurological, and psychosocial health of offspring warrant treatment, additional studies need to be conducted to better understand whether the risks associated with pharmacologic, behavioral, and light therapy would be effective and/or tolerated by mother and fetus. Further research comparing offspring health outcomes of women who receive pharmacologic treatment for major depressive disorder during pregnancy and during the postpartum period may provide greater clarity, and we encourage further studies on this topic.

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Funding Sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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