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Review Article

Impact of Hypertensive Disorders of Pregnancy on Cognitive Functioning of the Offspring

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Abstract:

Pregnancy-related hypertensive diseases, such as gestational hypertension and preeclampsia, pose serious health hazards to both the mother and the growing fetus. Emerging evidence indicates that these situations may have long-term effects on the cognitive functioning of the offspring, which goes beyond the immediate concerns for the health of the mother and the newborn. This review article summarizes the most recent findings on how hypertensive disorders during pregnancy affect children's cognitive development while highlighting potential long-term consequences. We explore the possible mechanisms by which a mother's high blood pressure during pregnancy may affect the neurodevelopment and cognitive outcomes of her offspring. Studies looking into the relationships between perinatal exposure to hypertensive illnesses and cognitive function, academic success, and the risk of neurodevelopmental disorders, such as attention deficit hyperactivity disorder (ADHD) and learning difficulties, are included in the discussion. Additionally, the study assesses possible strategies for prevention and intervention, such as the importance of maternal health, modifications to lifestyle, and early detection in reducing cognitive risks.

Keywords: Hypertensive disorders of pregnancy, Preeclampsia, Cognitive decline, Neurodevelopmental outcomes, Placental insufficiency, Maternal inflammation, Oxidative stress, ADHD, ASD.

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Introduction

Hypertensive disorders of pregnancy (HDP), encompassing chronic hypertension, gestational hypertension, and pre-eclampsia significantly contribute to adverse outcomes for mothers, and newborns increasing the risk of morbidity and mortality.[4]

A systolic blood pressure value of 140 mmHg or higher, or a diastolic pressure of 90 mmHg or higher, is considered to be hypertension during pregnancy.[4,9,12] When a woman has a history of hypertension before conceiving or before the 20th week of gestation, chronic hypertension (CH) is diagnosed. On the other hand, gestational hypertension is a type of elevated blood pressure that appears after the 20th week of pregnancy.[4] Preeclampsia (PE), a disorder that usually develops after the 20th week of pregnancy, is characterized by high blood pressure, increased protein levels in the urine, fluid retention that frequently results in weight gain and swelling, renal insufficiency, liver dysfunction or abnormalities of the brain or eyes.[1] The complicated relationship between hypertensive diseases of pregnancy and the cognitive development of children born to afflicted mothers is explored in this review.

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Mechanisms Underlying the Impact of Hypertensive Disorders on Cognitive Function

1. **Placental insufficiency:** Hypertensive disorders of pregnancy can result in placental insufficiency, which may impair the fetal brain's ability to receive oxygen and nutrients. This deficiency may obstruct neurological development, which could impact cognitive ability.[9,12,13]
2. **Systemic Inflammation and oxidative stress:** Inflammation and oxidative stress brought on by preeclampsia may have neurotoxic effects on the developing fetal brain.[2,4,8,10,13] Some studies analyzed that prenatal inflammation and oxidative stress results in an unfavorable environment in utero.
3. **Epigenetic modifications:** The fetal genome may undergo epigenetic modifications as a result of hypertensive disorders during pregnancy, which may have an impact on the fetus' neurodevelopment and cognitive outcomes.[4,18]

Mechanisms through which Preeclampsia Impacts and Modifies Brain Development

Preeclampsia (PE) can impair development through a number of

processes, including hypoxia, impaired glucocorticoid signaling, placental transmission of inflammation, and an imbalance in pro/anti-angiogenic mediators. Offspring with a genetic predisposition to Preeclampsia may also be more susceptible to cardiovascular health problems.

Hypoxia is an associated factor that can modify fetal development. Hypoxic stress during pregnancy can activate the fetal hypothalamic-pituitary-adrenal (HPA) axis and perhaps result in long-lasting alterations.[17,19] Growth limitation, immune system modifications, poor cardiovascular health, and histological changes in the hippocampus, cerebellum, and other parts of brain are all associated with these HPA axis changes.[17] As a result, hypoxia may alter brain development more significantly in pregnancies with intrauterine growth restriction (IUGR) linked to pre-eclampsia.[9,12,13]

The signaling pathways related to glucocorticoids can also be disrupted and this can have negative repercussions on the development of the fetal brain.[4] Cortisol, a widely recognized hormone, is known to influence the neural development of the fetus. Numerous studies have linked maternal stress to alterations in children's neurodevelopment, temperament, and mental health; cortisol may play a role in moderating the consequences of prenatal stress.[10,17] Furthermore, treatment with synthetic glucocorticoids has the potential to have an impact on how the fetal brain develops.[17]

Is it possible that maternal inflammation brought on by preeclampsia influences the course of offspring's neurodevelopmental functioning? Yes, IL-6 is undoubtedly one of the most well-studied mediators of the effects of maternal inflammation on the outcome of the offspring's neurodevelopment. Enhanced maternal-placental IL-6 signaling may have negative consequences on the fetal brain.[8,16] It is recognized that maternal inflammation during pregnancy elevates the risk of conditions like schizophrenia, autism, and other neurodevelopmental disorders.[8,10] Even in cases of normal development, the levels of maternal circulating cytokines are linked to the cognitive abilities of the offspring. While some cytokines are associated positively with a child's cognitive abilities, elevated levels of IL1β and IFN-γ are associated negatively with IQ and negatively with cognitive ability, respectively.[6,8,16,17]

Cognitive Outcomes in Children Exposed to Hypertensive Disorders

A child is categorized as having mild cognitive restrictions if their IQ fell within the range of 50 to 85, as determined by a standardized psychometric evaluation.[9] An increasing number of studies have shown that pre-eclampsia in pregnant women may cause anatomical and functional alterations in the brain. This raises the possibility of a predisposition to the emergence of neurological impairments later in life. Beyond the neurological changes in the mother, research into the long-term effects of pre-eclampsia on the brains of exposed offspring is gaining momentum. Adrenocorticotropic hormone and corticosterone levels in the blood were higher in children exposed to preeclamptic pregnancies, indicating an exacerbated stress response.[19]

After delivery, pre-eclampsia-related difficulties continue. Unquestionably, pre-eclampsia causes significant stress for both the mother and the fetus, frequently leading to premature birth and constrained fetal growth. One could argue that pre-eclampsia starts programming and results in adverse long-term health repercussions for the offspring through these secondary effects, which affect gestational age and birth weight.[13] Such pregnancies result in children who likewise have increased lifetime risks for heart disease and stroke, but they also reportedly exhibit cognitive decline. The mental development index (MDI), total intelligence quotient (IQ), less academic achievement, verbal reasoning skills of children born to preeclamptic pregnancies are all unsatisfactory.[1,15] Although there may be a link to hypertension, maternal pre-eclampsia doesn't hinder a child's development or cognitive capacities when they hit late adolescence.[20]

Children born to pregnancies complicated by pre-eclampsia were compared with those born without hypertension. The former group was more prone to encountering the mentioned difficulties: anxiety/depression, memory, thought, and irritable/disinhibited problems, as well as depressive and psychotic problems.[10] Notably, children born to mothers who have preeclampsia ought to be identified as a child population at risk for brain development. The connection between preeclampsia and child behavioral and mental issues is largely mediated, according to studies, by preterm birth, small of gestational age (SGA) birth, and low birth weight.[6] Compared to babies born to women without pre-eclampsia, those born to mothers with the condition had babies with noticeably lower birth weights.

In research to assess the effect of expectant care of HDP on newborn neurodevelopmental outcome, it was discovered neonates born to mothers with hypertensive pregnancies exhibited reduced APGAR scores, lower birth weights, increased occurrences of acidosis, the need for ventilator support, and less severe neurodevelopmental challenges.[3,12] Few infants had severe intraventricular hemorrhage complicated by post-hemorrhagic hydrocephalus, which is a common neurodevelopmental abnormality in preterm infants leading to life-long psychomotor and cognitive sequelae. Additionally, unusual neurological findings, minor global developmental delays, and borderline Bayley Mental Index scores, an approach that is frequently used to evaluate an infant's cognitive development stage were noted.[2,3] Notably, prenatal growth retardation had less of an impact on neonatal outcomes than the severity of hypertension.

Furthermore, maternal HDP was associated with two-fold higher increase in mental developmental abnormality, which is characterized by significant cognitive, behavioral and emotional decline in children aged 3 years.[7]

Analyses of Intellectual Abilities: 'Preterm/term born to Hypertensive Pregnancies'

Preterm infants born to pregnancies affected by hypertensive disorders performed worse on verbal reasoning tests than preterm babies born after normotensive pregnancies.[5,10] When infants are born at term, the presence of hypertensive problems during pregnancy is not linked to intelligence.[5]

Maternal preeclampsia (PE) affects the cognitive development of school-age children who were born extremely prematurely and had a history of IUGR and the absence or reversal of end-diastolic

blood flow (ARED). In comparison to the non-exposed IUGR children, the PE-exposed IUGR group had more severe verbal I.Q. (VIQ) and full- scale I.Q. (FSIQ) scores.[2]

Analyses of Intellectual Abilities: 'Parity and Hypertensive Disorders'

Hypertensive diseases complicated primiparous pregnancies resulted in lower verbal and arithmetic reasoning test scores in the offspring as well as worse scores on tests of their overall intellectual ability than infants born following primiparous and normotensive pregnancies.[5,10] Intellectual capacities were not linked to hypertension issues in children born following multiparous pregnancies.[5]

Analyses of Intellectual Abilities: 'Childhood Socio-economic Status and Hypertensive Disorders'

The children born to junior/senior clerical fathers following pregnancies complicated by hypertension performed worse on verbal, visuospatial, and arithmetic reasoning assessments, as well as on overall intellectual aptitude, in contrast to the children of junior/senior clerical fathers born after pregnancies without hypertension.[9,10] This emphasized the significant impact of the interaction between childhood socio-economic status and hypertensive disorders on verbal reasoning.

Analyses of intellectual abilities: 'Gender and hypertensive disorders'

Compared to men born after pregnancies with normal blood pressure, men born following pregnancies affected by pre-eclampsia had an increased greater likelihood of problems being reported on critical items scale and thought on syndrome scales. [8,9] The likelihood of boys being affected by mild cognitive impairment was higher, and small for gestational age, but growth limitation was commensurate.[17]

Analyses of Intellectual abilities: 'AGA/SGA and hypertensive disorders'

Comparisons between the H-AGA (Hypertensive - Appropriate for Gestational Age) and H-SGA (Hypertensive - Small for Gestational Age) groups revealed that the H-AGA group had a lower risk of dying, developing cerebral palsy, developmental delay, or dying before the age of three than the H-SGA group did [22]. According to numerous studies, extremely preterm babies who are born small for gestational age (SGA) have a greater mortality risk than babies who are delivered at an appropriate gestational age (AGA).

Autism spectrum disorder and Attention-deficit Hyperactivity Disorder

The mRNA and protein levels of IL-6 and IL-1, but not TNF- α were noted to be increased in the blood and brain samples of children exposed to preeclamptic pregnancies. These results are consistent with prior research showing higher levels of these markers in people with autism spectrum disorder (ASD).[16,19]

Children who were exposed to hypertensive disorders during their time in the womb had a 1.3-fold elevated incidence of ASD's, a condition marked by neurocognitive difficulties, including problems with executive functioning and social cognition and a slightly higher occurrence of Attention Deficit Hyperactivity Disorder (ADHD) and develops difficulties with working memory and impulse control and Intellectual Disabilities (ID), as well as somewhat lower average cognitive scores at the age of 18, in comparison to children who were not exposed to hypertensive disorders in utero.[6,11] Numerous studies have linked structural abnormalities of the brain, such as diminished overall cortical thickness, smaller overall brain size, and reduced gray matter volume, to ADHD.[19]

Contrary to mothers of children with typical development (TD), mothers of children with ASD and developmental delays (DD) were significantly more likely to have had placental insufficiency, severe preeclampsia, or a combination of both during their pregnancies.[12,14] Although the majority of the association was independent of birth weight, pre-eclampsia/eclampsia and ASD were associated in a way that was partially mediated by birth weight.[13] However, there is a strong correlation between DD and hypertension diseases, indicating a wider-ranging impact on neurodevelopment instead than being limited to ASD. More than twice as often as preeclampsia complicated pregnancies in children with TD, preeclampsia complicated pregnancies in ASD children.[12]

Conclusion

The relationship between hypertensive disorders of pregnancy and the cognitive functioning of the offspring is a multifaceted issue that requires further investigation. Although evidence points to possible cognitive problems linked to maternal hypertensive disorders, the exact mechanisms and extent of these issues remain areas of active research.

Children born to mothers who experienced hypertensive disorders during pregnancy may differ in their cognitive functioning, academic success, and even have a higher chance of developing neurodevelopmental disorders including ADHD and learning difficulties. It is important to note that not all children exposed to these situations will exhibit negative cognitive results, and that these outcomes are likely to be significantly shaped by the severity of the maternal disease, as well as genetic and environmental factors. This review emphasizes the significance of early detection, prompt interventions, and modifications to lifestyles to improve long-term cognitive outcomes for children born to mothers who experienced hypertensive disorders during pregnancy. Notably, the utilization of epigenetic mechanisms as potential indicators for spotting at-risk newborns represents the initial stride in formulating preventive strategies for future disorders in childhood. This may involve educating expectant mothers as a part of the process.

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