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Review Article

Effects of maternal hyperthermia on neurodevelopment: a literature review

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ABSTRACT

Maternal hyperthermia, defined as a body temperature above 38°C (100.4°F) is due to various etiologies during pregnancy, and has been a subject of growing research interest. This phenomenon is considered a potential environmental teratogen contributing to the development of neural tube defects (NTDs) and other neurodevelopmental disorders. NTDs such as anencephaly and spina bifida, are known to be multifactorial in origin, resulting from a complex interplay between genetic and environmental factors. In this review, we aim to comprehensively analyze the effect of maternal hyperthermia on neurodevelopmental disorders and associated congenital anomalies. In addition, we will highlight both the infectious and noninfectious causes of maternal hyperthermia, as well as any risks and potential preventive measures. The literature search identified studies reporting associations between maternal hyperthermia and adverse fetal outcomes. We have evaluated the link between maternal fever due to infections during pregnancy and the increased likelihood of NTDs, particularly anencephaly and spina bifida, as well as Neurodevelopmental disorders. In addition, the effects of non-infectious causes of maternal hyperthermia, including exercise and exposure to heat sources like saunas and hot tubs, on neurodevelopment have also been studied with varying degrees of evidence. Maternal hyperthermia elevates the risk of NTDs and neurodevelopmental disorders in infants, with folic acid offering partial protection, while other factors elevate this risk. However, further research is needed to define the precious association of these factors.

Keywords: Neurodevelopment, Fever, Neurodevelopmental disorders, NTDs, Pregnancy, Maternal hyperthermia

INTRODUCTION

In this study, we define maternal hyperthermia as any temperature greater than 38°C (100.4°F) that occurred 30 days before conception until the time of delivery. This article will review the literature's current outlook on the effects of this on neurodevelopmental disorders in hopes of increasing awareness of the issue and further studies to be done about the details and consequences of maternal hyperthermia and most importantly, prevent it.

Hyperthermia is common in the period around labor which may be due to many reasons including infectious diseases (e.g., Endometritis or chorioamnionitis), the administration of epidural anesthesia (which activates the inflammasome), or physiological.[1-3] About 20% of women reported at least one febrile episode during pregnancy. Second trimester seems to be the most risky one for development of neurodevelopmental disorders.[4,5] Maternal hyperthermia has been a hypothesized teratogen of various organ systems and causes a multitude of fetal deficits.[6] The teratogenicity is likely related to the extent, timing (i.e., within the gestational period), and length of time having endured hyperthermia.[7-9]

Outside nervous system, these defects include: Heart defects: pulmonary atresia, pulmonary/aortic stenosis, and conotruncal defects such as tetralogy of Fallot, facial defects: midface hypoplasia, cleft lip/palate and ear

defects, urinary system defects, microphthalmos and gastroschisis.[7-10]

The evidence for these organ systems has a wide range of strengths however a detailed discussion of this is out of the scope of this article. The neurological manifestations to be discussed that have a reported association with maternal hyperthermia (especially in the second and third trimesters) include NTDs, neurogenic limb contractures, seizures, cerebral palsy when the exposure to maternal hyperthermia is in the third trimester, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), developmental coordination disorder and developmental delay.[3-6,8-11]

INFECTIOUS ETIOLOGIES

Pregnant patients are generally more susceptible to infectious diseases due to multiple factors. A few examples of how this includes their susceptibility to urinary tract infections because the gravid uterus compresses the ureter and bladder along with hypotonia in their smooth muscle causing vesico-ureteric reflux and hence there is a 10x higher risk of pyelonephritis in pregnancy. They can develop chorioamnionitis and endometritis via ascending floral infections or infected retained products. Pulmonary infections are more likely because of the higher risk of Gastroesophageal reflux disorder (GERD) due to lower muscle tone in the esophagus and an increase in intra-abdominal pressure. An increase in pulmonary infections can also be attributable to lung volume changes during pregnancy. They also have lower CD4/CD8 ratio or lower T cell numbers and hence increased susceptibility to dangerous infections like listeria and fungi.[1] Increased susceptibility to infections along with physiologic hypervolemia (which can mask sepsis and hence organs can deteriorate) are good reasons to always keep a high index of suspicion of possible septicemia to avoid septic shock and long-term sequelae to fetus (from infection or the hyperthermia).[12]

NON-INFECTIOUS ETIOLOGIES

Hot Tubs, Saunas, heated blankets, and external heat exposure: especially in combination with infection was risky for NTDs and hence in pregnancy should be limited to 39°C for 15 minutes or less than 10 minutes at a temperature of 40°C, Doppler Ultrasound devices and exercise.[8,9]

The mechanism of hyperthermia-induced developmental damage is not well known. Some proposed mechanisms include hyperthermia disrupting protein synthesis via heat-shock proteins. Hyperthermia can also induce membrane disruption, cellular death, vascular disruption, or placental infarction, leading to serious malformation or death of the fetus.[7,9] Viral fevers (e.g., Influenza) turn cause the production of toxic metabolites that could pass the planta easily, or the damage could be caused by exposure to antivirals and antipyretics.[8]

Hyperthermia induces disruption in the cellular mitotic processes and thus affects gene expression with the gap junction a-1 gene being the most critical code which codes for protein connexin 43 (Cx43). This protein plays a crucial part in neural tube development. Experiments carried out on golden hamsters demonstrated an overexpression of this Cx43 mRNA in the heat-exposed group compared to the normal, leading to a possible direct association.[8]

Temperature can alter transient receptor potential (TRP) channels. TRPV1 and TRPV4, are present in neural crest cells during the developmental period of the face and heart. The use of TRPV1 antagonists demonstrated a protective mechanism against hyperthermia-induced defects in embryos of chickens and zebrafish and the use of TRPV1 and TRPV4 agonists showed a replication of these birth defects in both species. Acetaminophen might have a protective role against this mechanism and generally in the prevention of fetal complications associated with maternal hyperthermia, however, this is controversial.[4,5,9,10]

FETAL NEURODEVELOPMENT AND DEFECTS

Neurodevelopment starts in the 3rd week of embryonic development with the process of gastrulation, in which the 3 germ layers, ectoderm, mesoderm, and endoderm are formed. The underlying notochord then stimulates the ectoderm to thicken by releasing molecular signals forming the neural plate. In mammals, like some other animals, the neural plate is the basis of primary neurulation, giving rise to the neural tube from the plate and the neural crest cells. The caudal portion of the neural tube is formed directly by mesenchymal stem cell differentiation which then represents the primitive streak remnants.

Signals from the notochord include the sonic hedgehog (SHH) protein, which influences the ventral portions of the neural tube, on the other hand, bone morphogenic protein (BMP) - a signal released by the surface ectoderm and mesoderm has high specificity towards the dorsal portions and closure of the neural tube. The closure of neural tube is species-specific, with mammals having several closing zones that allow closure at the same time.[8] The neural crest cells are pluripotent cells at the junction of the neural plate and the rest of the ectoderm, they can migrate leading to the development of a wide range of tissues, such as the facial bones and cartilages, cardiac structures including the septation of aortic and pulmonic trunks.[7,10,13]

In vertebrates, the brain develops from the most rostral anterior portion of the neural tube, and the spinal cord from the most caudal part.[14] The brain is formed from the 3 primary vesicles-the prosencephalon, mesencephalon, and rhombencephalon. They go on to divide further into the secondary vesicles leading to the development of the

cortex, subcortical structures, cerebellum, brainstem, and the ventricles.

The anterior pore of the neural tube closes by day 25 of gestation, while the posterior pore closes by day 28, any defect in the closure of the neural tube leads to the formation of a neural tube defect.[13] They can be classified as open or closed defects depending on brain or spinal cord exposure. Open defects include craniorachischisis, anencephaly, and myelomeningocele, which result from a defect in the skull or vertebrae. These defects except myelomeningocele are lethal with no treatment options available. Closed NTDs include malformations that are concerned with anomalies of fat, bone, or membrane. These include encephaloceles, meningoceles, and spina bifida occulta.[8]

Detection of open NTDs can be done by measuring the maternal serum levels of alpha-fetoprotein (AFP), this can be done as a population-based screening test due to sufficient elevation in affected individuals. This is part of the routine 2nd trimester screening tests and about 80% of open spina bifida (myelomeningoceles) and 95% of anencephaly can be detected by the 16th week of pregnancy. However, elevations in the levels of ms-AFP could also be due to other conditions such as Down Syndrome.

Diagnostics methods for open neural tube include testing for AFP and acetylcholinesterase levels in amniotic fluid and/or the use of targeted ultrasound.[15] Identification of closed NTDs is usually carried out with the help of prenatal ultrasound.[16]

NTDs have multifactorial etiology, due to the interaction of genes and the environment. Some teratogens that contribute to the development of NTDs include industrial wastes and pollutants such as arsenic, pesticides, polyaromatic hydrocarbons, pharmaceuticals such as valproate and antibiotics, and maternal hyperthermia during the 1st trimester.[14]

Folate deficiency in the mother during conception and the 1st trimester is one of the main causes of NTD.[8] Thus, the recommendation for folic acid supplementation is considered at 400 ug/day.[9] Another supplement that helps in the prevention of NTDs is inositol, however, due to the limited number of participants in such studies, it is not clear whether inositol alone or when combined with folic acid led to these benefits.[8] According to some studies, folate supplementation led to a significantly lower risk of NTD development in mothers with febrile episodes compared to those who did not meet the required folate level.[14]

REVIEW

Maternal hyperthermia is considered a risk factor in the incidence of neurodevelopmental abnormalities. The exact mechanism by which maternal fever and thus hyperthermia in early pregnancy could lead to a disruption of neural tube closure has not been discovered.[14] During the 1st trimester, maternal hyperthermia is seen as a teratogen leading to increased risk of abnormalities, while exposure in the 2nd and 3rd trimester is linked to the development of adverse outcomes related to human neurologic development such as neurodevelopmental disorders, which are considered a group of illnesses that start in early brain development and can range from specific learning disabilities to severe cognitive impairment.[4,6]

A suspicion of an association between infection and neurodevelopmental defects was suggested in a rubella outbreak in 1964 in which the offspring mothers who were diagnosed had a higher chance of developing ASD.[5] This has since inspired more research into this.[8,9] Further details of the effect of maternal hyperthermia are discussed elsewhere together with observed data.

In the US, the leading cause of infant mortality is human congenital structural malformations. According to the center for disease control and prevention (CDC), 3% of all newborns in the US have some form of birth defect, this is less than the global figures which reach 6%.[14] NTDs are known as the 2nd most common cause of congenital malformation in humans.[8] They are estimated to affect 7 out of 10,000 pregnancies in the US every year.[11] It is believed that 70% of NTDs are due to genetic factors. However, there are no clinically known genes that help influence the management of risky pregnancies.[14] According to the global burden of disease data, the majority of deaths due to NTD (85%), are in nations with low gross domestic product (GDP), which could be due to scarce resources and lack of access to neurosurgical procedures.[8]

EFFECTS OF INFECTIOUS ETIOLOGIES OF MATERNAL HYPERTHERMIA

Data gathered from the national birth defects prevention study, a multi-year-case control survey of malformations of congenital origin in the US containing 17162 case mothers and 10127 controls that were collected over the phone (Waller et al) reported an evident association of anencephaly, spina bifida, encephalocele and 4 other birth defects in mothers who reported early pregnancy fevers.[14] Numerous other studies have shown similar results such as a collection of 9 case reports that included 1601 neonates born with NTDs with 5149 controls, reporting an elevated risk (OR=1.93) when the mother was exposed to high temperature.[8] Evidence from animal studies shows the presence of fever-induced neurotoxicity which is independent of the direct infectious process. This is suggested to be due to maternal immune activation instead of the direct effect of the infectious agent on the fetal brain.[4]

Another cohort study carried out by Kerr et al contained a total of 375 NTD cases and 8247 controls (non-

malformed). Mothers of infants with NTDs reported higher rates of febrile diseases during pregnancy (5.1%) compared to control (1.9%) leading to a 2.4-fold increase in febrile mothers. However, it was also reported that mothers who had folate supplementation had a significantly lower risk for NTD development than women with febrile episodes who did not meet the required folate levels.[14] Those who did not consume adequate folic acid had an adjusted OR for periconceptional fever of 3.4, while those who did consume adequate folic acid intake seemed to have an adjusted OR for periconceptional fever of 1.8.[11] The advantages of folic acid supplementation can be seen when a comparison of Canada and the EU takes place. Canada introduced supplementation of food with folic acid in 1998 and thus in the next 5 years reduced rates of NTDs by 50%. However, during the same time, the incidence of NTD was not affected in the EU, where supplementation of food is not regulated.[8]

Based on a systematic review and meta-analysis from 2018, a significant association was found between maternal fever and risk of neurodevelopmental disorders with an OR of 1.24 with a 95% CI=1.12-1.38. A positive association was specifically found between autism spectrum disorder and developmental delay. This positive association was found during the first trimester but no such association was observed between the risk of neurodevelopmental disorders and 2nd and 3rd trimester.[6] In addition to this, a study from 2001 showed an increased risk of seizures in 1st week of life among neonates born to women with intrapartum fever.[3]

Another case-control study from 2014 in China of 459 mothers with NTD-related births and 459 mothers without NTD-related births, showed that there was a significantly increased association with NTD in those with maternal flu or fever especially in addition to antipyretic use in comparison to no antipyretic use, this increased risk was not observed with antibiotic use.

Meanwhile, other studies such as Feldkamp, Meyer, Krikov, and Botto's study from 2010 showed that acetaminophen use in pregnancy in women reporting first-trimester infection and fever was associated with significantly lower OR for anencephaly, craniorachischisis, encephalocele, and other non-neurological defects. It was concluded that single-ingredient acetaminophen does not seem to increase the risk for major birth defects when used in febrile disease.[9] Most women in the developing world are now able to use antipyretics to help fight their fever, so it is sometimes difficult to associate whether the NTD could be a result of the fever or the medications used against it.[14]

EFFECTS OF NON-INFECTIOUS ETIOLOGIES OF MATERNAL HYPERTHERMIA

Based on a systematic review and meta-analysis of the effects of prenatal exercise on the incidence of congenital anomalies and hyperthermia from 2018, maternal body temperature was seen to increase significantly in 6 studies from rest to during exercise in all 3 trimesters but it is important to note that the increase in the maternal temperatures never reached hyperthermia, which is defined by an increase of body temperature by more than 2^0C which suggests safety of maternal exercise for the fetus. Evidence from 10 randomized controlled trials indicated that prenatal exercise did not affect the odds of congenital abnormalities. That said, this evidence was labeled as low quality due to many reasons such as risk of bias.[6]

In a study carried out by Milunsky et al in which 23491 pregnant women were exposed to different sources of hyperthermia (hot tubes, sauna, or fever) to determine the risk of development of NTDs. The use of hot tubes in the 1st trimester demonstrated an increased RR=2.8 when used together with the sauna, a RR of 1.8 when in combination with having a fever, and 1.2 with electric blankets. These demonstrated that the combined use of 2 heat sources can raise the RR from 1.9 to 6.2.[8]

MATERNAL HYPERTHERMIA AND COVID-19

Concerns have been raised regarding the vaccination of women against COVID-19, which may lead to maternal hyperthermia and thus congenital anomalies. A cohort study conducted by Blakeway et al at St George's university hospital in London, between March 2020 and July 2021, included 1328 pregnant women, with 140 women receiving at least 1 dose before birth and 1188 who didn't. The results when adjusted to the time and other factors of pregnancy showed no significant difference in adverse effects between the 2 groups: stillbirth (0.0 vs. 0.2%), and fetal abnormalities (2.2 vs. 2.5%). Another study by Ruderman et al demonstrated similar findings. These studies could indicate that COVID-19 vaccination in pregnancy does not affect outcomes, but further information is still lacking and research must continue in this field.[8]

DISCUSSION

Maternal hyperthermia has been a focus of extensive research in recent years. It is a common occurrence during pregnancy, arising from infectious and noninfectious etiologies. Approximately 20% of women report at least one episode during pregnancy.[4,5] In addition to the effect of maternal hyperthermia on neurodevelopment, it is essential to acknowledge its broader impact on fetal development including cardiac, urinary, ocular, facial, and abdominal abnormalities although the evidence may differ in strength.[7,9,10]

Maternal hyperthermia due to infectious causes especially in the early stages of pregnancy has been associated with anencephaly, spina bifida, and encephalocele.[14] It is suggested based on evidence from animal studies that the defects are mainly due to maternal immune activation

rather than the direct effect of the infectious agent on the fetal brain.[4] The precise mechanisms of hyperthermia-induced developmental damage are yet to be confirmed.[9]

Research conducted on acetaminophen use in febrile women during the first trimester has shown different results. A significantly increased association with NTD in those with maternal flu or fever, especially in combination with antipyretic use in comparison to no antipyretic use, has been reported. However, as evident in another study, single-ingredient acetaminophen use can significantly reduce the OR for anencephaly, craniorachischisis, encephalocele, and other non-neurological defects. Folate supplementation has also been shown to significantly lower risks of NTD development in comparison to those who did not receive folic acid.[9]

In addition to the risk of NTD development, a positive association is also observed between neurodevelopmental disorder and maternal hyperthermia. Based on different sources, this association has been reported in the first and second trimester of pregnancy. A noteworthy example includes a systematic review and meta-analysis carried out in 2018, which demonstrated a positive association in regards to autism spectrum disorders and developmental delay with maternal hyperthermia in the first trimester.[6]

Regarding non-infectious etiologies of maternal hyperthermia, exercise has been shown to increase maternal body temperatures although exercise-induced hyperthermia remains within safe limits. However, in reference to other etiologies of maternal hyperthermia such as the use of saunas and hot tubs, data suggested that a combined use of 2 or more heat sources leads to an elevated risk of congenital malformations with an increase in the RR of NTDs from 1.9 to 6.2.

Concerns were also raised regarding the vaccination of pregnant women against COVID-19 due to the risk of maternal hyperthermia. Two separate studies demonstrated similar findings that COVID-19 vaccination does not affect outcomes, but further information is lacking due to the novelty of the disease and its vaccination. Thus, further research is required in this field.[8]

CONCLUSION

NTDs including anencephaly, spina bifida, and encephalocele are shown to be more likely in infants born to mothers who experienced maternal hyperthermia. This seems to be irrespective of the etiology although different etiology may confer different odds ratios. Folic acid supplementation decreases this risk although it does not eliminate it. Maternal hyperthermia was also associated with autism spectrum disorder and developmental delay. Acetaminophen, while widely available and widely used, was suggested to contribute to neurodevelopmental disorders especially when used in combination with other antipyretics. Since enough evidence is lacking for this phenomenon, this should be studied further. Given the complexity of these associations, continued research is crucial to refining preventative strategies and better understanding the underlying mechanisms.

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REFERENCES

1. Le Gouez A, Benachi A, Mercier FJ. Fever and pregnancy. Anaesth Crit Care Pain Med. 2016;35(1):S5-12.
2. Sultan P, David AL, Fernando R, Ackland GL. Inflammation and Epidural-Related Maternal Fever: Proposed Mechanisms. Anesth Analg. 2016;122(5):1546-53.
3. Apantaku O, Mulik V. Maternal intra-partum fever. J Obstet Gynaecol. 2007;27(1):12-5.
4. Antoun S, Ellul P, Peyre Hl. Fever during pregnancy as a risk factor for neurodevelopmental disorders: results from a systematic review and meta-analysis. Mol Autism. 2021;12(1):60.
5. Croen LA, Qian Y, Ashwood P. Infection and Fever in Pregnancy and Autism Spectrum Disorders: Findings from the Study to Explore Early Development. Autism Res. 2019;12(10):1551-61.
6. Croen LA, Qian Y, Ashwood P, Ousseny Z, Diana S, Jennifer PM, et al. Infection and Fever in Pregnancy and Autism Spectrum Disorders: Findings from the Study to Explore Early Development. Autism Res. 2019;12(10):1551-61.
7. Sass L, Urhoj SK, Kjærgaard J, Dreier JW, Strandberg-Larsen K, Nybo Andersen AM. Fever in pregnancy and the risk of congenital malformations: a cohort study. BMC Pregnancy Childbirth. 2017;17(1):413.
8. Isaković J, Šimunić I, Jagečić D, Hribljan V, Mitrečić D. Overview of Neural Tube Defects: Gene-Environment Interactions, Preventative Approaches and Future Perspectives. Biomedicines. 2022;10(5):965.
9. Graham JM Jr. Update on the gestational effects of maternal hyperthermia. Birth Defects Res. 2020;112(12):943-52.
10. Hutson MR, Keyte AL, Hernández-Morales M, Eric G, Zachary AK, Ioannis A, et al. Temperature-activated ion channels in neural crest cells confer maternal fever-associated birth defects. Sci Signal. 2017;10(500):eaal4055.
11. Kerr SM, Parker SE, Mitchell AA, Tinker SC, Werler MM. Periconceptional maternal fever, folic acid intake, and the risk for neural tube defects. Ann Epidemiol. 2017;27(12):777-82.
12. Easter SR, Molina RL, Venkatesh KK, Kaimal A, Tuomala R, Riley LE. Clinical Risk Factors Associated with Peripartum Maternal Bacteremia. Obstet Gynecol. 2017;130(4):710-17.

13. Kuwar Chhetri P, M Das J. Neuroanatomy, Neural Tube Development and Stages. In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2023.
14. Finnell RH, Caiaffa CD, Kim SE, Yunping L, John S, Xuanye C, et al. Gene Environment Interactions in the Etiology of Neural Tube Defects. Front Genet. 2021;12:659612.
15. Palomaki GE, Bupp C, Gregg AR, Mary EN, Devin O, Robert GB, et al. Laboratory screening and diagnosis of open neural tube defects, 2019 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22(3):462-74.
16. Avagliano L, Massa V, George TM, Qureshy S, Bulfamante GP, Finnell RH. Overview on neural tube defects: From development to physical characteristics. Birth Defects Res. 2019;111(19):1455-67.

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