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Clinicopathological Insights to the Nerve Growth Factor NGF Associated Stress Response in Pregnancy and Therapeutic Potential in Fetal Neurodevelopment

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ABSTRACT

The nerve growth factor has a significant role in fetal neurogenesis and sustaining pregnancy. **Objectives:** To investigate the effects of nerve growth factor in stress response during pregnancy on developing fetus to bring clinicopathological correlation on the role of nerve growth factor in maternal stress markers (cortisol levels, glucocorticoids, depression, anxiety, and brain-derived neurotrophic factor levels) and fetal brain development. **Methods:** Following PRISMA guidelines, this study was extracted from PubMed, ScienceDirect, Nature, and Google Scholar articles from January 2014 to April 2024. The examination of pregnant women in published research gave a possibility to understand the application of nerve growth factor as a suitable biomarker for brain stress and fetal neuronal development. To exclude studies with lower ranks, each of the selected studies was assessed for adherence to evidence-based research methodology. The studies were taken from China, Europe, America and South Asia (including Pakistan). **Results:** Increased nerve growth factor levels were associated with maternal stress reactions which caused changes in cortisol levels and the amygdaloidal complex area. However, the increased nerve growth factor level was linked to changes in the fetal brain such as the weight of the fetal brain and stress biomarkers in the amniotic fluid sample inferring a critical role in the modulation of maternal stress on the fetal neurodevelopmental spheres. **Conclusions:** It was concluded that it is important to note how stress and nerve growth factors interact during pregnancy to create effective interventions to reduce stress dependence for the better health of both the mother and child.

INTRODUCTION

Nerve growth factor (NGF) has been found to have multifunctional tasks, including the contribution to the fetal neurodevelopment and stabilization of pregnancy processes [1]. Current studies reveal that hypoglycaemia is linked with preterm delivery, which affects the fetal organisms' growth, including the basic neurotrophin NGF present in maternal and umbilical cord plasma in lesser measure in our cases. On the other hand, increased levels of NGF have been associated with structural reorganisation of the fetal head, especially the amygdala and hippocampus thus causing developmental anomalies. Moreover, NGF plays a role in the modulation of physiological interactions between the nervous, endocrine, and immune systems and stress associated with the increase in NGF levels is able to cause negative pregnancy outcomes such as spontaneous abortion [2].

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There is an increased oxidative stress during pregnancy, coupled with variations in neurotrophin levels, which affect the growth of the fetal brain [3]. This can impose on preterm offspring cardiovascular, metabolic and neurodevelopmental risks throughout their lifetime [4]. Maternal stress levels also differ across the world with Asia having the highest (up to 31% of the surveyed mothers), Europe next and America, with up to 15% [5-7]. The situation is the same with maternal age; women above the age of 35 are more at risk of stress-related complications than younger women. These age differences may be attributable to age-related changes in stress buffering, as postpartum women reported higher levels of prenatal stress, increased cortisol, anxiety, and depressive symptoms [8]. For that, stress markers are significantly higher among Asians than Western people and give solid evidence of the impact of socioeconomic status on stress in mothers [9, 10]. Because of these internal and external factors combined, it is important to understand the role of maternal stress, NGF and fetal neurodevelopment [11].

This study aims to review and consolidate existing literature on NGF as a mediator of the stress response during pregnancy and its impact on the fetal brain. If NGF is proven to have a strong correlation with maternal stress and fetal neurodevelopment then by controlling its levels complications during pregnancies can be controlled. Thus, through making such linkages, this research aims to contribute to programmes that can reduce maternal stress with the view of enhancing the general welfare of pregnant and postnatal mothers and their unborn babies in different communities.

METHODS

According to the recommendations by PRISMA for reporting, the review was conducted from June 2024 to August 2024. Initially, it included 60 articles in English from 2014 to 2024. The articles were systematically sorted based on inclusion criteria searched and reported the details including author, year, region, title, design, analysis, method, variables, sample, outcome, and references. Several search engines were employed; Science Direct, Google Scholar, Springer and, PubMed. Google Scholar was used for 50% of the articles. Search phrases included China, Asia, and South Asia. It assisted in providing more relevant papers for scrutinizing research and its evaluation. Research conducted in peripheral regions was also represented in the pool of articles. Article searches were done using keywords: NGF, stress, pregnancy, fetal neurodevelopment, and stress response in pregnancy. Pregnancy, NGF, stress markers, fetus, neural development, young women, and maternal stress were significant words. The articles which did not fulfil our inclusion criterion were eliminated. The inclusion criteria were focused on NGF and its effects on neurodevelopment along with other stress markers and all papers taken were from the latest years, no paper older than the year 2015 was taken. Sixty articles in total were downloaded from databases. Eighteen duplicate articles were found and removed, leaving forty-two for analysis. A total of twenty articles from the systematic review were eliminated based on merely the qualitative data added to them. After elimination, twenty-two papers were picked and sorted which fulfilled inclusion criteria as shown in figure 1.

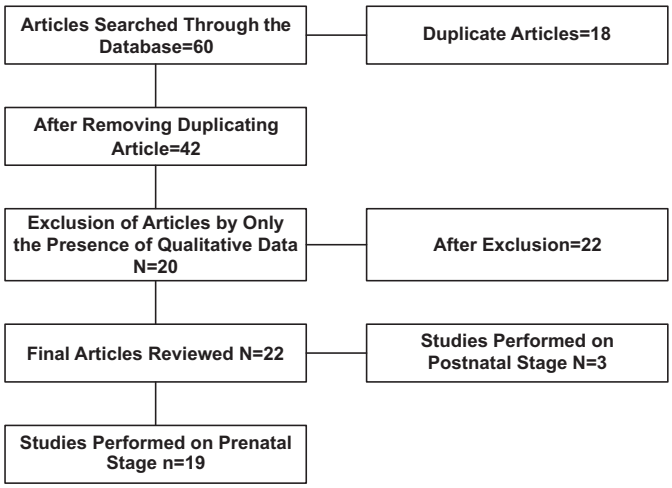

Figure 1: PRISMA Model Illustrating Selection of Studies for Review Process Showing Elimination of Studies That Were Not Lying Under the Inclusion Criteria.

RESULTS

The majority of the pregnant women in all the studies ranged from 18 to 45 years of age. The pregnant women taken as a sample had shown signs of stress. One of the studies took adolescent pregnant women between 14 to 19 years of age. 19/22 of studies were taken from the prenatal stage however 3/22 of studies were conducted on the postnatal stage. The studies were taken from all regions of the world including Asia, Europe and America. Research studies were taken from the last five years (70%) and from year 2014 to 2019 (30%). The study reviewed papers that were conducted in Europe (40%), Asia (30%) and America (30%) respectively. The studies were taken from Google Scholar (47%), Science Direct (30%), Nature (20%) and others (3%) from Research Gate and PubMed. The research used a cross-sectional study design (60%), longitudinal study design (30%) and perspective-based and observational studies (10%). Results of these studies [12-26] are shown in the Table 1.

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Table 1: Characteristics of The Studies Included in Systematic Review

Reference	Study Population (Mean Age in years ± SD)	Study Methodology, Statistical Tool, Software (Sample Size, N)	Study Variables	Key Findings
[12]	Normotensive women (27 ± 2.1) Women with preeclampsia (26 ± 3.6)	In a longitudinal study, Promega was used for measuring NGF levels in the plasma of the motherand cord, the analysis of data was done by SPSS/ PC+ package	Maternal: NGF levels, BP, BMI Fetal: Cord NGF levels, baby's birth weight, head and chest size	-Stable Maternal NGF levels-Higher Cord NGF levels in women with preeclampsia-NGF levels of cord affected by fetal parameters
[13]	Term infants at birth and at age 4 months	Longitudinal study, MILLIPLEX® MAP was used for determining NGF levels, IBM SPSS statistics 19.0 was used for statistical analyses	Fetal: Birth weight Z-score, NGF levels	-Higher NGF levels in SGA infants. -NGF levels remained elevated for 4 months -NGF levels correlated negatively with the index at birth.
[14]	Pregnant women with ≥20 years of age	Correlational study, Bayley 3 was used for the assessment of neurodevelopment, and ANOVA and chi-square tests were used for statistical analyses.	Maternal: Anxiety, Depression, Blood lead levels. Fetal: Umbilical cord blood lead levels	-Impaired neuro development in offspring due to lead and stress.-NGF downregulation is caused by hormonal stress during pregnancy. -Social-emotional skills, communication, and language development were affected.
[15]	Pregnant women of 18 to 43 years	Prospective study, NGF and NT-3 levels were determined using ELISA kits, statistical analyses were done by SPSS statistic package.	Fetal Variables: NT-3, NGF	-NT-3 levels rose as fetal growth velocity decreased.-NGF levels are affected by the nutritional status of the fetus.
[16]	Pregnant women from 20 to 40 years	Cross-sectional study, ELISA was used for the determination of FGF-2, and ANOVA was used for statistical analysis.	Maternal Variables: Depression, FGF-2	-Higher FGF-2 linked with maternal anxiety. - NGF regulates FGF-2 expression and signalling.
[17]	Pregnant women from 29 to 39	Cross-sectional prospective study, the Luminex 200 reader was used to measure BNDF levels,SPSS 20.0 package was used for statistical analysis.	Maternal Variables: BDNF levels. Fetal Variables: Umbilical cord blood BDNF levels	-Umbilical cord BDNF levels were generally lower than maternal serum BDNF levels.-NGF - NGF-induced BNDF expression enhances neuron survival and brain plasticity.
[18]	Pregnant women aged 23 to 40 years	Cross-sectional study, ELISA was used for the measurement of BNDF in amniotic fluid, Shapiro-Wilk test was used for statistics.	Fetal Variables: BDNF levels in amniotic fluid, glucocorticoids	-Higher glucocorticoids in amniotic fluid were linked with raised fetal BDNF levels.-Both BNDF and glucocorticoids are linked with the expression of NGF.
[19]	Pregnant women from 20 to 45 years	Longitudinal study, UPLC-MS/MS was used for measuring cortisol levels, LMR test was used for statistical analysis	Fetal Variables: FHR reactivity, salivary cortisol	-Fetuses in the PHSG showed slower central nervous system development. -Levels of cortisol and FHR are both factors that influence the levels of NGF,an important factor in neurodevelopment.

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[20]	Neonates at 30–40 days followed up to 2 years of age.	Observational prospective study,an ELISA kit was used for measuring biochemical parameters, and GraphPad Prism 6.01 was used for the statistical study.	Fetal Variables: Urinary levels of NGF	-NGF showed potential as an indicator of motor and cognitive impairment.
[21]	Pregnant women older than 18 years	Cross-sectional study, IA-LC-MS/MS was used for measuring NGF levels, and ANOVA was used for statistical analysis	Levels of total NGF (tNGF), proNGF	-tNGF levels rose significantly from the first to the third trimester
[22]	Pregnant women younger than 35 years	Prospective cohort study, an ELISA kit was used to measure BNDF levels, and Kruskal-Wallis and Kolmogorov -Smirnov tests were used for statistical analysis.	Fetal variables: BDNF levels in cord blood	-BDNF levels had a non-linear relationship with cognitive development.-During fetal neurodevelopment, the expression of BNDF is modulated by NGF.
[23]	Children aged 7-12 years, Specific Learning Disorder (SLD)	Correlational study, an ELISA kit was used for measuring neurotrophic levels in serum,IBM SPSS 20.0 statistics was used for statistical analysis	Neurotrophic factor (BDNF, NGF, GDNF) levels in serum	-BDNF and NGF serum levels were significantly higher in children with SLD.
[24]	Pregnant women less than 40 years of age	In longitudinal and cross-sectional studies, MRI was used, and Shapiro-Wilks and chi-square tests were used as statistical methods.	Maternal Variables: Psychological distress, anxiety Fetal Variables: Brain volume measurements, cortical features.	-Maternal depression scores were significantly higher in psychological distress. -Decreased volumes in fetal white matter, and cerebellar -Psychological stress plays an important factor in disrupting the expression of neurotrophic factors like NGF.
[25]	Pregnant young females 14 to 19 years	longitudinal study, maternal cortisol levels were assessed using 24-hour ambulatory cortisol collection, SPSS 23 and Spearman rank correlation was used as statistical analysis.	Maternal Variables: Depression scores, salivary cortisol Fetal Variables: Neonatal hippocampal connectivity, Infant memory	-Higher levels of perceived stress-Different dimensions of maternal distress on the neurodevelopment of fetus. -the change in maternal cortisol levels caused by stress can potentially affect neurodevelopmental changes influenced by NGF.
[26]	Infants 2 to 5 weeks	Cross-sectional study, MRI was used, and IBM SPSS Statistics 23 was used for statistical analysis	Maternal Variables: Psychological distress, anxiety	-Maternal psychological distress effects negatively on amygdala volumes. - NGF is crucial for the development of neurons in the amygdala.

DISCUSSION

This study aimed to address the NGF as a precursor to neurodevelopment in fetuses. By large studies showed that pregnancies related to stress and stress-related disorders faced complications in fetal neurodevelopment and NGF had been seen as an underlying cause of it. Stress, anxiety, and depression during pregnancy are associated with decreased fetal brain weight but the pathways are unclear [27]. Risk factors situated in maternal nutrition, exposure to toxins, and exercise behaviour can influence fetal brain development. Environmental stimuli such as polluted air and socioeconomic status may cause maternal inflammation and oxidative stress that may in turn have an impact on fetal brain morphogenesis through epigenetic regulation [28]. One of the proteins that are involved in

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stress responses and stress-induced disorders in the nervous system is NGF. Studies have demonstrated that levels of NGF rise with stress stimuli of psychological, aggression and other environmental pressures [29, 30]. As mentioned earlier, NGF is not only involved in stress responses but also takes part in communicating the external information to the physiological and pathological outcomes. Research has shown that NGF contributes to stress-induced mental disorders including schizophrenia and depression, as well as metabolic disorders [29]. The stress-induced skin disorders have been revealed to share the "brain-skin connection" system and the NGF-dependent pathways act within this system [31]. In addition, NGF has also been identified to rise in the plasma and central nervous system of both animals and humans during stress events, implying a role in vertebrate physiological regulation. Pregnancy-associated changes have been reported in the aspect of NGF with diverse trends. There are lower concentrations of NGF in maternal and cord plasma in preterm deliveries compared to term, which can influence fetal growth or neurodevelopment [32]. It has been established that NGF plays a vital role in normal pregnancy since both depletion and excessive amounts have been associated with adverse pregnancy outcomes [33]. Mature NGF -β reduces in rat uteri during pregnancy, while pro-NGF accumulates, which could aid pregnancy-associated uterine denervation [34]. In humans, serum total NGF levels exhibit a moderate upward trend in smokers. 7-fold increase through gestation, while pro-NGF levels were unchanged at 36 weeks. Neurotrophins (NTs) are a family of trophic factors that play a major role in controlling crucial traits of development, survival, and the function of neurons [35]. The complete form of NTs binds to high-affinity tropomyosin-related kinase (Trk) A, B, or C receptors or the low-affinity p75 pan-neurotrophin receptor (p75NTR). The TrkA receptor demonstrates the highest affinity for NGF. The major cytosolic/endosomal pathways stimulated by the TrkA are Ras-mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K)-Akt, and Phospholipase C (PLC)-γ [1]. The binding of NGF to p75NTR triggers additional signalling pathways that, in the absence of co-expressed TrkA, may lead to the apoptosis of the cell. NGF formed by hippocampal and cortical neurons is known to bind TrkA and p75NTR and create a trimeric complex with NGF, leading to neuronal survival pathways [36]. NGF is essential for the development and phenotypic maintenance of neurons in the peripheral nervous system (PNS) and its highest amount is produced in the cortex, the hippocampus, and the pituitary gland, although important amounts of this neurotrophin are also produced in other areas, including the basal ganglia, thalamus, spinal cord and in the retina. In pediatric neurology, NGF is progressively recognized as a key player in the pathophysiology of various brain disorders affecting children, such as autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), and pediatric epilepsy. Dysregulation of NGF signalling pathways has been implicated in the abnormal neurodevelopmental trajectories detected in these conditions, suggesting potential insights into novel therapeutic strategies targeting NGF modulation [37]. NGF is important for neuron survival and there are several issues when regarding findings of studies that include NGF. Hypotheses involving social demographics and population-specific factors including pre-terms and IUGR further add variability that reduces the possibility of the results reflecting the actual normal population. Because NGF supports neuronal growth, survival, and regeneration, it is considered a promising candidate for multiple neurological disorders [38, 39]. Thus, during pregnancy, NGF and other neurotrophins regulate fetal brain development and activity of placenta; disturbance in these processes may result in such complication as preeclampsia and preterm births [40]. The application of diverse assessment measures across multiple studies makes the integration of the results a challenging process; this is accompanied by the development of the divergent picture of the effect of NGF dysregulation in ASD, ADHD and pediatric epilepsy. Neurogenesis does not only occur during development but also during an adult life as part of neuroprotection and repair and may, therefore, be therapeutic for neurodegenerative disorders such as Alzheimers and Parkinsons diseases. For example, the relation between synthesis and release of NGF in the brain and cognitive deteriorization in Alzheimer's disease have been revealed and therefore, it may be used for diagnostic and treatment purposes [41]. Novel treatments intended for increasing NGF availability are under development and include intranasal application and the use of nano-carriers to increase concentration and reduce off-target effects. Further, including NGF therapy with blood-brain barrier techniques such as focused ultrasound may enhance treatment outcomes of neurodegenerative disorders [42].

CONCLUSIONS

It was concluded that this review highlights the importance of Nerve Growth Factor (NGF) in fetal

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neurodevelopment and the related maternal factors involved during pregnancy. It has been inferred that stress indirectly or indirectly correlates with disruption in levels of NGF. BNDF and cortisol levels are also other important factors of stress induction and find their linkage with NGF expression. To reduce the threats arising from stress during pregnancy there is a need to employ stress-reducing measures, which could comprise psychological interventions, relaxation, and treatment for maternal mental health. It would therefore be advisable for every pregnant woman to improve her lifestyle by taking a balanced diet, exercising and avoiding substances such as tobacco and alcohol. The considerations for further research include the use of better diagnostic markers of stress-associated ND risks in early pregnancy, as well as potential therapeutic interventions promoting NGF delivery and fetal brain development. By targeting these factors, we can improve the conditions of the mother and fetus to decrease inconvenient neurodevelopmental consequences.

Authors Contribution

Conceptualization: TS, SB, NS
Methodology: TS, SB, NS, MAJ
Formal analysis: TS, SB, NS
Writing review and editing: AZ, ST, HK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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REFERENCES

[1] Dhobale M, Mehendale S, Pisal H, Nimbargi V, Joshi S. Reduced Maternal and Cord Nerve Growth Factor Levels in Preterm Deliveries. International Journal of Developmental Neuroscience. 2012 Apr; 30(2): 99-103. doi: 10.1016/j.ijdevneu.2011.12.007.

[2] Tometten M, Blois S, Arck PC. Nerve Growth Factor in Reproductive Biology: The Link Between the Immune, Endocrine and Nervous System? Immunology of Pregnancy. 2005; 89: 135-48. doi: 10.1159/000087962.

[3] Tometten M, Blois S, Kuhlmei A, Stretz A, Klapp BF, Arck PC. Nerve Growth Factor Translates Stress Response and Subsequent Murine Abortion Via Adhesion Molecule-Dependent Pathways. Biology of Reproduction. 2006 Apr; 74(4): 674-83. doi: 10.1095/biolreprod.105.044651.

[4] Dhobale M. Neurotrophins: Role in Adverse Pregnancy Outcome. International Journal of Developmental Neuroscience. 2014 Oct; 37: 8-14. doi: 10.1016/j.ijdevneu.2014.06.005.

[5] Wu Y, Espinosa KM, Barnett SD, Kapse A, Quistorff JL, Lopez C *et al.* Association of Elevated Maternal Psychological Distress, Altered Fetal Brain, and Offspring Cognitive and Social-Emotional Outcomes at 18 Months. Journal of the American Medical Association Network Open. 2022 Apr; 5(4): e229244-. doi: 10.1001/jamanetworkopen.2022.9244.

[6] Lubrano C, Parisi F, Cetin I. Impact of Maternal Environment and Inflammation on Fetal Neurodevelopment. Antioxidants. 2024 Apr; 13(4): 453. doi: 10.3390/antiox13040453.

[7] Wu Y, De Asis-Cruz J, Limperopoulos C. Brain Structural and Functional Outcomes in the Offspring of Women Experiencing Psychological Distress During Pregnancy. Molecular Psychiatry. 2024 Feb: 1-8. doi: 10.1038/s41380-024-02449-0.

[8] García-Blanco A, Monferrer A, Grimaldos J, Hervás D, Balanzá-Martínez V, Diago V *et al.* A Preliminary Study to Assess the Impact of Maternal Age on Stress-Related Variables in Healthy Nulliparous Women. Psychoneuroendocrinology. 2017 Apr; 78: 97-104. doi: 10.1016/j.psyneuen.2017.01.018.

[9] Zhang L, Huang R, Lei J, Liu Y, Liu D. Factors Associated with Stress Among Pregnant Women with a Second Child in Hunan Province Under China's Two-child Policy: A Mixed-Method Study. BioMed Central Psychiatry. 2024 Feb; 24(1): 157. doi: 10.1186/s12888-024-05604-7.

[10] Kazi A, Fatmi Z, Hatcher J, Niaz U, Aziz A. Development of a Stress Scale for Pregnant Women in the South Asian context: the AZ Stress Scale. Eastern Mediterranean Health Journal. 2009: 15(2): 353-361. doi: 10.26719/2009.15.2.353.

[11] Graham AM, Doyle O, Tilden EL, Sullivan EL, Gustafsson HC, Marr M *et al.* Effects of Maternal Psychological Stress During Pregnancy on Offspring Brain Development: Considering the Role of Inflammation and Potential for Preventive Intervention. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2022 May; 7(5): 461-70. doi: 10.1016/j.bpsc.2021.10.012.

[12] D'souza V, Kilari A, Pisal H, Patil V, Mehendale S, Wagh G *et al.* Maternal Nerve Growth Factor Levels During Pregnancy in Women with Preeclampsia: A Longitudinal Study. International Journal of Developmental Neuroscience. 2015 Dec; 47: 340-6. doi: 10.1016/j.ijdevneu.2015.08.003.

[13] Sánchez-Infantes D, Cereijo R, Sebastiani G, Pérez-Cruz M, Villarroya F, Ibáñez L. Nerve Growth Factor Levels in Term Human Infants: Relationship to Prenatal Growth and Early Postnatal Feeding.

DOI:https://doi.org/10.54393/pjhs.v5i09.2249

International Journal of Endocrinology. 2018 Dec; 2018(1): 7562702. doi: 10.1155/2018/7562702.

[14] Guo X, Jiang S, Xu J, Tian Y, Ouyang F, Yu X *et al.* Effects of Single and Combined Exposure to Lead and Stress During Pregnancy on Offspring Neurodevelopment. Developmental Cognitive Neuroscience. 2022 Aug; 56: 101124. doi: 10.1016/j.dcn.2022.101124.

[15] Machairiotis N, Vrachnis D, Antonakopoulos N, Loukas N, Fotiou A, Pergialiotis V et al. Detection and Quantification of Neurotrophin-3 (NT-3) and Nerve Growth Factor (NGF) Levels in Early Second Trimester Amniotic Fluid: Investigation into a Possible Correlation with Abnormal Fetal Growth Velocity Patterns. Journal of Clinical Medicine. 2023 Jun; 12(12): 4131. doi: 10.3390/jcm12124131.

[16] Akbaba N, Annagür BB, Annagür A, Akbulut H, Akyürek F, Çelık Ç. Neurotrophins and Neuroinflammation in Fetuses Exposed to Maternal Depression and Anxiety Disorders During Pregnancy: A Comparative Study on Cord Blood. Archives of Women's Mental Health. 2018 Feb; 21: 105-11. doi: 10.1007/s00737-017-0774-1.

[17] Flöck A, Weber SK, Ferrari N, Fietz C, Graf C, Fimmers R *et al.* Determinants of Brain-Derived Neurotrophic Factor (BDNF) in Umbilical Cord and Maternal Serum. Psychoneuroendocrinology. 2016 Jan; 63: 191-7. doi: 10.1016/j.psyneuen.2015.09.028.

[18] Lamadé EK, Pedraz-Petrozzi B, Lindner O, Meininger P, Pisters A, Gilles M *et al.* Stress in Pregnancy-Implications for Fetal BDNF in Amniotic Fluid at Birth. Neurobiology of Stress. 2024 Jun; 32: 100658. doi: 10.1016/j.ynstr.2024.100658.

[19] Walsh K, McCormack CA, Webster R, Pinto A, Lee S, Feng T *et al.* Maternal Prenatal Stress Phenotypes Associate with Fetal Neurodevelopment and Birth Outcomes. Proceedings of the National Academy of Sciences. 2019 Nov; 116(48): 23996-4005. doi: 10.1073/pnas.1905890116.

[20] Aisa MC, Barbati A, Cappuccini B, De Rosa F, Gerli S, Clerici G *et al.* Urinary Nerve Growth Factor in Full-Term, Preterm and Intra Uterine Growth Restriction Neonates: Association with Brain Growth at 30–40 Days of Postnatal Period and with Neuro-Development Outcome at Two Years. A Pilot Study. Neuroscience Letters. 2021 Jan; 741: 135459. doi: 10.1016/j.neulet.2020.135459.

[21] Walsh J, Palandra J, Goihberg E, Deng S, Hurst S, Neubert H. Analysis of β-nerve Growth Factor and Its Precursor During Human Pregnancy by Immunoaffinity-Liquid Chromatography-Tandem Mass Spectrometry. Scientific Reports. 2023 Jun; 13(1): 9180. doi: 10.1038/s41598-023-34695-7.

[22] Zhang T, Wang H, Ouyang F, Yang H, Zhang J, Zhang N. Does Brain-Derived Neurotrophic Factor Play a Role in the Association Between Maternal Prenatal Mental Health and Neurodevelopment in 2-Year-Old Children? Journal of Affective Disorders. 2024 Aug; 359: 171-9. doi: 10.1016/j.jad.2024.05.074.

[23] Uncu GS, Karayağmurlu A, Kaynar TB, Baki AM, Vural P, Soylu N. Serum Levels of Brain-Derived Neurotrophic Factor, Nerve Growth Factor, Neurotrophin-3, and Glial-Derived Neurotrophic Factor in Children with Specific Learning Disorder. Archives of Neuropsychiatry. 2022 Nov; 59(4): 260. doi: 10.29399/npa.28043.

[24] Lu YC, escavage N, Wu Y, Kapse K, Andersen NR, Quistorff J *et al.* Maternal Psychological Distress During the COVID-19 Pandemic and Structural Changes of the Human Fetal Brain. Communications Medicine. 2022 May; 2(1): 47. doi: 10.1038/s43856-022-00111-w.

[25] Scheinost D, Spann MN, McDonough L, Peterson BS, Monk C. Associations Between Different Dimensions of Prenatal Distress, Neonatal Hippocampal Connectivity, and Infant Memory. Neuropsychopharmacology. 2020 Jul; 45(8): 1272-9. doi: 10.1038/s41386-020-0677-0.

[26] Lehtola SJ, Tuulari JJ, Scheinin NM, Karlsson L, Parkkola R, Merisaari H *et al.* New Born Amygdalar Volumes are Associated with Maternal Prenatal Psychological Distress in a Sex-Dependent Way. NeuroImage: Clinical. 2020 Jan; 28: 102380. doi: 10.1016/j.nicl.2020.102380.

[27] Massaro AN, Rothbaum R, Aly H. Fetal Brain Development: The Role of Maternal Nutrition, Exposures and Behaviors. Journal of Pediatric Neurology. 2006 Mar; 4(01): 001-9. doi: 10.1055/s-0035-1557300.

[28] Fenster T, Rao M, Mamzhi Y, Tsou Jr H. Fetal Neurobehavioral Development: The Role of Maternal Psychosocial, Pathological, and Pharmacological Stress. Georgetown Medical Review. 2020 May; 4(1). doi: 10.52504/001c.12642.

[29] Ceci FM, Ferraguti G, Petrella C, Greco A, Tirassa P, Iannitelli A *et al.* Nerve Growth Factor, Stress and Diseases. Current Medicinal Chemistry. 2021 May; 28(15): 2943-59. doi: 10.2174/0929867327999200818111654.

[30] Cirulli F and Alleva E. The NGF Saga: From Animal Models of Psychosocial Stress to Stress-Related Psychopathology. Frontiers in Neuroendocrinology. 2009 Aug; 30(3): 379-95. doi: 10.1016/j.yfrne.2009.05.002.

[31] Zoumakis E, Kalantaridou SN, Chrousos GP. The "Brain–Skin Connection": Nerve Growth Factor-

DOI:https://doi.org/10.54393/pjhs.v5i09.2249

Dependent Pathways for Stress-Induced Skin Disorders. Journal of Molecular Medicine. 2007 Dec; 85: 1347-9. doi: 10.1007/s00109-007-0270-6.

[32] Alleva E, Petruzzi S, Cirulli F, Aloe L. NGF Regulatory Role in Stress and Coping of Rodents and Humans. Pharmacology Biochemistry and Behavior. 1996 May; 54(1): 65-72. doi: 10.1016/0091-3057(95)02111-6.

[33] Nilsen-Hamilton M. Growth Factor Signaling in Early Mammalian Development. In growth Factors in Mammalian Development. CRC Press. 2021 May: 135-166. doi: 10.1201/9781003210351-8.

[34] Lobos E, Gebhardt C, Kluge A, Spanel-Borowski K. Expression of Nerve Growth Factor (NGF) Isoforms in the Rat Uterus During Pregnancy: Accumulation of Precursor proNGF. Endocrinology. 2005 Apr; 146(4): 1922-9. doi: 10.1210/en.2004-0925.

[35] Al-Yozbaki M, Acha-Sagredo A, George A, Liloglou T, Wilson CM. Balancing Neurotrophin Pathway and Sortilin Function: Its Role in Human Disease. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2020 Dec; 1874(2): 188429. doi: 10.1016/j.bbcan.2020.188429.

[36] Dou SH, Cui Y, Huang SM, Zhang B. The Role of Brain-Derived Neurotrophic Factor Signaling in Central Nervous System Disease Pathogenesis. Frontiers in Human Neuroscience. 2022 Jun; 16: 924155. doi: 10.3389/fnhum.2022.924155.

[37] Capossela L, Gatto A, Ferretti S, Di Sarno L, Graglia B, Massese M *et al.* Multifaceted Roles of Nerve Growth Factor: A Comprehensive Review with a Special Insight into Pediatric Perspectives. Biology. 2024 Jul; 13(7): 546. doi: 10.3390/biology13070546.

[38] Li R, Li DH, Zhang HY, Wang J, Li XK, Xiao J. Growth Factors-Based Therapeutic Strategies and Their Underlying Signaling Mechanisms for Peripheral Nerve Regeneration. Acta Pharmacologica Sinica. 2020 Oct; 41(10): 1289-300. doi: 10.1038/s41401-019-0338-1.

[39] Sims SK, Wilken-Resman B, Smith CJ, Mitchell A, McGonegal L, Sims-Robinson C. Brain-derived Neurotrophic Factor and Nerve Growth Factor Therapeutics for Brain Injury: The Current Translational Challenges in Preclinical and Clinical Research. Neural Plasticity. 2022 Mar; 2022(1): 3889300. doi: 10.1155/2022/3889300.

[40] Sahay A, Kale A, Joshi S. Role of Neurotrophins in Pregnancy and Offspring Brain Development. Neuropeptides. 2020 Oct; 83: 102075. doi:10.1016/j.npep.2020.102075.

[41] Ciafrè S, Ferraguti G, Tirassa P, Iannitelli A, Ralli M, Greco A *et al.* Nerve Growth Factor in the Psychiatric Brain. Rivista di psichiatria. 2020; 55(1): 4-15.

[42] Xhima K and Aubert I. The Therapeutic Potential of Nerve Growth Factor Combined with Blood-Brain Barrier Modulation by Focused Ultrasound for Neurodegenerative Disorders. Neural Regeneration Research. 2021 Sep; 16(9): 1783-5. doi: 10.4103/1673-5374.306076.