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Brain Derived Neurotrophic Factor in Pregnancy: Stress Responses and Fetal Neurodevelopment

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ABSTRACT

BDNF was a protein that has crucial role in development of brain in fetuses however its levels were affected by maternal stress response that cause complications. **Objective:** To study the effects of Brain Derived Neurotrophic Factor (BDNF) in stress response during pregnancy on developing fetus in order to bring clinicopathological correlations. **Methods:** As PRISMA guidelines suggested, an extensive database search was made from PubMed, Science Direct, and Google Scholar for articles that were released between 2016 and 2024. Included studies analyzed differences in BDNF as a function of maternal stress responses expressed by increased levels of maternal stress activity and changes in maternal brain. This review also included fetal neurodevelopmental issues which related to brain development and stress biomarkers. Google Scholar was used for 60% of the articles with various locations. **Results:** The review also revealed strong relations between high levels of BDNF and mothers' stress reactions that included tangible changes in cortisol levels and some parts of the brain as the amygdaloid complex. The effect of maternal stress was observed to be regulated through alteration of brain plasticity by BDNF. Additionally, maternal BDNF concentration has been associated with the changes in fetal brain development such as modifications in brain weight and stress related biomarkers in cord blood serum samples. **Conclusions:** Maternal stress was hence a critical driver of neurodevelopmental outcomes of fetuses and newborns through BDNF. If implemented, this information may help to understand how BDNF regulates the types of stresses that a mother experiences along with fetal brain development.

INTRODUCTION

Brain-Derived Neurotropic Factor (BDNF) is a critical protein that plays a big role in the development of neurons and neuronal connections inside the brain. It is most important during pregnancy because physiological changes in a mother can influence BDNF levels, and thus, fetal brain development. Studies show that maternal stress during pregnancy averages from 10 percent to 35 percent with higher occurrence in susceptible mothers [1]. In the higher income region, the aggressiveness of maternal stress, in general, is described in a range of 10-20% [2]. Both in maternal and fetal serum, stress was found to be directly linked to decreased levels of Brain Derived Neurotrophic Factor (BDNF) that is vital in fetal brain development. Decreased levels of BDNF impact crucial areas of the brain including the hippocampus and the prefrontal cortex that affect a person's ability to think or

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respond emotionally [3]. These changes are usually associated with increased cortisol levels that act to impair fetal neurodevelopment [4]. There are many other factors besides stress that affect BDNF levels during pregnancy tied to maternal behavior. In this regard, nutritional factors count for a lot. It was found that increase in omega 3polyunsaturated fatty acids as well as vitamins improved the BDNF level while reduction in folic acid and iron interfered with the improvement of the BDNF level [5]. Moreover, physical activity is positively associated with BDNF because exercise promotes the release of neurotrophins to help improve maternal well-being as well as to help positively impact fetal brain [6]. Glial cell Line-Derived Neurotrophic Factor (GDNF), affiliated with neuronal survival and differentiation as well as trkB, associated with neuronal differentiation and survival are also important here. GDNF aids in the survival of dopaminergic neurons and has also been observed to have a role of neuroprotection during pregnancy [7]. TrkB, the receptor for BDNF, is involved in the regulation of neuronal survival and growth and those axons pathways involved in fetal development [8]. Maternal stress is characterized by increased levels of cortisol in the body of the mother that effects the intrauterine environment and ultimately fetal development. Neurodevelopment is affected when neurotrophic support system is disrupted, one of such systems are directed by BDNF therefore BDNF levels play an important role as they are affected by maternal stress factors and then they disturb the neural development in fetus. By understanding this pathway, it is easier to mitigate risk factors. Another important contributing factor to pregnancy outcomes is maternal age with those that are over 30 considered to be advanced in their pregnancy. Although there is no direct evidence that links advancing maternal age with reduced BDNF levels. But it has been associated with stressful conditions like gestational hypertension and preeclampsia, both affect fetal development. This revelation has highlighted a critical gap in the literature, as indirect effects of maternal age on BDNF through these complications have not been touched yet. Addressing this gap will help understand the connection between maternal factors and fetal outcomes more comprehensively [9]. This review aims to provide an up-to-date synthesis with regard to the way BDNF translates maternal stress and other influencing factors during pregnancy as well as their impact on the fetal brain. Through offering an understanding of how BDNF and other related neurotrophins engage with maternal health.

This study was positioned to help guide procedures that could enhance health of pregnant people and their children including the treatments that involve BDNF supplements.

METHODS

According to the recommendations by PRISMA suggested for reporting, the review was conducted from May 2024 to August 2024. Initially it included 89 articles in English from 2016 to 2024. The articles were systematically sorted based on inclusion criteria searched and reported the details including: author, year, regions, title, design, statistical analysis, methodology, maternal and fetal variables, sample size, key findings, and references. Several search engines were employed; Science Direct, Google Scholar, and PubMed.The search through databases emphasized upon comprehensiveness. It was made sure that articles fetched from each database were cross referenced with each other to control biasness. Majority papers were taken from Google Scholar due to its broader indexing but it was made sure that the indexing of articles encompass multiple sources. Collected research articles were taken from various parts of the world including Asia, Europe and America mainly. Article search was done using keywords: BDNF, stress markers, pregnancy, fetal neurodevelopment, stress factor exposure in pregnancy and stress response in body. Pregnancy, BDNF, stress markers, fetus, neural development, old women and maternal stress were the significant words. The articles which did not fulfil this inclusion criterion were eliminated. The inclusion criteria were focused on fluctuations in levels of BDNF and its effects in neurodevelopment along with other stress markers and all papers taken were from latest years, no paper older than year 2016 was taken. The collection and filtering process were done by two independent reviewers and to avoid reviewer's conflict and biasness Cohen's Kappa method was used. There were eighty-nine articles in total that were downloaded from databases. Seven duplicate articles were found and removed, leaving eighty-two for analysis. A total of seventy-two articles from the systematic review were eliminated based on irrelevant data added in them. After elimination, seventeen papers were picked and sorted which fulfilled inclusion criteria. Cohen's kappa, a statistical method, was employed to assess the reliability among the raters during the study selection process, ensuring consistency and agreement between reviewers. PRISMA model in Figure 1 illustrated selection of studies for review process showing elimination of studies that were not lying under the inclusion criteria. Total 50 articles were excluded according to specific reasons which were described in Figure 1.

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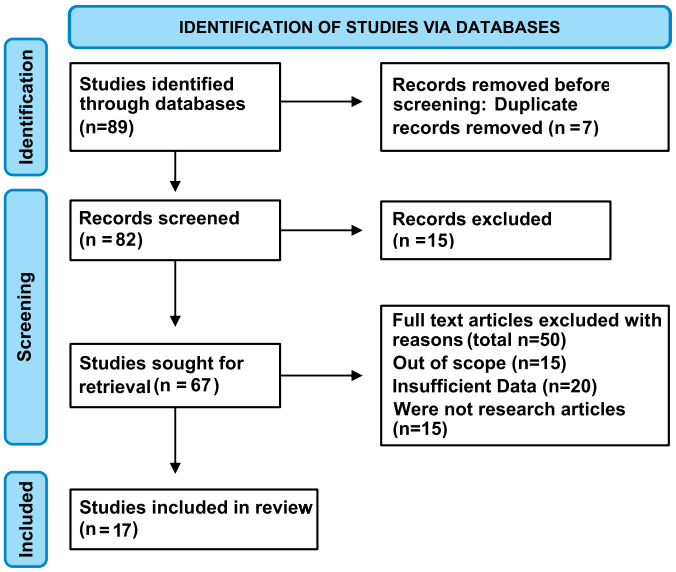

Figure 1: PRISMA Flowchart of Study Selection and Exclusion Criteria

RESULTS

The majority of the pregnant women in all the studies ranged from 18 to 45 years by age. The pregnant women taken as sample had shown symptoms of stress. 6/17 of studies were longitudinal studies, 5/17 were correlational/ prospective studies, 5/17 were experimental/ observational studies and 1/17 was exploratory study. The studies were taken from all regions of the world including Asia, Europe and America. Research studies were taken from last five years i.e. 2020-2024. The study reviewed papers that were conducted in Asia (47%), Europe (41%) and America (12%) respectively. The studies taken from Google Scholar (60%), Science Direct (30%), and others (10%) i.e. PubMed. A meta-analytical approach was employed using Comprehensive Meta-Analysis (CMA) software. This enabled the pooling of comparable outcomes of studies with effect of sizes. The trends related to impact of maternal stress on BDNF levels and fetal neurodevelopment were identified and pool effect size of -0.45 (95% CI: -0.65, -0.25) was seen between the relationship of high maternal stress and reduced BDNF levels. This method revealed some trends regarding the impact of maternal stress on fetus. Confidence intervals and biasness indices were also included to solidify the robustness of results. A variability in effect sizes ($I^2 = 62\%$, $p < 0.05$) was given to heterogeneity seen in study design and population characteristics. Results of these studies were shown in the Table 1 [10-26].

Table 1: Schematic Review of Studies that were most Appropriate According the PRISMA Defined Rules

Authors and Year (Region)	Study Population (Age Range)	Sample Size (N)	Maternal Variables related to BDNF	Fetal Variables Related to BDNF	Study Methodology (Longitudinal, Correlational etc) and Statistical Tools	Key Findings Related to BDNF
Dai Y *et al.*, 2024 [10] (China)	Pregnant Women (<35 Years Old)	1189	Pre-Preg Bmi, Weight Gain At Gestational Period, Maternal Age, Smoking, Education, Occupation	BNDF Levels In Cord Serum	Prospective Cohort Study, GLMs, QGC, BKMR, and Sex-Stratified Analysis	Four PFAS were Negatively Proportional to BNDF Levels in Females, Especially in Female Fetus
Lamadé *et al.*, 2024 [11] (Germany)	Pregnant Women (18-50 Years Old)	41	Depressive Symptoms, Prenatal Stress, Cortisone and Cortisol Levels in Amniotic Fluid, Socioeconomic Status	BDNF Levels In Cord Blood	Correlation Prospective Study, Linear Regression Models, Stratified Analysis, Natural Logarithmic Transformations	Depressive Symptoms and Socioeconomic Status were Related to the Higher BNDF Levels Positively
Cuiping Wang *et al.*, 2023 [12] (China)	Pregnant Women (>=20 years old)	711	Exposure to PM2.5 During Pregnancy, Age, Smoking, Education, Pre-Preg BMI	BDNF in Cord Blood, Birth Weight, Gender, Delivery Mode	Prospective Cohort Study, Linear Regression Models	PM2.5 Exposure in Pregnancy were Associated with Lower Levels of BDNF Especially in Male Infants. Normal Deliveries had Higher BDNF Levels than Caesarean
Chung-Hao Su *et al.*, 2021 [13] (Taiwan)	Infants (Birth to 12 Months Old)	24 (8 IMGD, 16 non-IMGD)	Gestational Diabetes Mellitus	Serum BNDF Levels	Prospective Cohort Study, P and S Correlation, Logistic Regression Models	Infants of Mothers with GDM had Lower BDNF Levels and Poor Language Composite Scores. POOR LCM Defines Defective Neurodevelopment in Subjects. IMGD Has Lower BNDF Levels
Mercado *et al.*, 2024 [14] (USA)	Fetuses (36 to 39 Weeks GA)	23	BNDF Levels Before Delivery	BNDF Levels in Cord Blood After Delivery	Exploratory Study, fMEG, Pearson Correlation, Partial Correlation, PSD Analysis	BNDF Levels of Mother Showed Negative Association with fetal Delta Brain Activity but Showed Positive Association with Alpha, Beta, and Theta Activity. Cord Blood BNDF Didn't Show Any Association with Brain Activity

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Richter *et al.*, 2022 [15] (Netherlands)	Children of 4 Years Old	21	Not Examined	BNDF DNA Methylation at 4 Years Old	Prospective Observational Cohort Study, Methylation Analysis, Neuro-developmental Testing, Regression analysis	Fetal Brain Sparing was Associated with Hyper-methylation of BDNF at CREB Binding Site in Children. This Correlates with Better Inhibitory Self-Control
Karunanithi Sivasangari *et al.*, 2020 [16] (India)	Babies of Prenatally Stressed Wister Rats (15-30 Days Old)	19 (7 Control, 6 PNS, 6 BME)	Exposure to Bacoppa monnieri Extract in GA	BNDF Levels, Postnatal Behaviour	Longitudinal Study in Vivo Experiments, ANOVA and Bonferroni Post Hoc Analyses	Prenatal Reduced Levels of Mature BDNF and Increased Levels of Pro-BDNF. Treatment with Bacoppa Monnieri Restored the Levels of BDNF
Abdollahi *et al.*, 2021 [17] (Iran)	Pregnant Wistar Rats and Fetuses	40	Hesperidin Dosage, Oxidative Stress, BDNF, TrkB	BDNF, TrkB, Oxidative Stress	Experimental Study with Longitudinal Design, ANOVA and Tukey's Post Hoc Tests	Hesperidin Increased the Levels of BDNF and TrkB. BDNF-TrkB Signalling Pathway is Necessary for Neurodevelopment of Fetus
Szymanski & Minichiello, 2022 [18] (UK)	Hippocampal Dentate Granule Cells of Immature Mouse, CA3 Principal Cells for Postnatal Development Study	Not Mentioned	Oxytocin, NKCC1, GABA	NKCC1, BDNF, TrkB, GABA	Longitudinal Experimental Study, smFISH and Wilcoxon Tests were Used	BDNF-TrkB Pathways was Significant for NKCC1 Modulation Which is Important for Formation of Hippocampal Circuits
Yu G *et al.*, 2021 [19] (China)	Pregnant Women	725	PFAS Levels	BDNF Levels	Prospective Cohort Study, Linear Regression Models and SPLS was Used	Prenatal Exposure to PFHxS Results in Increased Levels of BDNF in Fetal Cord Blood
Marchese MJ *et al.*, 2021 [20] (China)	Trophoblast of Human Placenta Tissues	Not Mentioned	PFAS Levels	BDNF, PFAS	Experimental Lab-Based Study, Western Blotting, Immunofluorescence, and ANOVA was Used	Placental Cells Showed Presence of BDNF Signalling. PFAS Didn't Significantly Alter BDNF Signalling
de Mendonça Filho *et al.*, 2021 [21] (Canada)	Children (Birth to 12 Years Old)	157	Mental Health, Smoking, Socio-economic Factors etc.	BDNF Levels	Longitudinal Study, LME and pICA was Used	BDNF Network Balances the Effect of Prenatal Adversity in Neural and Cognitive Development
Pascual-Mancho *et al.*, 2022 [22] (Spain)	Fetuses	130	Age, Preeclampsia, Use of Corticosteroids	BDNF Levels in Cord Blood, Fetal Doppler Alterations, IUGR	Longitudinal Study, ELISA, Mann- Whitney and Chi Square Tests Were Used	Cord Blood BDNF Concentrations Are Lower in Fetus with Growth Restriction Compared to AGA fetus BDNF May Play a Role in FGR Related Neuro-developmental Disorders
Zhang T *et al.*, 2024 [23] (China)	Infants (6 Months to 12 Months)	24	Diabetes Status	BDNF in Serum	Prospective Cohort Study, BSID III, t Tests, P and S Correlations and Logistic Regression Models are Used	Infants of Diabetic Mothers had Low BDNF Levels. These Infants Showed Poor Language Development Outcomes Compared to Healthy Ones. BDNF Showed Positive Association with Language Composite Scores
Granitzer *et al.*, 2024 [24] (Austria)	Pregnant Women (18-45 Years)	65	Lead and Cadmium Exposure, Iron Levels, BDNF Levels, KISS-1 Levels	BDNF Levels	Cross-Sectional and Correlational Study, ELISA, Spearman Correlation and CATREG Analysis	Maternal and Fetal BDNF levels were correlated to each other. Iron Deficiency was Associated with Lower BDNF Levels
Dingsdale *et al.*, 2021 [25] (UK)	Pregnant Women (18-45 Years)	251 Maternal and 212 Fetal Pairs	Anxiety, Depression, BDNF Levels	BDNF Levels in Serum of Cord Blood	Longitudinal Cohort Study, Spearman Correlation and Logistic Regression was Used	Stress Symptoms in Mothers were Related to Higher BDNF Levels
Shchelchkova *et al.*, 2020 [26] (Russia)	Pregnant C57BL/6 Mice	36 Pregnant Mice and 88 Parturient Mice	Chronic Hypobaric Hypoxia, BDNF Levels During Pregnancy	BDNF, GDNF, NSE, HIF-1β	Longitudinal Study with Experimental Components, Statistica 10.0 Software and Mann Whitney U-Test was Used.	Chronic Hypobaric Hypoxia is Related to Low Levels of BDNF in Pregnant Mice. Up Regulation of the Neuro-trophic Factors (BDNF, GDNF) were Associated with Protection of Neonates Against Hypoxic Damage.

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DISCUSSION

This review provided the evaluation on the contribution of BDNF as a biomarker in fetal neurodevelopment with a focus on maternal stress and related disorders. These studies provided evidence that stress and related psychological conditions make pregnancies lead to poor neurodevelopment of fetuses. BDNF was found to play a major role in this relation, affecting the neural circuits that were vulnerable to maternal influences. In particular, stress during pregnancy, hormonal changes, and numerous psychosocial disorders may negatively impact fetal brain formation. It had been proved that maternal anxiety and depression were associated with decreased fetal brain weight and changes in the pattern of fetal neuronal development, but the exact pathways had not been investigated comprehensively [26]. Other external factors such as maternal diet, toxic exposure and physical activity levels also played particular roles in the development of the fetal brain [27]. In addition, environmental factors including air pollution and socioeconomic status might also further have contributed to increase in inflammation and oxidative stress in the maternal side thus modifying fetal brain morphogenesis through epigenetic change [28]. BDNF played an important role in the stress response system and was known to be upregulated by many stressors, including psychological and environmental [29]. This neurotrophin does not only play the role of the neuronal survival and development but also guarantees the interaction between nervous system and the organism's reaction to stress. Increased levels of BDNF had been reported to over mood disorders including the depression and schizophrenia demonstrating that BDNF contributes differently in neurodevelopment and mental disorders [30, 31]. Also, there was an emerging body of evidence on so called 'brain-skin connection', which suggests that BDNF may impact skin conditions related to stress as well [32]. The mechanisms of BDNF action include BDNF binding to its high affinity receptor tropomyosin receptor kinase B (TrkB). BNDF binds-and-activates the extracellular domain of the TrkB receptor, which in turn triggers several intracellular signaling cascade, namely the Mitogen Activated Protein Kinase (MAPK), Phosphatidylinositol 3-Kinase (PI3K)/Akt and phospholipase C-gamma (PLC-γ signals [33, 34]. These pathways were involved in cell differentiation, proliferation and survival, neuronal development and activity-dependent synaptic plasticity. For instance, MAPK pathway activation was involved in neuronal differentiation and survival. However, PI3K/Akt signalling was necessary for cell survival and growth [35]. BDNF can also bind to the low affinity receptor p75NTR, which may promote either survival/survival or apoptotic signals [36, 37]. There was evidence of changes in BDNF levels during pregnancy. Some investigations had shown lower concentrations of BDNF in cord blood in the context of preterm birth compared with pregnancies at term. This difference may well hold a part in having an impact on fetal development as well as development of the nervous system [1]. BDNF concentration must remain optimal throughout gestation as both the high and low levels were proven to be detrimental for pregnancy [34]. For example, although it had been shown that BDNF levels decrease as pregnancy progresses, pro-BDNF had been found to increase and it had been established that there was intricate control of neurotrophin levels that was important in maintaining the health of both uterine and fetal environments [35, 36]. Smokers had higher serum BDNF levels during pregnancy and this has elevated questions on its impact to fetal neurodevelopment [37]. BDNF was vital to the pregnancy progress as its concentration lack during pregnancy which may cause preeclampsia and preterm delivery that harm both the mother and baby [38]. Moreover, it also has neuroprotective functions which may be of importance in its therapeutic use especially for Alzheimer diseases and other neurodegenerations. Reduced BDNF levels have been reported in Alzheimer's patients and help study the chances of using this protein as diagnostic and remediations markers at an initial stage of the disease [39]. So far, the experiments were undergoing experimental strategies for sustaining effectual delivery procedures for BDNF therapy, such as intranasal delivery system and the utilization of nanocarrier to increase the availability of BDNF with also lowering adverse effects [40, 41]. However, there were limitations in studying BDNF that stem with research studies on neurodevelopmental processes. These include population characteristics, method differences, and differences in instruments used when conducting the studies [36, 37]. Many studies relied on small sample sizes or cross-sectional designs which hinders the inference of casual relationships. For example, Dai Y et al., associated prenatal stress factor exposure with reduced BDNF levels but their study was not generizable due to narrow cohort [10]. Zhang T et al., found that infants of diabetic mothers had lower serum BDNF levels, which were positively associated with poor language development outcomes [23]. Granitzer S et al., focused on small European population that limited the study's applicability on other nations [24]. Similarly, Richter AE et al., showed significant finding but ignored environmental factors that could have confounding results [15]. Mercado et al., incorporated fMEG to analyse maternal BDNF levels but couldn't include biochemical assays limiting mechanistic insights [14]. There was also publication biasedness on BDNF's effectiveness since trials with

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negative outcomes were often ignored. Another factor which poses a challenge to the selection of research options in vulnerable patient groups such as infants and children was ethical issues especially when evaluating long-term development al impact [39]. Considering the variation of BDNF's roles in fetal development and potential relation to ASD and ADHD, large-scale extension studies were needed. Longitudinal studies were required to track the levels of BDNF with outcomes of neurodevelopment overtime. These studies should try to establish the method and the kind of assessment that should be used to further the knowledge on the normal as well as the abnormal developments of brain derived neurotrophic factor BDNF [38]. Standardized protocols were needed to make the measure of BDNF and maternal stress marker comparable across studies. In sum, BDNF seems an attractive target to improve neurodevelopmental outcomes in high-risk children. However, since the above was a consolidation of studies, there were limitations that were experienced throughout this research. Firstly, the studies were highly heterogeneous including differences in methodological approaches, study sample size, and methods used in BDNF assessment. Secondly, while comparing the study populations, demographic and distributional differences between geographic regions and various socioeconomic statuses were likely to put into questions the generalizability of the results. Furthermore, the ethical concerns regarding measuring BDNF in pregnant women and fetuses restricted the validity of long-term observation studies of maternal stress and BDNF on fetal neuronal development which was important to the scope of the analysis. Lastly, there was publication bias in which experiments with negative or incomplete results were less likely to be published, which could lead to an incline towards positive relationships between BDNF and fetal brain development.

CONCLUSIONS

This review highlights how BDNF was important in relating maternal stress with fetal neurodevelopment. Increased levels of maternal stress activity affect BDNF levels and fetal brain growth as well as stress biomarkers in offspring. Since such findings hold high levels of significance the results could be applied to women during early prenatal care for indicative of risk of poor neurodevelopmental outcome. Stress intervention measures such as mindfulness, nutritional and physical activity may be incorporated into the antenatal care to possibly reverse the abnormal BDNF levels due to stress induced neuro developmental problems. Moreover, strategies that focus on modulating the levels of BDNF, such as BDNF administration or neurotrophic support therapies, may be considered for treatment in high-risk pregnancies. Thus, by practicing such approaches it will be possible to decrease the threat of neurodevelopmental disorders in children, especially in mothers experiencing a high level of stress, and improve further cognitive and emotional development.

Authors Contribution

Conceptualization: AA, SP
Methodology: SP
Formal analysis: NA, MAA, AS
Writing, review and editing: MA, SP, KA, NA, AS, MAA

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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