DOES MATERNAL STRESS, DEPRESSION AND ANXIETY AFFECT FETAL NEUROBEHAVIORAL DEVELOPMENT? A REVIEW

By

Aysha Rufaka

17146022

A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

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Brac University
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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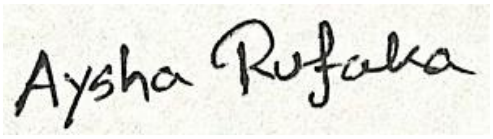

Aysha Rufaka
17146022

Approval

The thesis/project titled “Does maternal stress, depression and anxiety affect fetal neurobehavioral development? A review” submitted by AyshaRufaka (17146022) of Spring, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.).

Examining Committee:

Supervisor:

Dr. Sharmind Neelotpol
Associate Professor, Department of Pharmacy
Brac University

Program Coordinator and
Deputy chair:

Dr. Hasina Yasmin
Professor, Department of Pharmacy
Brac University

Departmental Head:

Dr. Eva Rahman Kabir
Professor and Chairperson, Department of Pharmacy
Brac University

Ethics Statement

No living organism were harmed during this project.

Abstract

When a mother experiences stress, depression or anxiety during pregnancy, it can be referred to as maternal or prenatal stress. Various environmental sufferings and stressful occasions can develop maternal stress. Often hormonal changes in the mother can negatively influence the brain development of the fetus. By following two pathways maternal stress transfers to the fetus and these are Fetal-Maternal Hypothalamic Pituitary Adrenal Axis Dysregulation and Uterine Artery Resistance. Moreover, maternal stress also has an impact on the fetal brain structure and so many parts of the fetal brain cannot develop properly. Therefore, the child suffers from impaired neurobehavioural development. Furthermore, different maternal modulators also impairthe neuronal development offetus. For instance, elevated cytokines level can develop psychiatric disorders in the infant, increased cortisol levels can also disrupt the HPA Axis mechanism etc. Therefore, this study aims to highlight how maternal stress hampers the neurobehavioral development of the fetus by reviewing various articles.

Keywords: Maternal stress, fetus, fetal brain development, maternal immune mediators, prenatal depression, pregnancy, fetal cognitive impairment.

Dedication

Dedicated to my parents

Acknowledgment

Firstly, I am grateful to almighty Allah for making me able to choose this field and study Pharmacy. Without His blessings, I would not be able to continue this project paper and submit it for passing my Bachelor's degree in Pharmacy.

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List of Acronyms

PS	Prenatal Stress
NE	Norepinephrine
E	Epinephrine
PMS	Premenstrual Syndrome
CRH	Corticotropin Releasing Hormone
FHR	Fetal Heart Rate
ACTH	Adreno-Corticotropic Hormone
HPA	Hypothalamic Pituitary Adrenal axis
MRI	Magnetic Resonance Imaging
IVH	Intraventricular Hemorrhage
TNF	Tissue Necrosis Factor
5-HT	5-hydroxytryptamine
11β-HSD-2	11β-hydroxysteroid dehydrogenase-2

Chapter 1
Introduction

Depression can be defined as a feeling of sorrow, deprivation, or frustration that interferes with the daily activities of an individual (Legg, 2020). The most prevalent medical conditions seen in primary care practice are depressive symptoms. Sadly, many occurrences of depression go unaddressed. National Institutes of Mental Health (NIMH) of United States studies indicate that about 70 % of patients are depressed and not treated for their sickness . In addition, most of the patients with depression who commit suicide have seen their private doctors, with the depression going unrecognized (Rakel, 1999).

Over the past few decades, the physical treatment of pregnant women in the modern world has changed significantly; yet, their psychological issues have not been considered the same manner. This is the most overlooked part of obstetric medicine, undoubtedly. It is essential for the betterment of the pregnant woman herself, and also for her future child. Significant evidence from several longitudinal studies indicates that if the mother is depressed, stressed, or exhausted during pregnancy, her child is more likely than other mothers' children to develop a variety of adverse neurodevelopmental effects. These involve an elevated risk of problems with emotion, behavior, and cognition. It is also observed that maternal depression may trigger lower birth weight for gestational age, induced hypertension, earlier delivery and pregnancy, and altered physical performance (Glover, 2014).

Moreover, scientists showed that nearly 25% of postnatal depression cases within women begin during pregnancy, and stress, anxiety can intensify at this time. Many experts showed little attention to the symptoms that can be seen physically because they did not desire to mortify the physical effects of pregnancy with symptoms of depression (such as lack of appetite, exhaustion, and insomnia). The 8th month of pregnancy and the first eight months after

childbirth were the highest rates of depression (British Medical Journal, 2017). For both mother and infant, ignoring depression during pregnancy may be dangerous. Women who are stressed also do not take care of themselves. They may drink to excess, smoke or lack proper nutrition. And some evidence has showed that stress may have direct effects on the fetus. The babies, with abnormal sleep schedules, are frequently frustrated and lethargic. With behavioral problems such as aggression, these newborns can develop into newborns who are emotionally unresponsive, slow learners and underweight (*Depression during Pregnancy and after*, 2017).

Depression endured by women during pregnancy is referred to as a prepartum depression. It is not only a feeling of sadness but also the mother can be anxious and angry (Wisner, 2020). Raging hormones play a vital role in triggering depression during pregnancy. The brain chemistry that regulates sentiments and mood is directly influenced by hormones. Prepartum depression may result from the same hormonal changes that cause the premenstrual emotional disorder. Research has found that women who suffer from prominent PMS are at higher risk during pregnancy for depression (Mazel, 2018). As every woman undergoes hormonal changes during pregnancy, that is unlikely the only reason to be depressed during pregnancy. Other key factors may cause depression in this case. For example, a family history of depression, domestic violence, a lack of support from friends or family, relationship problems, a recent traumatic life event, money problems, and so on (Guilbeault, 2020).

When people are nervous, their body secret hormones to cope with the elevated stress, such as corticotropin-releasing hormone (CRH), which leads to a rise in the stress hormone cortisol. This process continues throughout pregnancy, and the placenta, which provides nutrients to the fetus, can also release CRH which is a stress hormone. Consequently, a small quantity of this hormone finds its way into the amniotic fluid and is used by the fetus. Animal tests have shown that this hormone can help the unborn child develop normally: adverse growth conditions in the mother induce an increase in the secretion of hormone, raising the probability of survival

in the event of premature birth (Karaer et al., 2013). This increment, however, may have negative effects in some cases. This can result in an unnaturally rapid rate of growth at the cost of proper organ maturation (La Marca-Ghaemmaghami et al., 2017). Moreover, prepartum maternal depression can impair cognitive function during early childhood and triggers a decline in volume of brain in areas connected with memory and learning in 6 to 8 year old children (Sandman et al., 2012).

One of the main mechanisms present in stress response and control is the Hypothalamic–Pituitary Adrenal (HPA) axis. Many studies have proved that, perinatal maternal stress is related to increased cortisol levels of the mother throughout pregnancy, that can move between the placenta in adequate concentrations and raise cortisol concentration of the fetus (O'Donnell et al., 2009). However, pregnancy does not cause the HPA axis to be less susceptible to psychosocial stress in women. Furthermore, it was revealed that the young adult offspring of pregnant women who had been subjected to a traumatic event had a poor plasma cortisol but a elevated adrenocorticotropic hormone (ACTH) stress response than the unaffected community. As a consequence, the cortisol response to stress is variable among studies (Entringer et al., 2009).

Interestingly, the maternal modulators have impact on fetal brain development. The vertical transfer of immune and endocrine markers of mother are becoming more commonly accepted as a way to influence fetal neurodevelopment and offspring's potential mental wellbeing. The effect of cytokines on the brain development of the fetus has been extensively researched, and is generally agreed that cytokines modulate fetal brain development milestonesphysiologically. As a consequence, fetal brain growth could be compromised by an inconsistent cytokine response, raising the possibility of neurodevelopmental disorders (Bauer et al., 2007). Alike cytokines, in rodents and humans, exposure of fetus to high levels of parental glucocorticoids has been shown to have partly sex-specific and long-lasting impacts onneuronal morphology

and function of the offspring (Mychasiuk et al., 2012). Moreover, in humans, higher maternal cortisol levels during pregnancy have been related to greater amygdala volumes, impaired neural connectivity, as well as affective symptoms and adopting issues in girls (Claudia Buss, Davis, et al., 2012).

1.2 Aim

The aim of the study is to evaluate the effect of maternal depression, anxiety and stress on fetal neurobehavioral development. .

1.3 Objectives

The objectives of this study are:

i. to evaluate the mechanism of action of maternal distress to the fetal brain outcome.

ii. to evaluate the fetal neurobehavioral development due to maternal depression.

iii. to evaluate the after effect of maternal stress in the offspring's childhood.

Chapter 2
Methodology

To conduct this study, various search engines like journal articles and books have been used. Literature searches were completed by: PubMed, science direct, google scholar, nature, Elsevier, Mendeley, research gate, NCBI resources, Scopus which contains peer-reviewed articles. Various surveys were studied to gather information from these literature. Moreover, different books were gone through to include some basic information.

The keywords that we have used to search the relevant articles were: Maternal stress, fetus, fetal brain development, maternal immune mediators, prenatal depression, pregnancy, fetal cognitive impairment.

Chapter 3
Result and Discussion

3.1 Effect on infants due to maternal depression

It is really hard to say the correlation between the effects of chronic prenatal depression on the baby and child and the effects of continued maternal depression and anxiety, postpartum treatment, symptoms of paternal mood and other reasons (Pearlstein, 2015). Depression among pregnant women can affect infants. Children of depressive parents, a mixture of both genetic and environmental factors, are at an elevated risk of developing depression themselves (Rifkin-Graboi et al., 2013). The results of maternal stress correlate with significant changes in neurodevelopment in the fetus. Although low to moderate prepartum stress levels can increase fetal maturation and have an adaptive function, higher persistent stress contributes to negative neurodevelopmental results (DiPietro et al., 2006). Spatial learning and memory are affected by repeated prenatal manipulations, with an consequence that can be seen not only in puberty but also in later life (Richetto & Riva, 2014).

Furthermore, depression, stress and anxiety in pregnancy has been connected with numerous factors, both during pregnancy and in the postpartum period. Premature birth, postnatal complications, fetal growth restriction, and low birth weight have been linked with depression during pregnancy. Hypertension, preeclampsia, and gestational diabetes have also been associated with perinatal depression (Becker et al., 2016). Stress causes people to consume a high-fat, high-sugar diet, which can suppress the body's response to cortisol stimulation, leading to emotional and a higher risk of obesity and other metabolic disorders. Besides, the interaction between stress and depression and high-fat consumption intake can cause a pro-inflammatory response in women, which could facilitate modifications in the neuronal structure and connectivity of the offspring in the context of pregnancy (Lindsay et al., 2019).

A study has reported that depressed and stressed pregnant women had increased levels of prenatal cortisol and their fetuses were smaller and had slower rates of fetal development and lower birth weight. The depressed mothers had a 13% high rate of premature childbirth, and the low birth weight incidence of their neonates was 15 % higher (Field et al., 2006).

3.2 Physiological Mechanisms for Transmitting Maternal Distress to the Fetus

Several studies have shown that, maternal psychological distress trigger both maternal cardiac, respiratory and fetal heart rate and motion differences in baseline and research stimulatedreactivity of stress. Furthermore, it has been reported that, these physiological changes have been observed to largely independently of each other. There are few important associations between simultaneous FHR and movement and maternal autonomic interventions, with the irregularity of a slight correlation between elevated reactivity of skin conductance of mother and increment in movement of fetus (DiPietro et al., 2008), alsoa connection between blood pressure of mother and FHR (C. et al., 2004). Researchers have observed to theuterine functioningand HPA axis asthe conceivable ways through which maternal emotional state is transferred to the fetus.

3.2.1 Dysregulation of Fetal-Maternal HPA Axis

The hypothalamic–pituitary–adrenalaxis is often considered even as the vital controlling process for psychological discomfort (Tsigos & Chrousos, 1994). The principal modulator of the psychological distress hypothalamic–pituitary–adrenal axis is the corticotrophin-releasing hormone (CRH) that is mostly secreted into the hypothalamic-pituitary portal system by the hypothalamus. The portal delivers CRH into the pituitary gland anterior, activating corticotropes and releasingadreno-corticotropic hormone (ACTH) (Gold et al., 1998; King & Laplante, 2005; Mastorakos & Ilias, 2003). ACTH activates the ACTH receptors found in the

adrenal gland, allowing glucocorticoids to produce and release into the bloodstream, mainly cortisol. Cortisol generatesphysiological responses, for example, elevated heart rate and blood pressure, also down-regulation of CRH hypothalamic secretion (Gold et al., 1998). Moreover, throughout the pregnancy the placenta gets induced and secrets Corticotropin-releasing hormone into the bloodstream, triggering HPA axis hyperactivation. Moreover, in this stage a major increase in the ratio of free/bound cortisol occurs and reaches standards similar to those seen in Cushing's disease. In the period of the 2nd trimester, CRH of placenta development and the occurrence of excess cortisol begin and upraise linearly in a manner, with a spike in the last 6-8 weeks of pregnancy. This perinatal control of the HPA axis is shown in Fig. 3.1. The figure specifies that cortisol responses to acute stress declines as pregnant women undergo gestation, showing the HPA axis blunting because of elevated stages of placental CRH. In humans, a barrier to maternal glucocorticoids is created by the 16th gestational week of the 11β-HSD-2 enzyme of placenta, which helps the cortisol transforming into cortisone which is inactive.

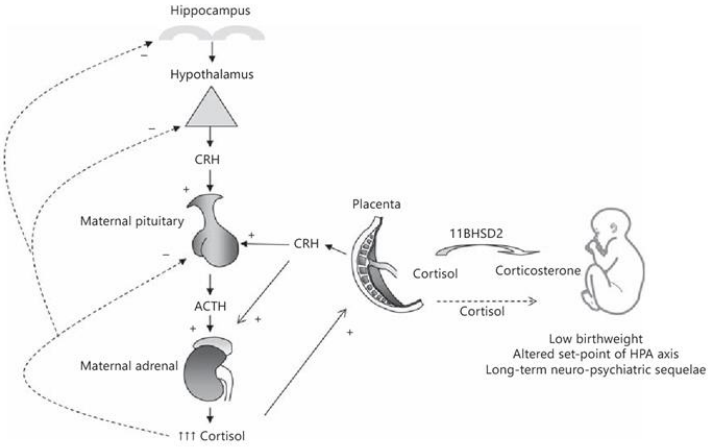

Figure 3.1:Prenatal HPA axis regulation (Duthie & Reynolds, 2013)

Nevertheless, 10 to 20% of maternal cortisol travels across to the fetus, which can be enough to induce long-lasting impact on fetal growth of brain. The mechanism of this effect lies under

the circumstances of stress-induced increased HPA activity of the mother (Kinsella & Monk, 2009).

In the psychiatric studies, increased HPA axis reactivity is usually observed in the neurobiology of stress and other psychiatric disorders (Heim et al., 2004). The connection has been less reliable during pregnancy. It was recently discovered that women who are pregnant having anxiety did not predict amniotic fluid cortisol and after 17 weeks of gestation, the modest connection between maternal anxiety and plasma cortisol is no longer observable, possibly because of the HPA axis hypercortisolemia in last phases of pregnancy (Sarkar et al., 2008). Nonetheless, another study from the same laboratory found that after 18 weeks of gestation, maternal amniotic fluid cortisol and plasma are associated. In this state of anxiety after amniocentesis together over several trimesters observed the association between maternal plasma and amniotic fluid cortisol. This proves that a clear optimistic relationship exists for extremely anxious women. These results indicate that placental function may be impaired by antenatal anxiety and which in turn influences exposure of the fetus to maternal cortisol. In a different study, higher self-reported stress scores were correlated with elevated levels of ACTH and cortisol after 28 weeks (Wadhwa et al., 2001). Compared to safety controls, we have established that 3rd trimester women who are co-morbid for anxiety and depression have greater level of cortisol as well as those with only one psychiatric condition (Evans et al., 2008).

During exposure of women to stress, parental cortisol gets positively correlated with greater fetal heart rate. Moreover, maternal CRH level has been shown to have a linear relationship between women in 31 to 32 weeks of gestation with baseline FHR, on the other hand the opposite is shown to habituate to an abdominal vibrio acoustic stimulation in FHR time (Sandman et al., 1999). Incidentally, the correlation with FHR is not demonstrated by ACTH. In maternal plasma, however, dysfunctional and separable levels of β-endorphin and ACTH influenced increases in FHR (Sandman et al., 2003).

3.2.2 Uterine Artery Resistance

The modification of the blood flow to the fetus by the uterine arteries is one more mechanism through which the psychological state of the mother can influence the fetus. Utilizing the color Doppler ultrasound to assess resistance of uterine artery and to identify the existence of notches in the waveform pattern of the ultrasound, uterine blood flow may be evaluated. The existence of a notch signifies very high blood flow resistance. Assessments of elevated resistance of uterine artery has been confederated with lower weight for gestational babies and maternal pre-eclampsia (Harrington et al., 1996)

With only two contradictory reports, this possible maternal-fetal psychological mechanism remains relatively unstudied. Uterine artery resistance within women who experience stress versus controls at 32 weeks of gestation has been found. Among both maximal artery resistance scores and mean artery resistance and stress levels, an important positive correlation was found (Teixeira et al., 1999). There is also an important dichotomous association between women with high anxiety and the occurrence of the waveform notching (Kent et al., 2002).

Although the HPA axis may be implicated in developing resistance to the uterine artery, noradrenaline has been suggested to be a possible mediator of sympathetic-adrenal activation (Teixeira et al., 1999). In a research, Starkman has found a linear association between the concentration of anxiety and noradrenaline plasma. Animal research has related levels of noradrenaline and reduced blood flow to the uterus. There is a need for further studies on this relationship using a larger body of psychological, neuroendocrine andphysiological measurements.

3.3 Influence of maternal stress, anxiety and depression on fetal neurobehavioral development:

Different human research indicates that manifestation of the evolving brain to an extreme and elongated maternal stress can lead to impaired mood-related andcognition disorders (King & Laplante, 2005; Wadhwa, 2005; Weinstock, 2008). Stressful activities may, in specific, raise maternal stress hormone concentrations, such as placental CRH and cortisol, which in turn may modify the growth and development of the brain of fetus and reprogram hypothalamus-pituitary-adrenal axis of the fetus (Weinstock, 2008).

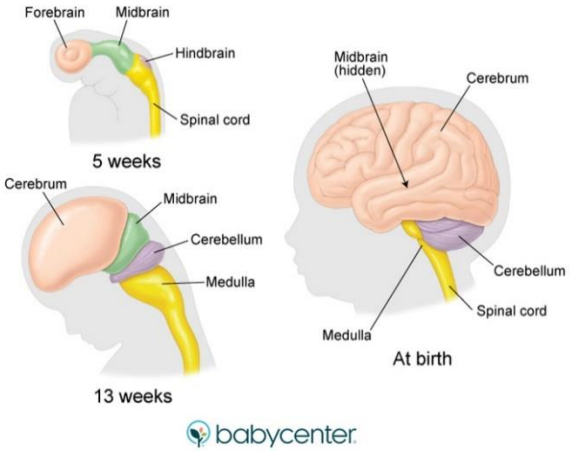

Figure 3.2:Fetal Brain Development (Scogna, 2018)

The prepartum phase is the crucial time for neuronal development and therefore it is a time of uncertainty throughout which a variety of aspects have been identified to influence long lasting changes in brain development and actions with physical and mental health implications. For instance, intake of essential fatty acids during pregnancy is associated with low birthweight and decreases in motor and cognitive function, while neurocognitive deficits are associated with exposure of fetus to methylmercury and PCBs via seafood in women's diets (Perera et al., 2006).

3.4 Changes in fetal brain structure due to maternal stress

Maternal exposure during pregnancy to acute psychosocial stressors can have detrimental effects on fetal and child neurodevelopment, including delayed behavioral and motor development, challenging temperament, and diminished cognitive performance (Sandman et al., 2012). Stress-related changes in brain structure and communication are thought to be the underlying causes for these effects. Recent studies have shown that the maternal emotional state during pregnancy and changes in the brain development of the offspring are closely related. In the early second trimester of pregnancy, infants born to mothers who endured elevated levels of anxiety had region-specific declines in volume of gray matter and decreased executive function in middle childhood. In susceptible offspring, prenatal stress affects multiple brain areas, including the hippocampus, amygdala, cerebral cortex and cerebellum (Claudia Buss, Entringer, et al., 2012).

3.4.1 Fetal Hippocampus

The development of the hippocampus plays a vital part in the cognitive system of learning and memory. The hippocampal development is sensitive to hypoxic-ischemic insult, metabolic distress, stress and undernutrition during its formation in utero. Hippocampal growth damage or deficiency can be a contributor to the neurodevelopmental burden of affected individuals. Indeed, declines in hippocampal volume in older premature children have been correlated with decreased memory and learning (Jacob et al., 2011).

A study about the prenatal and postnatal maternal stress and hippocampal growth of offspring during the first 6 months of life demonstrated that bilateral hippocampal volume at birth was not impacted by prenatal anxiety. Rather, during the first six months of life, mothers reported elevated anxiety throughout pregnancy and showed slower development of both the left and right hippocampus of their child. Therefore, because of higher postnatal anxiety, the right hippocampal growth is stimulated, although antenatal anxiety restricts it. Nevertheless, the left

hippocampal volume is probable to reflect the effect of exposure to perinatal anxiety during early development. In favor of a significant neuroanatomical theory of anxiety, it will appear as concrete proof, that formation of hippocampus is critical due to the development of maternal anxiety (Qiu et al., 2013).

3.4.2 Effect of depressed fetal Amygdala in adolescent period

The amygdala is the region of the brain that works to regulate mood disorders through stress reactivity and vulnerability. Various studies using structural magnetic resonance imaging (MRI) have shown that in adolescents and adults suffering with major depressive disorder, the amygdala is bigger in size. Furthermore, in patients with severe depression, functional MRI studies have shown hyperactivation of the amygdala (*Maternal Depression and the Fetal Brain (Amygdala)*, 2015).

The amygdala contains multiple nuclei, along with the lateral, basolateral, cortical, central, basomedial, medial, and basomedial nuclei of the amygdala. In PS-exposed offspring, the quantity of the neurons by 49%, the size of the lateral amygdal nucleus increased by 30%, its glial cells by 43% and its density of neurons by 22% compared to normal offspring at postnatal time (Salm et al., 2004). From different animal model studies it has found that, as no alterations are studied for the centralor basolateral, dorsal endopiriform or medial amygdalar nuclei, postpartum volume increase arises exclusively for the lateral amygdalar nucleus (Salm et al., 2004). This means that prenatal stress can not modify the developmental trajectory of all nuclei ofthe amygdala similarly. In the lateral amygdal nucleus, a reduced volume and quantity of glial cells and neurons are found during the early postnatal developmental stages, while there is an increased volume and number of neurons and glial cells in this nucleus compared to control animals during the subsequent developmental stages (Charil et al., 2010).

3.4.3 Effect on fetal Cerebral Cortex

The cerebral cortex comprises of a hemisphere on the right and left, and lies on head of the limbic system.The cerebral cortex includes the temporal lobe (for hearing, communication and social interaction), the parietal lobe (for bodily sensations like pain, pressure, heat and cold) the frontal lobe (for learning, personality, planning and problem solving), and occipital lobe (for vision). The brain development of the offspring starts when it is in the mother's womb. Furthermore, nerve connections are formed in the first trimester, allowing the fetus to travel around in the womb, while in the second trimester other brain tissue and nerve connections are developed. The cerebral cortex begins to develop from the stem of the brain in the third trimester, enabling the fetus for future learning (Australia, 2021).

The cerebral cortex is the outer layer of the brain structure that is consist of gray matter. In a greater group of first time mothers by comparing to a sample of nulliparous females, a current longitudinal MRI study analyzed gray matter modifications before and after birth. Women who are pregnant reported greater declines in the gray matter from the beginning of pre-conception to post-birth sessions compared with nulliparous women, primarily in the posterior and anterior cortical midline and parts of the prefrontal and bilateral cortex. However, this alteration in the gray matter can potentially be beneficial if it represents neurobiological pruning. In addition, changes in gray matter volume over pregnancy were correlated with the self-reported relation of mothers to their child in the postpartum period (Hoekzema et al., 2017). Also, there is evolving indication of continuing structural modifications linked with the number of children birthed (e.g. optimisticconnections between parity and brain structures) in a sample a long way of the prepartum period (De Lange et al., 2019). Combindly,all these outcomes showed that improvements in certain human brain structures are associated with pregnancy and child rearing. Some of these improvements can be persistent, while others can revert to the size of pre-pregnancy (Cárdenas et al., 2020).

3.4.4 Effect on fetal Cerebellum

The cerebellum, which precedes most brain structures of human and develops quickly all through the 2nd half of pregnancy, arises from 6 weeks of gestational age (GA) onwards(Chang et al., 2000). An elevated risk for development of neuronal disability is correlated with fetal cerebellar changes and injury(Shevelkin et al., 2014). MRI studies have recently shown the association between decreased cerebellar diameter and undesirable neurodevelopmental outcomes in young children, including overall motor control, behavioral development and severe neurological impairment(Park et al., 2014; Spittle et al., 2010).

In preterm infants, cerebellar damage is gradually recognized as a problem, but the importance of decreased volume of cerebellum in the preterm population and subsequent neuronal development is less evident. In precise, current stats of reduced volumes of cerebellum in children with spastic diplegic cerebral paralysis have been observed, further supporting the view that cerebellar development is impaired by motor dysfunction (Kułak et al., 2016). This research shows that the decrease in diameter of cerebellum in term predicts future motor issues at the age of 3 months. There are records of decreased cerebellar volumes in preterm infants.

It is recorded that premature children have decreased cerebellar volumes relative to children born at term (Shah et al., 2006), continuing into adolescence (Parker et al., 2008). In a recent study, however, researchers observed that infants with decreased cerebellar volumes are at an greater risk of irregular general movements at three months, even when the abnormality of white matter and IVH were responsible for, promoting a major correlation for very preterm infants between the cerebellum and general movement quality. Due to the white matter irregularities which can be found on MRI so early in the neonatal period, premature children are at higher risk of a wide variety of developmental difficulties (Spittle et al., 2010).

3.5 Maternal modulators effect on fetal brain development

Definitive proof has been given by human and animal studies that chronic activation of microglial cells (Wohleb et al., 2012) induces mood disorders (Czeh et al., 2011) by the release of different neurotoxins, pro-inflammatory cytokines and chemokines (Rosenblat et al., 2014), inducing neuronal malfunction or aggravating underlying pathology (Venneti et al., 2013). Cytokine concentration changes as pregnancy progresses. In the last weeks of pregnancy, pro-inflammatory cytokines appear to elevate, whereas anti-inflammatory cytokines give a contradictory profile (Snegovskikh et al., 2006). Many authors have proposed that cytokines associated with Th1 show anessentialpart in subjects who have both depression and anxiety during pregnancy. Moreover, numerous studies have thoroughly reported that increment of inflammatory biomarkers in non-pregnant womenis correlated with psychosocial stress and depressive symptoms (Coussons-Read et al., 2007; Raison, 2014).

There are many mechanisms by which the fetal brain can be affected by psychosocial stressors in the mother. Increased cytokine levels will cross the barrier of the placenta and induce a neuro-inflammatory immune response of the fetus. Abnormal level of 5HT homeostasis can affect neuronal development. To defend the fetus from extreme maternal cortisol,released throughout acute phases of maternal stress, the enzyme of the placenta (11β-HSD-2) breaks high cortisol that inactivatesmaternal cortisolby 80-90% until it reaches the fetus.It can also disrupt this negative feedback mechanism during increased periods of stress, particularly at higher levels of cortisol and CRH that can interrupt the regulation of the fetal HPA axis. Through the excitotoxic andapoptotic effect of ROS on nerve tissue, oxidative stress can influence brain growth. Finally, stress alters the vaginal microbiota that can damage the growing gut-brain axis at an primary level, causing the neurobehavioral changes of offspring (Rege & Graham, 2020).

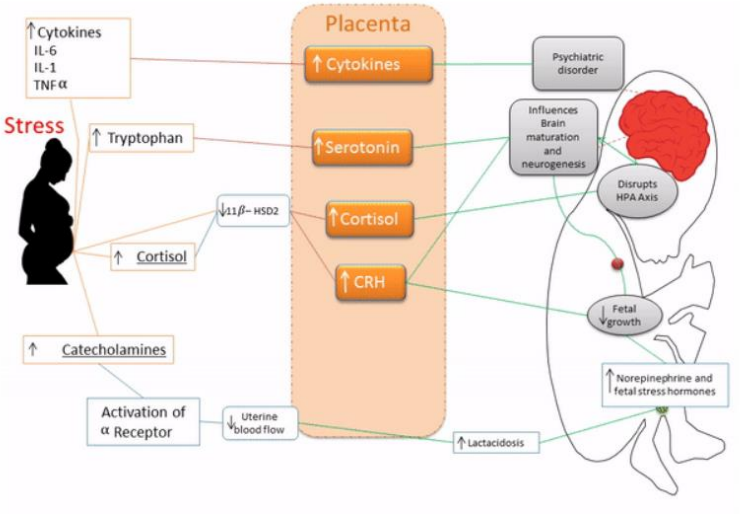

Figure 3.3: Different mediators effect on fetal brain development (Rege & Graham, 2020)

3.5.1 Effect of depressed/stressed maternal Cortisol on fetus

Increased levels of maternal endogenous cortisol (Zijlmans et al., 2015) have often been correlated with prenatal maternal stress. The hormone cortisol plays a significant role in healthy fetal development (Munck et al., 1984). The frequency of maternal cortisol rises by two to four times during pregnancy (Mastorakos & Ilias, 2003). This increment has a beneficial impact on the development of neurons (Kapoor et al., 2006). The HPA axis is stimulated by prenatal distress and cortisol is synthesized and released by adrenal cortex. Cortisol is strongly lipophilic and can enter fetus through the placental barrier. Researchers found that until the third trimester, the fetus still depends on the maternal cortisol, after which point it can then generate its own. There is an enzyme of the placenta (11β-HSD-2) that disables maternal cortisol by 80-90 % before it reaches the fetus, although the fetus depends on the mother for cortisol throughout gestation. This is to defend the fetus during acute periods of maternal stress from elevated maternal cortisol (Van Den Bergh et al., 2008).

However, as a result of neurotoxicity, exposure of fetus to excessive maternal cortisol can cause impaired brain development (Bruschettini et al., 2006; Uno et al., 1990). Animal studies have

determined that prenatal stress exposure triggered a substantial increase in the secretion of maternal cortisol by stimulating the maternal HPA axis. Once within the fetus, by resetting the negative feedback system of the fetus to its own cortisol development, excessive maternal cortisol will damage the fetal HPA axis. This can occur serious damage that in adulthood can establish impaired behavioral phenotype (Van Den Bergh et al., 2008).

3.5.2 Effect of depressed/stressed maternal Catecholamine on fetus

Not only by cortisol, but also through catecholamine-dependent pathways, maternal psychosocial stress is conveyed to the fetus. While catecholamine do not cross the placenta in significant quantities under physiological conditions, endogenous release of catecholamine induced by maternal stress can decrease uterine blood flow. As a result, fetal stress and a change in fetal metabolism towards an anaerobic metabolic state can be caused by decreased uterine perfusion.The adrenal medulla of sympathetic nervous system which controls the secretion of epinephrine (E) and norepinephrine (NE) from the adrenal medulla, is stimulated by psychological stress.

Furthermore, it is reported that catecholamine facilitate short-term metabolic, immunological and behavioral responses to stressors in the environment. Catecholamines are hydrophilic and do not readily pass the placenta, apparently. However, excessive catecholamine through indirect interactions can disrupt fetal neuronal development. Researchers have proposed that alpha-adrenergic receptors that in the uterus and placenta constrict blood vessels, can be activated by NE and E (Levine et al., 2016).Mental stress and corresponding increased vascular tone decrease the umbilical blood flow in the uterus and placenta, i.e. decreaseduteroplacental perfusion. The influence of maternal catecholamine on uteroplacental perfusion may delay fetal development and even lead to premature birth (Rege & Graham, 2020).

3.5.3 Effect of depressed/stressed maternal Cytokine on fetus

It has been proven that mental stress is associated with a higher risk of prenatal infections. The immune system of the fetus can be modified by these infections through the release of maternal immune system modifiers known as cytokines (Rege & Graham, 2020).The over-expression of pro-inflammatory cytokines, mainly TNF and IL-1β, is a significant mechanism by which glial cells contribute to pathological processes (Paraschivescu, 2020). In addition to being almost related to reactive oxygen species (ROS) and oxidative stress, cytokines play a significant role in inducing or suppressing inflammation. Cytokines can move over the placenta and go into the bloodstream of the fetus, where they caninteract directly with fetal immune system cells (Rege & Graham, 2020).

Numerous studies have shown that cytokines, with mostly detrimental effects, can regulate brain function and behavior. In particular, cytokines can cause anxiety, nausea, depression and impaired cognitive processes (Paraschivescu, 2020). Stress-induced maternal inflammation can play a role in causing the stimulation of pro-inflammatory genes of placenta to lead to modifications in the developing immune system of the fetus. This involves impaired expression of gene in the hippocampus of fetus where reduced cognitive ability, excess body weight and declined insulin sensitivity in the later life of an offspring are associated (Samuelsson et al., 2006).

3.6 After-effect of maternal stress in the offspring's childhood

The emotional state of the mother during pregnancy will influence the brain development of the infant. This is because of "fetal programming," where the growth of the fetus can be altered by a shifting environment in the womb over various sensitive phases. In the longer term and also into adulthood, thesechanges can also interrupt in the development of the child (Glover, 2014). Many studies have examined neurodevelopmental and psychopathological results.

Some investigators have focused on the newborns of mothers who experience stress during pregnancy and found a poorer outcome on the Neonatal Behavioral Evaluation Scale compared to newborns of mothers who do not experience stress during pregnancy (Buitelaar et al., 2003), indicating that adverse behavioral effects seem to be from the very beginning. Studies of infants and toddlers have shown them to have a more difficult temperament, sleep issues (O'Connor et al., 2007), and poorer cognitive ability and elevated fearfulness linked to higher maternal stress during pregnancy (Bergman et al., 2007).

3.6.1 Impaired cognitive development

Stress related to pregnancy can affect the development of the brain of the fetus even more than general stress (C. Buss et al., 2011). The cognitive functioning may be impaired by a decrease in the grey matter of the prefrontal cortex (Andiarena et al., 2017; C. Buss et al., 2011). The growth of cognitive abilities may be influenced by this. Studies of the relationship between stress during pregnancy and long-term cognitive growth have shown that an abundance of cortisol in the brain of fetus can cause significant harm to myelin sheaths in the central nervous system, causing issues associated with poor cognitive growthin the period of adolescence. In particular, this relationship was stronger when, between 12-22 weeks of pregnancy, the mother encountered greater levels of anxiety, but not after that time (Van den Bergh et al., 2020).

3.6.2 Abnormal Behavior

Anatomical and functional changes related to behavioral changes, future behavioral disorders and the development of anxiety during pre-adolescence can be triggered by acute stress during pregnancy. The influence of this stress on behavior depends on the duration of pregnancy, the severity of pregnancy, and often on the sex of the fetus (Hamada & Matthews, 2019). In relation to the most sensitive time of pregnancy, each research demonstrates different results: on the one hand, many studies say that at the beginning it should haveoccurred; but on the contrary, other studies suggest that when it occurs in the last trimester, there will be further alterations

(Werner et al., 2013). There are also minor sex-specific variations, enlightening that boys aremore likely to experience from emotional and hyperactivity issues but the girls are more likely to experience emotional problems (Sejbaek et al., 2020).

3.6.3 Impaired learning and memory ability of fetus

A connection is identified between maternal depression and changes in memory and learning capabilities, as elevated cortisol levels can disrupt the fetal hippocampus, reducing neurogenesis and neuronal density (Richetto & Riva, 2014). Some researchers have revealed that memory modifications may have a greater effect on girls, whereas boys can show advances in math and reading skills (Hamada & Matthews, 2019). From different researches the connection between this depression and visuospatial memory, it was determined that both boys and girls may be influenced by this kind of memory (C. Buss et al., 2011).

3.6.4 Impaired motor development of fetus

Some authors found that increased cortisol levels found in the hair of pregnant women during the first and second trimesters of pregnancy may be connected with decreased fetal growth of motor. This may be because of the impact on the cerebellar function of glucocorticoids. In addition, in some instances, sex-specific variations were observed, with girls being more impacted than boys (Andiarena et al., 2017).

3.6.5 Dysfunctional Fetal Temperament

From a study it has found that, changes of temperament in children were mostly allied with the mental stress observed in the mother, however not that much to plasma cortisol levels. Elevated levels of stress could also support the growth of a dysfunctional temperament with maladaptive difficulties and negative humor (Blair et al., 2011).

Chapter 4
Conclusion

4.1 Conclusion

To conclude it can be stated that, the mental health of pregnant women greatly affects the neurobehavioural development of the infant, even these have a long-term effect on the child. Moreover, for less common occurrences, for example, gestational diabetes during pregnancy, women are regularly called for checkups but often this depression, stress, anxiety of pregnant women are overlooked by the physicians (Kinsella & Monk, 2009). Not only the doctors but also the patients think that these psychiatric disorders are normal and can happen due to hormonal changes which are inappropriate. Very few people have the idea regarding the effect of maternal stress on the fetus.

Moreover, antenatal stress affects multiple parts of the fetus brain, including the hippocampus, amygdala, corpus callosum, neocortex, cerebellum, and hypothalamus, most frequently leading to lower volumes of tissue. Both at the microscopic and macroscopic level, these changes are apparent (Charil et al., 2010). Because of the changes in the different regions of the brain, after birth, the infant has impaired neurobehavioural and cognitive functions.

Furthermore, it has only just begun to discover the processes underlying such fetal programming and, sometimes, a weak association between psychometric and biological ones. A study is also needed to determine which interruption during pregnancyis most successful in improving the outcomes of children. To identify and treat mental issues and conditions during pregnancy, more research must be done. This will favor the woman herself, and the next generation will also benefit eventually (Glover, 2014).

Finally, it can be stated that maternal depression, anxiety, and stress can directly or indirectly influence neurobehavioral fetal development. Maternal distress can affect different sectors of neuronal development. However, not only neurodevelopment can be impaired but also premature birth and low birth weight can happen. As we know there are few studies regarding maternal stress during pregnancy, hence further studies are needed to understand the mechanism and neurobehavioural development of the infant more clearly.

4.2 Limitations of the study

Few limitations were confronted while conducting the study. Some limitations of the study are given below:

1. Some of the information was collected from resources that are not recent.
2. Moreover, information in the context of Bangladesh was not available regarding prenatal maternal depression.

4.3 Future Research Plan

Future research could be done by animal and human studies on fetal brain development as there are very few studies about maternal stress on the neurobehavioral development of the fetus. Moreover, to widen the area of research other fetal outcomes, for instance, low birth weight, impaired heart condition,etc due to maternal stress can be focused on.

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