Association of Ante-natal Depression with Fetal Outcome: A review

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Declaration

It is hereby declared that

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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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Approval

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Ethics Statement

This study does not include any animals or human trails.

Abstract

Antenatal depression is the most prevalent mental health disorder among pregnant mothers which is at the same time, least addressed. If left untreated, antenatal depression can have various potentially harmful outcome on the growing fetus and can also have long term impacts on the children in later lives. The aim of this review is to assess how antepartum exposure to untreated maternal depression affects fetus both in the long-term and short-term. The stressed mother may release hormones that can be damaging to the fetus and cause it to have a reduced immunity, malnourishment and have an impaired neuro development. The consequences of this may cause the child to have learning and cognitive disability. The child in later life may also develop other mental health disorders such as ADHD, schizophrenia, anxiety and depression. However, limited data are available to comprehend the rationale of these effects on the fetus. Researchers should put more importance into finding out the etiology of this disease and reach towards the treatment strategies.

Keywords: Pregnancy; Fetal; Prenatal depression; Prenatal anxiety; Antenatal depression

Dedication

Dedicated to all the mothers and their unconditional love.

Acknowledgement

I would first like to thank the Almighty for all His blessings, which helped me throughout the journey.

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List of Acronyms

WHO	World Health Organization
ADHD	Attention Deficit Hyperactivity Disorder
BMI	Body Mass Index
PTSD	Post-Traumatic Stress Disorder
FHR	Fetal Heart Rate
HPA	Hypothalamus-pituitary-adrenal
NE	Norepinephrine
E	Epinephrine
UPP	Utero-placental perfusion
ANS	Autonomic nervous systems
SNS	Sympathetic Nervous System
IRS	Insulin Receptor Substrate

Chapter 1

Introduction

According to facts, pregnancy is a joyful and life-changing experience in women's life. However, in some cases it goes the opposite. The WHO (World Health Organization) definition of mental health (Atif Rahman et al., 2008) defines it as a state of well-being that includes changes in lifestyles, in which mothers will realize their own capacities, can effectively deal with the stress of the situation, can work productively, and are capable of contributing to their society (Prince et al., 2007). This vast definition is important in comprehending the cognitive and emotional abilities of mothers who are capable of assessing and responding to the needs of their infants. It is evident that to be mentally well, it does not mean that one is without mental illness. We fixate on maternal depression as the most prevalent and fundamental risk factor, because maternal depressive disorders are at a higher rate compared to other mental disorders, and linking them to adverse child outcomes has the most robust evidence (Aktar et al., 2019).

When carrying a child, woman's body adapts to her role as mother. Many pregnant women have trouble dealing with stress and anxiety due to the hormonal changes they experience during pregnancy (Coussons-Read, 2013). Post-natal depression has significantly gained importance while antenatal depression is still a taboo (Shrivastava et al., 2015). Pregnant women often experience antenatal depression, which is the depression that they experience during the nine months of pregnancy. Depression during pregnancy can have serious effect on mother and child as well. It is estimated that 20% of pregnant women in high-income countries experience antenatal depression, whereas above 20% of prenatally depressed women are in low-income countries (Biaggi et al., 2016). It is found that during the first trimester 11 percent of antenatal depression occurs and then decreases to 8.5 percent in second and third trimester (Gavin et al., 2005).

The mental disorder, depression, is the most likely occurring disease, as listed by the World Health Organization (WHO) (Coronavirus Disease (COVID-19). Depression has an impact on 6% of the world population in general and 10-15% of pregnant women suffers from depression after giving birth or while pregnancy (Cattane, Räikkönen, et al., 2020). Depression is also the number-one environmental cause of disability for women (Kessler, 2003). A great number of surveys have shown that depression and anxiety are of greater frequency in the developing world where they are said to occur at 25% male and 66% female (Mirzaei et al., 2019).

Its classification would include an emotion of negative self, inferiority, defilement and difficulty coping, lack of trust, prolonged feeling of sorrow, irritability, bad emotions and anxiety manifestations, more likely to overthink the infant's health issues and being fatigue, (Pitt, 1968) along with lack of appetite, sleeplessness, or weight gain (Robertson et al., n.d.). In untreated maternal depression, the emotional and cognitive functioning of a mother is impaired. They become less responsive, miscommunicate and an increase in hostility is observed in them. It has an effect as a caregiver and it provokes an influence on parenting skills (Lovejoy et al., 2000). Depressed mothers might experience challenges while performing household chores and mood disorders which can affect a person's quality of life (Pitt & Cox, 1968; Cox, 1986). Moreover, the unwelcome signs, signals, and portents have a devastating impact on the advancement of the child and family (Patel et al., 2002). The mothers who have this disease often display other signs of depression, such as feeling unrelated and sometimes passive, as well as being intrusive and demanding.

As a result of antenatal depression, mothers have been unable to meet their children's needs. In previous studies, it was found that exposure to maternal depression can result in a number of adverse effects on the child's physical and psychological state, but also a considerably higher threat of obesity during childhood and adolescence can result from prolonged exposure to maternal depression (Suarez et al., 2018). Depression in pregnancy can lead to cognitive

deficits in children, emotional maladjustment, psychiatric disorders, and physical problems later in life (Slomian et al., 2019). The consequences of maternal depression often extend into the lifespan of the offspring and can be observed throughout childhood, teenage years, and adult years.

Regardless, depression during pregnancy is misdiagnosed frequently as symptoms can be confused with women's normal hormonal fluctuation (Gordon et al., 2015). Unfortunately, pregnant women tend not to receive enough attention on mental, spiritual, and cultural aspects of health. Another concerning problem is that many pregnant women do not receive treatment for depression while they are expecting. Physical health issues during pregnancy are dealt with promptly but the mental health of pregnant women is often disregarded (Jalali et al., 2020).

1.1 Aim of study

The aim of this review is to assess how antepartum exposure to untreated maternal depression affects fetus and the impacts on the fetal psychological and physical health both in the long-term and short-term.

1.2 Objectives

- To find out the probable effects of antepartum exposure to untreated maternal depression on fetus.
- To evaluate the negative impacts of antenatal depression on the fetal health.
- To explain the possible mechanism of action of antenatal depression on the fetus.

Chapter 2

Methodology

This study was conducted by reviewing PubMed, Elsevier, ResearchGate, Nature (1990–2020) for relevant literature, searching for relevant information with keywords ‘pregnancy', ‘neonate', ‘fetal’, ‘prenatal depression’, ‘prenatal anxiety', ‘antenatal depression' in addition to articles relevant to the research. The review paper discusses the various effects of maternal depression on the fetus and the mechanism associated with it. The information from these articles were retrieved manually. Besides, the sources of the information were cited using the software, Mendeley.

Chapter 3

Result and Discussion

Stress represents a standardized term that can be acute and chronic for a variety of diverse exposure types. It is characterized in various ways and one of those ways it could mediate biologically as well. However, no particular biological parameters, high cortisol formation for example, have been found to be associated with the kinds of prenatal stressors involved with the impaired output, that have been found to be on the child (Entringer et al., 2015). It has also been recommended that moderate stress may have various impacts than more significant stresses (DiPietro et al., 2006). Stressors which have been shown to be involved with disrupted effects on children vary from very extreme stresses, such personal stress factors, to quite mild stresses, such as the death of an older child. Included signs of anxiety and depression experienced by the mother, as well as depression diagnosis, anxiety particular to pregnancy and day-to-day anxiety, deprivation and stress caused by poor partner relationships.

In about 6–13% of pregnant women, depression occurs (Grigoriadis et al., 2013). The exposure to antenatal depression is associated with important health consequences such as pre-term birth and low birth weight (Jarde et al., 2016b). Some of the factors of these consequences are found in developed countries such as the United States and Australia, with one in every ten babies are born premature. Pre-term birth and low birth weight are two severe symptoms that can cause death in newborns (Mochache et al., 2018). In addition, other premature infants who thrive, pre-term birth can also result in several recurrent neurodevelopmental disabilities and health problems (Dadi et al., 2020)(Chawanpaiboon et al., 2019). It may lead in a disproportionally large amount of money required to care for the premature infant compared to that of the total costs of neonatal care and living with long-term medical costs for the family and health system alike (Bauer et al., 2016).

The fetus born from a mother suffering from antenatal depression may have greater risk for the disease which includes mental and emotional disturbances, brain alterations and the progression of metabolic disorders (Sharmin et al., 2019). Symptoms of depression in women seem to have an unfortunate outcome on the engagement of the woman with the child (Field et al., 2004). It was found that some women with depressive symptoms have increased difficulties in developing a loving relationship with their infants and expressed the apparent lack of compassion, indifference, negligence as well as impulses to harm the infants (Lutkiewicz et al., 2020). Evidently, it has been found that a significant portion of new mothers are diagnosed with postnatal depression, and investigations done by Brockington et al. (2001) seems to point to evidence of disturbances in mother-infant bonding. Beyond this, several studies show that children of a depressed mother have a higher probability of having a cognitive functioning problem, psychic functioning problem and emotional functioning problem throughout their whole development (Murray, 1992).

Previous study has shown that maternal depression is associated with children's growth potential. During pregnancy increased psychosocial stress has been associated with negative children's developmental outcomes, such as low birth weight and shorter gestation duration, decreased neonatal focus, and elevated incidence of attention deficit hyperactivity disorder (ADHD), psychosis, impaired speech and social deformities. It has been shown that children of depressed mothers are at elevated risk of stunted growth and are malnourished in developing countries (Surkan et al., 2012) (Murray & Stein, 1989). Added research has found that stress in pregnancy is associated to a variety of physical and physiological difficulties. For example- fingerprints that have been modified, reduced mixing of hand preference, reduced density in specific brain areas, and increased use of other drugs and alcohol (Buss et al., 2010).

Even though psychiatric disorders in expectant mothers have been associated with post-partum depression in the past, existing studies have indicated a higher incidence of mental disturbance

during pregnancy. It is fairly similar to the occurrence of mood disorders in women of similar age who are not pregnant, about 14%, with an increasing number of mental illness among pregnant women. It occurs 7.4% in the first trimester, 12.8% in the second trimester and 12.0% in the third trimester, along with 7.7% of PTSD instances, as well as other mental illnesses (6.6%). (Andersson et al., 2003). Expecting women who are suffering from anxiety and depression might stay stable through all stages of pregnancy and while on pregnancy. However, emotional problems during pregnancy are a direct signal that the mother might experience postpartum depression (Sutter-Dallay et al., 2004). Therefore, it is very essential that not only the developed countries but also developing countries take maternal depression into account. The consequences of maternal mental health could be majorly detrimental to children's mental health during their childhood (McGrath et al., 2008).

The Effects of Antenatal Depression on Fetus

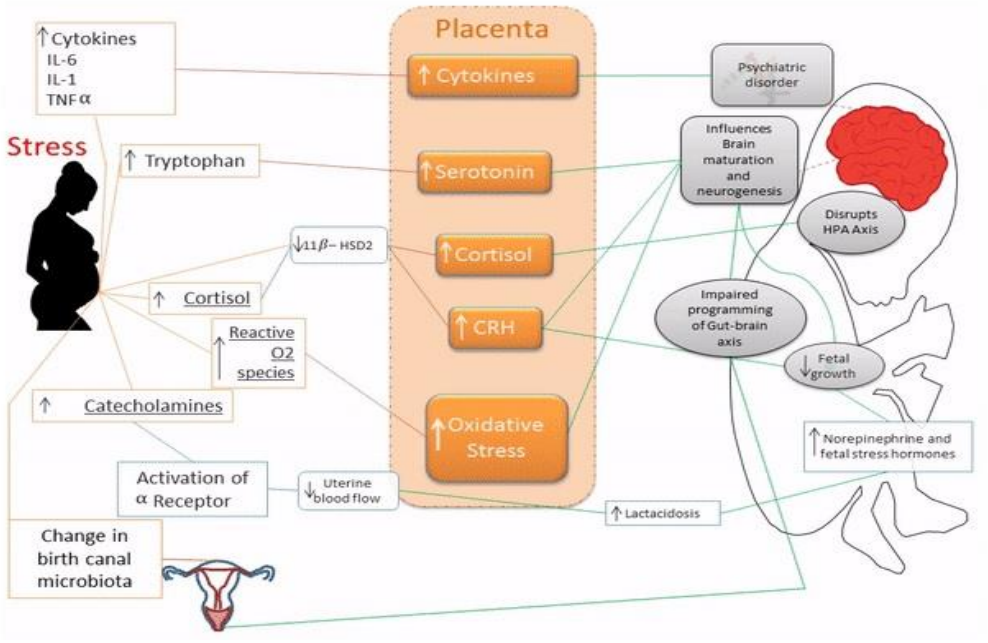

Figure1: Effect of maternal stress on fetal development (The Impact of Maternal Stress on the Fetal Brain - Key Mechanisms)

Prenatal stress causes an increase in the level of cytokines which passes through the placenta and affects the growing fetus. It triggers the immune response of the fetus and can cause

neuroinflammation (Samuelsson et al., 2004). The abnormal homeostasis can lead to dysfunctional brain maturation which in turn has a lot of negative influence on the developing fetus (Betts et al., 2015).

3.1 Maternal malnutrition

The burden of undernutrition still exists and it is one of the most critical problems in many of the impoverished countries in the world. Although nutritional deficiencies have been recognized as a cause of disability and mortality as 50 percent of child dies due to it under five years of age, it continues to be a significant cause of mortality and morbidity, and is still listed as the number one cause of the worldwide burden of illness (Muller, S. G., L. Bitencourt, et al., 2005; Bryce, L. Kelly, et al., 2005).

Research has shown that depression can affect feeding practices, breastfeeding, hygiene, and healthcare seeking behaviors. (Patel & Prince, 2006) found that the depression that occurs in mothers during pregnancy can actually have a negative effect on the mother-child breastfeeding relationship. Mothers who are breast-feeding may not be able to help prepare food as well as other mothers, who are not suffering from depression. Furthermore, the mothers who are breast-feeding maybe less likely to handle their infant crying. Therefore, the relationship between depressive mothers on the wants and needs of the child is severely affected. If a mother is depressed, she may be less sensitive, emotional and accustomed, which results in her tendency to disconnection and complacent towards her children (Murray & Cooper 1997).

In Jamaica, the study found that maternal depression greatly affects how much stimulation is introduced to the child at home. Both the insufficient child stimulation in the home, as well as bad mother-child relationships have demonstrated a link (“Maternal Depression and Child Development,” 2004). A severely malnourished child requires much more attention from parents, if they are hospitalized.

Depression affects one's functioning in the workplace and in social settings, a mother with mild depression might have issues in carrying out every day work and social activities (Woo & Postolache, 2008)(“Maternal Depression and Child Development,” 2004). The effects of maternal depression can cause undernutrition among children through detrimental parental behavior. Depression can have tremendous adverse effect on the mother's ability to care for her baby, and can be detrimental to the baby’s health. Having a severely malnourished child is an extremely distressing ordeal. In the current study, the children who are malnourished have become ill at varied times and have developed general deterioration of health that has caused psychological distress in mothers (Ashaba et al., 2015).

3.1.1 Etiology of maternal malnutrition

Even if it is true that nutrition and other external conditions serve as a significant role in children's health status, maternal mental state of the mother has been shown to play a major contributing role, presumably by affecting with the mother's duties for caregiving (Surkan et al., 2011). Adequate protein intake and energy, vital fatty acids and multiple major micro nutrients such as homocysteine, methionine, vitamins B6, B9 (folic acid), B12 and the end products of it are needed during development in the womb. It provides the necessary substrates for fetal tissue production and as co-factors in biological mechanisms that integrate the development of the physiological brain. Therefore, nutrition of the prospective mother strongly impacts the fetal environment during the whole gestational period, which in turn can influence the outcomes of the fetal central nervous system (Kennedy, 2016). Furthermore, animal studies show that the infants of undernourished pregnant dams have poor neuron development and function, as well as feeding mechanism dysfunction, altered glucose detection, and tolerance to leptin and insulin (Breton, 2013).

In general, more obstetric complications occurs for women with signs of depression, have been found in studies addressing the impact of anxiety or depression signs causing complications during pregnancy. In addition, women with prenatal anxiety and depressed symptoms report more physiological side effects such as nausea, see their obstetrician quite often, and during their pregnancy they have more days of disability than healthy women. Domestic violence during pregnancy has still not been evaluated as such, but it is also likely to be significant because of its negative impacts on the fetus and the child (Alder et al., 2007a). They may be able to influence the result, but in a somewhat different context. Barker et al. showed that maternal depression had a wider influence than maternal anxiety on several types of child dysfunction during the prenatal and postnatal periods, which appeared to be more precise to internalizing challenges in the child.

Environmental factors, including nutrition, in formative years can substantially damage or "programme" the body's function and structure, according to animal research (Alharbi et al., 2007). Animal model studies suggested that if the mother is inadequately fed then the fetus will have a deficiency in nutrition as it can damage the fetal food supply line by interrupting the placental growth or by causing uterine artery ligation and can also have long term consequences on other system or tissues (Bleier, 1971)(ANAND & BROBECK, 1951) (Almind & Kahn, 2004). For instance, a lot of animal models suggested that malnourished mothers had children suffering from obesity, diabetes and changes that occurred in tissue and molecular levels such as altered arrangement of cell types and gene expressions. Studies from animal model suggested that birthweight of an infant and the health of the mother are interlinked through internal environment of the fetus and programming of various tissues (Fernandez-Twinn et al., 2019).

3.1.2 Mechanism of action of maternal malnutrition

Biochemical fluctuations lead to disparity of the relative homeostasis, and as a result, the body will respond with various physiological and biochemical changes to regain homeostasis (Kotas & Medzhitov, 2015). For example, cortisol is released as a result of stress; it is a significant physiological marker of stress. Malnourishment and depression are two such states that comprises the homeostasis in mothers and effects the development of the embryo before implantation (Chason et al., 2011). It can have an impact on the development of placenta, implantation and can also get into the fetal circulation through placenta, which can have adverse effects on the growth of cells and tissues (Jansson & Powell, 2007). The relations between maternal malnutrition and symptoms of depression can increase development problems and alteration in the intelligence and mental ability of children.

Links between depression during pregnancy and DNA methylation of genes for cord blood OXTR, placental HSD11beta2 and cord bloodNR3C1 have been found (Unternaehrer et al., 2016) (Seth et al., 2015). Loss of maternal nutrition during pregnancy also led to changes in NR3C3C methylation, even though this was only examined in animals, suggested that both these instances may cause alterations in methylation of the same NR3C3C gene (Begum & Sehrin, 2013). The NR3C3C is also known as the progesterone receptor or PGR gene, it is important in regulation of progesterone during pregnancy (Manuck et al., 2010). Further studies on this demonstrated changes in the brains' reward system in infants of sheep fed a high fat during gestation resulted in more dramatic changes in their DNA methylation of the genes related to dopamine and opioid, dopamine reuptake transporter (DAT) and μ-opioid receptor (MOR), which could mean having higher risks of developing depression (Vucetic et al., 2010) (Nestler & Carlezon, 2006).

The fetal brains are susceptible to damage by oxidants, and various factors contribute to oxidative stress (Dennery, 2007). High concentrations of reactive oxygen species molecules

which may act as signaling pathway for boosting symptoms of prenatal malnutrition and depression which can impact the fetus development particularly, neurogenesis. Pregnant depressed women had lower antioxidant level compared to non-depressed pregnant women (Camkurt et al., 2017). Food with saturated fats in general can increase the level of oxidative stress, whereas vegetables and fruits are antioxidant-rich, therefore diet influences the level of oxidative stress (Wu et al., 2004).

3.2 Reduced immunity of fetus

Maintaining a healthy childhood development may be the result of upholding a healthy childhood. Rahman et al. (2007) found elevated incidence of diarrhea amongst infants whose mothers had been diagnosed with a major depressive disorder in Pakistan. Potential justification for this could be unhealthy eating practices, cessation and issues concerning breastfeeding. As a consequence of depression and suffering, a depressed mother can be less effective at obtaining general health care services for herself and her newborn (Stewart, 2007c). Significant amounts of health education and advice are already included in a large number of maternal and child well-being programs.

3.2.1 Mechanism of action of reduced immunity

An increased risk of prenatal infections has been linked to stressful events. Obesity and depression can cause inflammation, which can result in transmission of antibodies or cytokines to the developing fetus through the placenta during pregnancy (Leff-Gelman et al., 2016). Clinical studies have also revealed that women with symptoms of depression have different cytokine levels (E. Leonard, 2010). Research shows that having more fat in the diet as well as well as following a high fat food intake which increases the level of adipose tissue, mobilizes and activates the immune system (Ferrante, 2013). These infections can affect the fetus' immune system by releasing immune system modifiers called cytokines, which are released by

the mother. Cytokines are involved in both the activation and inhibition of inflammatory response, and also being related to oxidative stress and reactive oxygen species (ROS) (Buglione-Corbett et al., 2018). However, cytokines can cross the placenta and get into the fetal circulation, where they can directly interact with immune system cells of the fetus. Even though cellular migration of stress from the mother to the fetus is assumed to be an element, much of the research in this area is contradictory, and the biological mechanism is unspecified (Yockey & Iwasaki, 2018).

Stress-induced maternal inflammation, on the other hand, may play a part in the growth of the fetal immune system by up-regulating pro-inflammatory placental genes (A. M. Samuelsson et al., 2006). The latter involves modified gene expression in the fetal hippocampus, which has been linked to lower learning abilities, increased weight, and lower insulin sensitivity in late adolescence of children (A.-M. Samuelsson et al., 2004).

3.3 Lower birth weight

As documented by Rahman et al. (2004a) in Pakistan and as documented by Patel & Prince (2006) in India, an association was discovered between antenatal depression and birthweight in two different countries. The studies of this interaction may also shed some light on the duration of the relationship between infant growth and maternal depression. There is some evidence that this process begins antenatally. Moreover, many studies have found that mental illness is prevalent in socially deprived developed countries. Many variables could be the result of the antenatal connection, including the effect of mental disorder. However, it could be that the maternal physical health and behaviors seeking health during pregnancy is influenced by the adverse impact of mental disorder.

Studies have found that low birth weight and prematurity can be interpreted as the direct result of maternal depression (Zax et al., 1977). There was a particular greater risk of unexpected

preterm labor in depressed mothers who had low Body Mass Index (BMI) and pregnant women who had Post Traumatic Stress Disorder (PTSD) (Shaffer et al., 2001). Furthermore, infants of women who have been depressed, clearly spent more time being active over the course of gestation (Kołomańska et al., 2019). These symptoms became most pronounced between 5th and 7th month of pregnancy. Fetuses exposed to ultrasound showed less movement during fetal stimulation and lower mean baseline FHR (Fetal Heart Rate). Hormonal and neurotransmitter effects can be very important in this area of research. A meta-analysis by Grote and colleagues (Alder et al., 2007a) suggested compelling prematurity and reduced birthweight associations, while the other by Grigoriadis and colleagues proposed that prematurity is only mildly associated (no gestational age associations and limited birthweight associations). While this claim has been verified by a few studies, depression in pregnancy has been found to be correlated with negative neonatal effects, such as premature birth and poorer anthropometry for neonatal.

3.3.1 Mechanism of action of low birth weight

The mechanism underlying the effect of maternal BMI and antenatal depression on birthweight is uncertain (Grote et al., 2010). The abundance of maternal nutrients and the capacity of the placenta to distribute these nutrients from maternal circulation to the fetus are both important factors in fetal growth. The mother must provide glucose, amino acids, and fatty acids to the fetus through the placenta in order for proper fetal development to continue (Carey et al., 2014).

Another possible correlation between maternal obesity, antenatal depression, and neonatal complications is the hypothalamus-pituitary-adrenal (HPA) axis (Horowitz et al., 2013). HPA alterations appear to be regulated in a different manner in depressed pregnant women than in healthy pregnant women (Horowitz et al., 2013) (Wilson & Thayer, 2017) (Hannerfors et al., 2015). The cortisol to cortisone ratio, which may be an indicator of maternal and placental 11-

hydroxy steroid dehydrogenase 2 action, has been shown to be significantly correlated with birthweight in women and psychiatric morbidity (Iliadis et al., 2015). In addition to this, psychiatric morbidity significantly increases fetal cortisol exposure which has an impact on fetal growth (Petursdottir Maack et al., 2019).

A study done by Lundy et at (1999), found that newborn babies of mothers with depression are shown to have elevated levels of norepinephrine (NE) and plasma cortisol. Moreover, it has also been found that an elevation in NE and plasmatic cortisol levels, a decrease in levels of dopamine and an increase in the plasmatic levels of the hormone glucocorticoids (also referred to as cortisol) are also present in a study (Field et al., 2004). In babies of mothers from low socio-economical classes, NE and plasmatic cortisol levels were believed to be the highest. Newborns of women who are stuck in depression after childbirth have poorly habitable situation, awareness, motor, autonomic reliability and on the Brazelton Scale had relatively higher scores on depression (Field et al. 2004).

The sympathetic adrenal medullary system, which integrates the activation of norepinephrine (NE) and epinephrine (E) from the adrenal medulla, is induced in response to mental stress. Short-term behavioral, metabolic, and immunological reactions to environmental triggers are known to be influenced by these catecholamines (Tsigos et al., 2000). Catecholamines are hydrophilic and cannot traverse the placenta. Increased levels of catecholamines, on the other hand, have been shown to interfere with fetal development via indirect interactions. Researchers believe that norepinephrine (NE) and epinephrine (E) can trigger adrenergic receptors in the uterus and placenta, causing blood vessels in the uterus and placenta to constrict (Levine et al., 2016).

Umbilical blood flow is reduced as a result of mental stress and increased vascular tone in the uterus and placenta, resulting in reduced utero-placental perfusion (UPP). The consequences

of maternal catecholamines on UPP can cause the fetus's development to be stunted and even lead to premature birth (A. M. Samuelsson et al., 2004).

3.4 Effects on neuro development of the fetus

In the prenatal period, the child's brain is the greatest possible organ that is susceptible to the consequences of trauma, because it experiences tremendous influence of the different development and interconnection during the fetal life (Laloux et al., 2012). Personal neurocognitive trajectories are molded by environmental factors during prenatal life which is indicated by The Developmental Origins of Health and Disease (DOHaD) framework (D. J. P. Barker, 2007). The study suggests that prenatal exposure to environmental stressors, including maternal incompetent and obesity, diabetes (Pantham et al., 2015), anxiety and high blood pressure (Girchenko et al., 2018), and depression (Pantham et al., 2015), are linked to child adverse outcomes in particular intelligence and mental disorders (Tuovinen et al., 2018).Moreover, many health experts agree that the factors imposed during the intrauterine environment have a lasting impact on the growing fetus and may affect the development of a child in later years of life (Strauss, 1997).

Numerous lines of findings from preclinical models have shown that prenatal stress exposure results in long periods of modifications in behavior as well as in regions which are engaged in cognitive ability at molecular levels (Marrocco et al., 2012). For example, the concepts such as excessive people, malnutrition, bright light or constraint stress are factors related to antenatal depression. These also causes an increase in negative behavioral patterns in children as experimented by many social tests that evaluate stress (Grigoryan & Segal, 2013). In addition, autonomously depending on the source of stress that was used, all the research conducted repeatedly saw how persistent prenatal distortions affect spatial memory retention, with an

impact that can not only be witnessed in childhood or adolescence but also in later life (Luoni et al., 2017).

From several studies, it is known that depression in pregnancy can cause variations in various biological systems. On the other hand, various researches have shown that the involvement of environments, that includes depression and stress may lessen the activation of 11β-HSD-2, that could risk exposure of the fetus to detrimental levels of increased cortisol in the womb (Davis & Sandman, 2010). In fact, decreased placental 11-HSD-2 activity has been linked to fetal weight loss and higher stress reactions in the offspring (Seth et al., 2015). Structural brain alteration in childhood pre-frontal cortex, inferior temporal and frontal areas, amygdala (Rifkin-Graboi et al., 2013), and in neurons interconnection between amygdala and front-ostriatal areas (Burgueño et al., 2020), have also been associated with maternal depression during pregnancy.

Maternal distress during pregnancy can manifest in a variety of ways, ranging from mild triggers to short and acute anxiety, to greater stressors which can lead to chronic stress. It can be classified as clinical anxiety and depression. Even though these scenarios may differ significantly for different pregnant women, it is postulated that the consequences on the fetus are quite similar, leading mainly to an enhanced expression of the autonomic nervous systems (ANS) and hypothalamic pituitary adrenal (HPA) (Talge et al., 2007). The HPA axis, which is stimulated during stress and hazard, is one of the most important systems involved in stress response and regulation, the end product cortisol is an endocrinological marker for depression. Prenatal stress, however, appears to affect the placenta's characteristics and the expression of the 11b-hydroxysteroiddehydrogenase enzyme, according to research based primarily on animal studies (Welberg et al., 2005). Multiple sources of risk are typically exposed to depressed women who are pregnant and their children. Therefore, the correlations of prenatal depression with increased suffering of domestic violence, drug abuse, antisocial behavior by

parents, childhood abuse and other social risk factors partially explain the increased incidence of adverse effects of offspring.

3.4.1 Etiology of effects on neuro development of the fetus

Increasing research demonstrates that in both ill and healthy individuals, inflammatory cytokines influence the formation of depression. For growth and functioning of normal brain, cytokines are important and have the potential to control neurocircuitry and neurotransmitter process to achieve alterations in behavioral patterns. Stimulation of the body's immune response acutely generates adaptive behavioral responses that encourage energy efficiency to tackle infection or injury recovery. As the neurotransmitter system keeps changing constantly and prolonged exposure to inflammatory cytokine can lead to depression or other mental disorders. Cytokine behavioral effect mechanisms include activation of inflammatory signaling pathways in the brain that lead to changes in the systems of glutamate, monoamine and neuropeptide, and tends to decrease growth factors, e.g., neurotrophic factor derived from the brain. In addition, inflammatory cytokines may serve as an intermediate of variable that attribute to the development of depression, both environmental and genetic (In 2013, Felger & Lotrich).

There is concern about the extent to which behavioral and neurological disorders can be caused by brain alteration. A range of research demonstrates that prenatal found to correlate with a modified diurnal composition or pattern of impaired HPA axis function, which is a complicated process.

Interestingly, research findings have also shown that prenatal anxiety levels are associated with shorter telomeres, which shrink with age (Entringer et al., 2013). The finding is enthralling; however, the reduction in telomere length related with shortened average lifespan is worrisome.

However, some research indicates that the developmental window when the negative effects of prenatal stress are most apparent is during the mid-gestation. It is very likely that one could be sensitive in distinct periods, and relying on the output on the way one's brain has developed responsiveness (Fernandez-Twinn et al., 2019). Disease begins with the migration of neurons from the beginning of the brain to their final place in the brain, which may be disturbed in many psychotic disorders. Studies have shown that the most sensitive period for people who have schizophrenia occurs in the first trimester of pregnancy. Perhaps, schizophrenic patients often experience disturbance in migration neurons (Stouffer et al., 2016). In contrast to the aforementioned findings, two studies also reported the greatest associations between stress and the development of psychosis during later stages of pregnancy (Zhu et al., 2010a).

Also, during pregnancy, mothers with depression can cause the body to release more cortisol, a hormone that can be topically transported through the blood to the fetal brain to affect brain development. Indeed, placenta plays a crucial role in mediating the transmissions of hormones from the mother to the fetus and serves as a boundary that blocks fetal stimulation to glucocorticoids levels in the mother's blood through the activity of the 11-beta-hydroxysteroid dehydrogenase type 2 (11β-HSD-2) enzyme, that transforms cortisol into its inactive state cortisone (Cattane, Richetto, et al., 2020).

3.4.2 Mechanism of action of effects on neuro development of the fetus

The stimulation of the HPA axis is one of the major biological processes that causes the impact of symptoms of depression during pregnancy, and there is growing human research that supports this theory. Higher maternal cortisol is interconnected to antenatal depression, which is linked to an increased risk of harm to the offspring (Waters et al., 2014). Extreme neonatal stimulation to both synthesized and endogenous glucocorticoids can result in negative

consequences later in life (Seckl & Holmes, 2007). Furthermore, the fetus is mainly protected from cortisol activation by the placental enzyme, 11-hydroxysteroid dehydrogenase type 2 (11-HSD2), 80-90% are inactivated by the enzyme but a percentage of cortisol from the mother crosses the placenta impacting the developing fetus (Gitau et al., 1998).

Although catecholamines are manufactured by the SNS (Sympathetic Nervous System) and do not traverse the placental boundary under environmental stresses at biologically relevant concentrations. SNS maybe be excited by stressful events and may have an impact on utero-placental perfusion, affecting fetal growth indirectly and activating the fetal HPA axis in turn (Rakers et al., 2020). In addition, catecholamines may reduce the expression of the 11β-HSD2 gene, thus possibly increasing exposure to fetal glucocorticoids (Wyrwoll et al., 2011).

Emerging findings indicate that cognitive impairment, and in especially depressive symptoms, are linked with IRS (Insulin Receptor Substrate) down regulation with increased amounts of inflammatory markers such as Interleukine-6 and C-reactive protein have been found in both non-pregnant and pregnant samples (Miller and Raison, 2016) (2019, by Nazzari et al.).

3.5 Long term effects on the children

Several researches consistently show, maternal depression during pregnancy anticipates the depression of the offspring in childhood and that childhood trauma is a harmful variable for the development of this disorder. The inability to respond in stressful situations may be increased in children whose mothers had depression during pregnancy. This concept is reinforced by the analysis (Pawlby et al., 2009) which showed that children were 12 times more likely to develop a mental disorder if they had been exposed to both maternal depression and child abuse comparing to children who were not exposed to either. Nevertheless, various studies suggested greater effect of maternal antenatal depression than prenatal anxiety (E. D. Barker et al., 2011). However, in comparison to maternal anxiety, depression during and after

the birth were more impactful. It was found to be connected to incremental increases in both child challenging behavior and decreases in child intelligence to antenatal depression, whereas mothers with antenatal anxiety had infants having a higher risk of showing developmental difficulties.

3.5.1 Academic development on the children

These problems persist even in the adolescent and later age groups, especially with the struggle to concentrate during intellectual thinking, poor memory, and they may also suffer from ADHD. In a longitudinal survey of 132 children by (Hay et al., 2001), lower scores of IQ, inattentiveness, problems in mathematical concepts, and special education services, were found to be considerably more prevalent in children with mothers suffering from depression at 3 month post pregnancy. In addition, Boys were also affected in a greater percentage than girls (Visser et al., 2007). However, academically difficult children of depressed mothers have not been shown to be influenced by parental intelligence, demographic characteristics such as race/ethnicity, and mental health of the mother after she has overcome her mental illness ("Maternal Depression and Child Development," 2004). Though studies have showed an association between depression and impaired ability to learn new things especially related to deprivation, poor concentration, and decreased memory (Williamson, 2008), depressed mothers may be at risk of impaired concentration and learning

3.6 Behavioral effects on the children

Infants born to mothers who were diagnosed with depression during the postpartum period were evaluated and found to spend time making a fuss and weeping and exhibit more stress behaviors (Diego et al., 2005).

In addition, both antenatal anxiety and depression in mothers had children of age 3 to 4 years with attention problems (Van Batenburg-Eddes et al., 2013). Children experiencing anxiety

and depressing symptoms had showed increased behaviors of internalizing in four-year-old children (Misri, Pratibha Reebye, et al., 2006). It was also found that 4- to 7-fold increase in the risk of depressive symptoms between childhood and adulthood were observed in adults who had experienced prenatal depression (Pawlby et al., 2009). Increased risk of becoming depressed even in later years of life was also noted by Hay et al. (2008), although more of these impacts were observed in girls than boys. An association with prenatal depression and an elevated risk of children suffering from autism has recently been found, although these links have primarily been confined to children whose mothers were found to be taking antidepressants while pregnant (Rai et al., 2013). In addition to it, infants of 18 months, prenatal depression has also been shown to cause delayed development (Deave et al., 2008a). Both the outcome of maternal depression and anxiety have adverse effects on development of the child. Few studies concluded found that children may be especially susceptible to the effect of chronic and acute anxiety during pregnancy, with others suggested they were more susceptible to the effects of antenatal depression. It can be difficult to distinguish between maternal depression and maternal anxiety because comorbidity between these disorders is common (Glover, 2014a).

Many poor aspects adversely affect the child who goes through prenatal stress during pregnancy, such as depressive symptoms, anxiousness, aggressive behavior and antisocial behavior. As a result of not experiencing a great amount of stress, pregnant women tend to have smaller amount of weight and a shorter time from conception to delivery. It was also found that there are many differences in the sex ratios among those who are stressed, such as birth defects, problems caused by pregnancy complications, and problems induced by stress (Zhu et al., 2010). Studies showed the relationship somewhere around prenatal stress and behavioral pathways in children between the ages of 3 years and 16 years old, instead of children from infancy to adulthood. A lot of studies have shown that the stress that comes when

a woman is expecting a child raises the risk for behaviors like anxiety, ADHD and conduct problems in offspring (Laplante et al., 2008). A few other studies have shown a correlation among pre- and postnatal stress and a higher likelihood of autism (Karanja et al., 2009) (Nemeroff et al., 2010), and elevated stress levels in gestational period which may impact brain development. The relation that exists between prenatal stress and autism and the impact those stress levels have on brain development remains unclear at this time. However, there is some evidence suggesting that pregnant women who are under stress while they are pregnant may have a higher chance of having their children develop schizophrenia. Both patients showed clear effects to stress during the first trimester. They also showed clear effects to experiencing the dying of a family member of the, the conquest in 1940 of the Netherlands and the exposure of the patient to the trimester during which the brain is forming (Fineberg et al., 2016).

3.7 Hormonal effects on the children

Children may also demonstrate greater salivary cortisol levels when exposed to slight laboratory source of stress in the research (Ashman et al., 2002) in comparison to children of healthy mothers. The Viva Project is a prospective cohort study that examines the link between antenatal and postpartum depression, as well as child weight and adiposity. Furthermore, infants of mother with depression had higher cortisol levels and lower levels of dopamine and serotonin levels (5-HT) (Perng et al., 2014).

3.8 Gene alteration of the fetus

In the development of the fetus, the placenta plays a crucial role. A gene expression research on the fetal side of the placenta was conducted to examine gene expression variations in mothers with antenatal depression and mothers taking antidepressant medication during pregnancy. Placental samples were collected from mothers with normal pregnancies, mothers with antenatal depression, and mothers who were using antidepressants. To investigate

alterations in gene expression, a pilot microarray study and selected several genes from the microarray for biological validation with qPCR in a larger sample was conducted. 108 genes were differentially expressed in mothers with antenatal depression, whereas 109 genes were differentially expressed in those using antidepressants. Therefore, microarray validation revealed more robust differences in gene expression in the seven genes selected for confirmation in women treated with antidepressants than in depressed women who were greater than those who were not exposed (Gentile, 2017). Briefly, gene expression is modified by antenatal depression and treatment with SSRI in the fetal placenta. It was concluded that the effects of SSRI intake during pregnancy are more robust for these subsets of genes because more changes in placental genes have been validated in a greater subset of women treated with SSRI compared to those with antenatal depression. It is still unclear how these differently impacted genes affect a child's growth, and whether these variations are still present in the fetus (Jocelien D.A. Olivier, Åkerud, Skalkidou, et al., 2015).

3.8.1 Mechanism of action of gene alteration of the fetus

In an enzymatic reaction called methylation, methyl groups can attach on specific points on the DNA through cytosine (Meltzer-Brody, 2011). Silencing of the gene occurs at a most basic level due to methylation, and forms a bond between DNA cytosine and methyl groups which alters the gene expression in a stabilized but reversible form (Jones & Taylor, 1980). Nevertheless, DNA methylation persists during an organism's lifetime and still affect behavior and health in later generations as they are passed along (Weaver et al., 2004). In a study done in rats, it was found that chronic stress caused the methylation in DNA profile of the promoter of genes in the germline of separated male offspring (Franklin et al., 2010). Inadequate prenatal care causes an increase in intensity of response to stress as it directly boosted glucocorticoid gene expression through methylation in the promoter region, thus lowering the number of receptor (Weaver et al., 2004). In response to poor care causing poor maternal behavior,

methylation of the estrogen receptor in the alpha gene have been found in rats. Therefore, this may lead to triggering of the oxytocin gene which is responsible for maternal love and influences attachment with the child (Champagne et al., 2006).

3.9 Other effects on fetus

3.9.1 Fetal movements

Fetal movements were measured for 5 minutes at different weeks of the gestation period from 13-35 weeks, prior to a standard ultrasound examination (Dieter et al., 2001). The number of times the fetus moved were recorded and divided into 3 parts, which were single limb movement, multiple limb movement and gross body movement. Depression and anxiety were assessed and groups (symptoms of increased level of depression and no symptoms of depression) were formed according to CES-D scores. Therefore, during the gestational periods of five to seven months, sum of the fetal movements throughout the group had shown a positive association with depressed mood and anxiety scores of the mother.

3.9.2 Fetal Heart Rate (FHR)

Studies have examined the impact of various types of stressful events on the fetal heart rate reaction in patients with higher depressed mood or anxiety levels (Sjöström et al., 2002). In general, no differences in baseline FHR (fetal heart rate) compared to non-distressed groups were found with the fetuses of mothers experiencing anxious or depression. Monk et al. (2004) established that in their studies that fetuses at the 36th to the 38th week of gestation show a greater heart rate when they had mothers with depression challenged with a psychological task. Fetuses of pregnant women who are found to have a higher risk of prenatal depression and anxiety also tend to have similar effects (Monk et al., 2011). It has also been proven, as noted by Allister et al. (2001) who found that the heart rate of 32- 36-week-old fetuses was

higher for mothers with depression compared with non-depressed mothers. However, a study used 32 to 36week old and midterm fetuses to determine whether maternal depression affects heart rate acceleration. It was found that for those fetuses from depressed mothers, their heartbeat went down in response to vibrational excitation and also tend to have decreased motion and heart rate variable with decreased vibration (Allister et al., 2001; Emory and Dieter, 2006). This attribute indicates that environmental responses are smaller and take longer to occur, but the effects last long-term.

3.9.3 Apgar scores and infant cardiac vagal tone

Higher levels of anxiety at 16 to 18 weeks or any time of pregnancy has shown to have lower Apgar score at 1 to 5 minutes (Stuart et al., 2011). On the other hand, Ponirakis et al. (Negative Emotionality and Cortisol during Adolescent Pregnancy and Its Effects on Infant Health and Reactivity of the Autonomous Nervous System - PubMed) reported a link between increased emotionality of the trait (anxiety, anger, depression, hostility of NEO) soon after pregnancy with higher Apgar score at first 5minutes, than with mothers having higher levels of cortisol assumed to have lower Apgar score. Therefore, the findings indicate that stress hormones are responsible for the delay of accommodation after birth, whereas there is a lack of adequate explanation for the association between emotionality and improved birth adaptation. Higher trait emotionality was associated with infant having lower tone of cardiac vagal, which was evaluated four weeks postnatal, however, cortisol level at 16 weeks of gestation were not considered (Bush et al., 2017). Therefore, during pregnancy, the maternal psychological state could result in longer adaptation period for the fetus. However, the absence of valid research and improper comprehension of the underlying mechanism of action, Ponirakis et al. lack of significant data has reduced the effectiveness of these results.

Chapter 4

Conclusion

Majority of pregnant women suffering from antenatal depression goes unnoticed, maternal depression imposes health hazards on the growing fetus (Muzik & Borovska, 2011b). The effects of antenatal depression are associated with both the mother and children, and are also seen in later lives of the children as well. Varying stressors of life has been associated with antenatal depression, however it is yet to be determined which type of stress leads to antenatal depression and the mechanism of action linked with it (Dadi, Miller, Woodman, et al., 2020). Lack of focus on mental health activities has caused a rise on the global burden of depression during pregnancy. The adverse outcomes on child include low birth weight, pre term birth, decreased movement and heart rate of the fetus in mothers with depression (Dadi, Miller, Bisetegn, et al., 2020b). Therefore, it is crucial for primary care to identify the mental illness of pregnant women and increase access to mental health services.

4.1 Future Implication

Such research may ultimately help in building bridges between the disciplines of healthcare. Most studies are done where mental health professionals concentrating their attempts on mental health care and child health professionals on decreasing the rate of morbidity and mortality of children. The theoretical framework of studies in this field will be derived from many fields of study, including psychiatry, pediatrics, primary care, public health, sociology, epidemiology, and medical anthropology. The approach to healthcare issues is more likely to succeed if it is more specific and collaborative. (A. Rahman et al., 2002b).

Identifying the causes of women's illness would mean to understand their social status and how it is undermined by the engagement of cultural and economic forces. In order to accomplish

the goal of improving the well-being of women from early life through older years is needed. The social status and all kinds of healthcare needs to be addressed and policies targeting these requirements, are to be developed. If the goal of improving the well-being of women from early life through older years is to be accomplished, healthy policies aimed at improving women's social status are needed, along with health policies that target the full spectrum of women's health needs. Although the motive for changing the direction of such well-established forces is often difficult to develop. We believe that the connection between maternal well-being and child health can provide a socially agreed 'entry point' to help create such a motivation, contributing to policies that promote women's social status.

The key consideration involves the relevance of activities for children's health in developing countries. Appropriate measures are mostly directed towards the mother, such as appropriate feeding advice, hygiene, vaccination, health education, and health-seeking behavior patterns. Consequently, the impact of these programs is linked to the functional ability of this group, their willingness to the message and their acceptance of the support offered. The psychological well-being of mothers is likely to be crucial to the success of these programs. For instance, it could be feasible to include the appraisal of maternal capability in the World Health Organization’s Integrated Management of Childhood to properly institute care. There are recommendations for checking mothers' understanding of home-based intervention strategies and observing their practice, but mental health is not addressed in the maternal health section (Child and Adolescent Health and Development Division 1998). Simple mental health techniques to engage with these mothers, provide counseling, practical assistance and advice on child health in a more efficient manner could be taught to health workers.

4.2 Limitation of the study

Most of the research findings are done in animals not in humans. One of the most significant obstacles to depression screening's effectiveness is that it is done poorly or when done, inappropriate instruments are used. In addition, the findings indicate that maternal depression is difficult to detect and mostly missed if informal screening is used alone (Evins et al., 2000). In contrast to the standardized queries of formalized screening tools, some of the flaws of informal investigation include the lack of consistency and the use of non-specific questions. Therefore, with the objective of providing adequate services for women of childbearing age, the implementation of an appropriate toolkit is a must for the versatile primary care clinician.

Reasons why people may find it difficult to get help include physical, social, and logistical barriers, such as difficulty finding treatment and accessing suitable referrals, fear of being viewed as a "bad mom," and being educated accurately about depression to make an informed decision about when to seek. Although practicalities have an influence on women with resource constraints, or all women would prefer to receive treatment at the obstetrics clinic, contrary to the current system, where their needs are met when they go off-site. It is well known that African-American mothers have less faith in the advice and assistance of friends and family members or professionals than other ethnic groups do (O'Mahen & Flynn, 2008).

There are several consequences that arise from this postulate. The first relates to perception of mental illness. There is an extensive lack of comprehension regarding mental health problems in developing countries, and mental illness has a stereotype that hampers the search for treatment (Rahman et al. 1998). In the developing world, mental health stays weak on the ideology of decision makers and policy-makers. If it was shown to be linked to mental health of the mother and physical health of the child, this could contribute to the health strategy for the mental health of mothers, in a way that could be ethnically and relationally acceptable.

4.3 Future Research Plan

Prenatal depression is currently lacking a clear answer as to its causes, which makes it an area of major interest to scientists. New research for prenatal depression on human and animal models has great promise for comprehension of etiology and the identification and treatment of future prevention for the long-term issues, as well as for women at risk of experiencing postpartum depression (Meltzer-Brody, 2011). However, future research should focus on finding ways to reduce antenatal depression through exercise or better partner relation (Daley et al., 2015; Rwakarema et al., 2015).

In addition, future research should also take into account the role of HPA axis in pregnant women and its function in fetal brain programming, embryo maturation and immune responses. Researchers should also consider factors that are stressful for women and ways to cope with that. Moreover, stress hormones other than cortisol, or other markers for stress such as insulin, salivary enzymes, eating habits and physical activities should also be taken into consideration while accessing stress (González-Ochoa et al., 2018).

Monitoring the likes and dislikes of women, regardless of ethnicity, it is still up to the women and the doctor to participate in decisions, and to provide and take into account ethnic/cultural support networks when consulting their patients. To provide pregnant or postpartum women and mothers with the most implement effective assistance (Muzik & Borovska, 2011).

Chapter 5

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