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The Epigenetics of Stress Reactivity Related to the Risk for Cardiovascular Disease: The Impact of Maternal Stress Levels on Offspring

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ABSTRACT

Intrauterine development establishes the systemic foundations that dispose the offspring to certain functional uniquities or health outcomes. During embryonic/fetal maturation, adverse conditions during critical periods vulnerable to structural/functional defects can spur disease processes in later life, such as cardiovascular diseases or metabolic syndromes. Aside from established teratogens and toxins, budding research is revealing that sustained maternal levels of excessive prenatal cortisol catalyzes an epigenetic cascade in the offspring that ultimately increases stress reactivity and risk for cardiovascular diseases/metabolic syndromes. This paper reviews literature discussing the epigenetic repercussions of excessive prenatal maternal cortisol levels on offspring and how these may influence outcomes. The literature identifies a correlational trend, but causal identification is limited by a discrepancy and laxity in methods. Conclusively, more longitudinal research with uniform methodology is necessary to strengthen the relationship between maternal prenatal stress and fetal outcomes.

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Chapter 1 : Introduction

Maternal stress levels during pregnancy manifest in the epigenetic makeup and developmental course of a developing fetus. When the mother consistently endures abnormally elevated antepartum stress levels, the infant's genetic expression adapts accordingly. Thusly, research supports that these offspring are more prone to trigger a stress response to minor stimuli and their developmental trajectory may differ from offspring that weren't exposed to an atypical intrauterine environment. Furthermore, research supports an insidious relationship between prenatal uterine stress levels and chronic complications, such as cardiovascular disease (CVD).

My thesis project aims to underline the relationship between prenatal stress exposure and stress reactivity/risk for CVD in offspring.

- How does cortisol impact metabolism, and how might that increase the risk for metabolic syndrome?
- How might HPA activity/sensitivity change in the offspring as a result of prenatal stress exposure?
- Are the prenatally stressed offspring more sensitive to minor stimuli postpartum?
- Is there a stress-threshold difference in offspring exposed to abnormal levels of prenatal stress compared to offspring with typical exposure?

An in-depth written analysis of the research will provide a comprehensive perspective of the impact of prenatal stress on later life. This paper should outline any and all sources, conclusions, shortcomings, or areas for future research.

Research into the impact of maternal stress on the development and gene expression of the fetus plays a vital role in understanding adult psycho-social-physical health. A glimpse into how chronic stress can increase the likelihood of developing later diseases (such as CVD) may allow future research to develop better preventative methods. This thesis aims to underline the connection between maternal stress and offspring stress reactivity/risk for CVD.

Chapter 2 : Relevancy of Cortisol in the Pathophysiology of Stress

Anatomy and Physiology of the Adaptive Stress Response and Cortisol

This section will outline the conclusive science of the stress response in an effort to inform the research in the succeeding chapters.

The endocrine system uses hormones (chemical messengers) that travel via blood or lymph to signal the body by binding to the target cell through specific cell receptor sites, which produce a programmed cellular response depending on the hormone (OpenStax Rice University, 2022). It is important to understand that the hormone will only impact target cells with receptors specific to that hormone (OpenStax Rice University, 2022). The receptor may be intracellular or extracellular, depending on the hormone. The specific hormone and the cells involved both equally determine which processes the hormone triggers. These cells are found ubiquitously, making the possible outcomes from hormone-cell binding expansive. The target cell's response may vary based on the cell location and cell type (OpenStax Rice University, 2022).

Certain hormones are integral to systemic responses towards environmental stimuli and to maintenance of internal homeostasis (ex: fight or flight response—adrenal hormones), with some hormones serving multiple roles (OpenStax Rice University, 2022).

Many factors contribute to which cascade of responses are provoked and when they are provoked. Downregulation is an action by the cell, where the number of receptors for a cell are lessened, thus causing the cell to be less reactive to excessive hormone production. Upregulation is the opposing action to downregulation, where the cell increases sensitivity to messages by increasing receptor responsiveness to accommodate chronically low levels of hormones. Moreover, the amount of hormone exposure can alter the target cell's gene expression and phenotype, altering the cell's sensitivity to stimuli and reactivity (Tsigos et al., 2020).

Conclusively, cells can regulate their sensitivity to hormones and hormones can impact target cells' responsiveness (OpenStax Rice University, 2022; Tsigos et al., 2020).

This paper will primarily focus on hormones within the stress response systems of the sympathetic nervous system (SNS) and autonomic nervous system (ANS). Cortisol is a lipophilic hormone produced by the adrenal cortex that serves in metabolism, immunity, reproduction, behavioral and cognitive functions (Gjerstad et al., 2018). Classified as a glucocorticoid, it originates from lipid cholesterol, meaning it can easily cross the cell membrane, unlike some other hormones that are dependent on receptor availability (OpenStax Rice University, 2022). It is regulated using inhibitory mechanisms to prevent overproduction and toxic cortisol potency; these inhibitory mechanisms include hormonal negative feedback loops and counter/dual processes within the parasympathetic nervous system (PSNS) of the ANS (Tsigos et al., 2020). In appropriate doses, the stress response can prove positive for development and a rewarding experience founded in control and focus. Furthermore, cortisol can elicit genomic actions, such as gene transcription and protein synthesis, and nongenomic actions. As Gjerstad et al. (2018) points out, research is beginning to show evidence of rapid nongenomic effects that can manifest in mere seconds to minutes, such as autoregulation of cortisol production and synthesis.

Appreciating the role of cortisol involves navigating the stress system and the hypothalamic-pituitary-adrenal (HPA) axis. As discussed earlier, hormones can play many roles in maintaining bodily homeostasis, especially in the face of external and internal stimuli. When a threat to homeostasis is perceived by the amygdala, which store the behavioral ques to learned stressors, it activates the SNS. Of note, the amygdala is also stimulated by the production of glucorticoids. Activation of the SNS arouse behavioral adaptations that induce an enhanced state

of arousal and vigilance with physical adaptations that are focused in diverting all energy towards survival-equip systems, such as cardiopulmonary (Tsigos et al., 2020).

The stress system cascade involves the slower PVN CRH-AVP and faster LC/NE systems. Glucocorticoid production via the HPA-axis is primarily activated by corticotropin-releasing hormone (CRH; formally known as corticotropin-releasing factor (CRF)), which is synthesized in the hypothalamic paraventricular nucleus (PVN), and the hypothalamic arginine-vasopressin neurons (AVP) (Gjerstad et al., 2018; Tsigos et al., 2020). AVP and CRH triggers the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH), which will act on the adrenal cortex to synthesize and release circulatory cortisol. CRH is the main hormone that triggers the HPA axis; however, some research has noted the presence of ACTH and cortisol in spite of CRH (Gjerstad et al., 2018). The hippocampus is responsible for inhibiting the amygdala, PVN CRH-AVP, and LC/NE systems when the stressor is perceived as harmless. It is important to mention that hippocampal atrophy/damage can impair the inhibitory mechanisms against the amygdala, leading to prolonged HPA-axis activation (Tsigos et al., 2020).

While cortisol can activate both glucocorticoid receptors (GR) and mineralocorticoid receptors (MR), GRs will be the focus for this paper because the other hormones often occupy MRs before cortisol can act. Moreover, this paper focuses on the anatomical/physiological processes of sustained stress which is more appropriately associated with GRs. GRs are exclusively activated during peak cortisol stimulation (stress response and circadian peaks). GRs are essential in the regulation of cortisol-based process, listed as fat/protein metabolism and immune function (Gjerstad et al., 2018).

Outside of the adaptive stress response, individual's CRH/AVP/ACTH/cortisol levels ordinarily peak in the morning and deflate as the day progresses. Circadian synthetization of

cortisol follows a pulsatile pattern that is dependent on changes in light, feeding, and physical activity, all of which define an individual's unique circadian rhythm. An acute stressor interrupts the basal pulsatile pattern to temporarily amplify CRH/AVP/ACTH/cortisol production and activate the acute stress system (Tsigos et al., 2020).

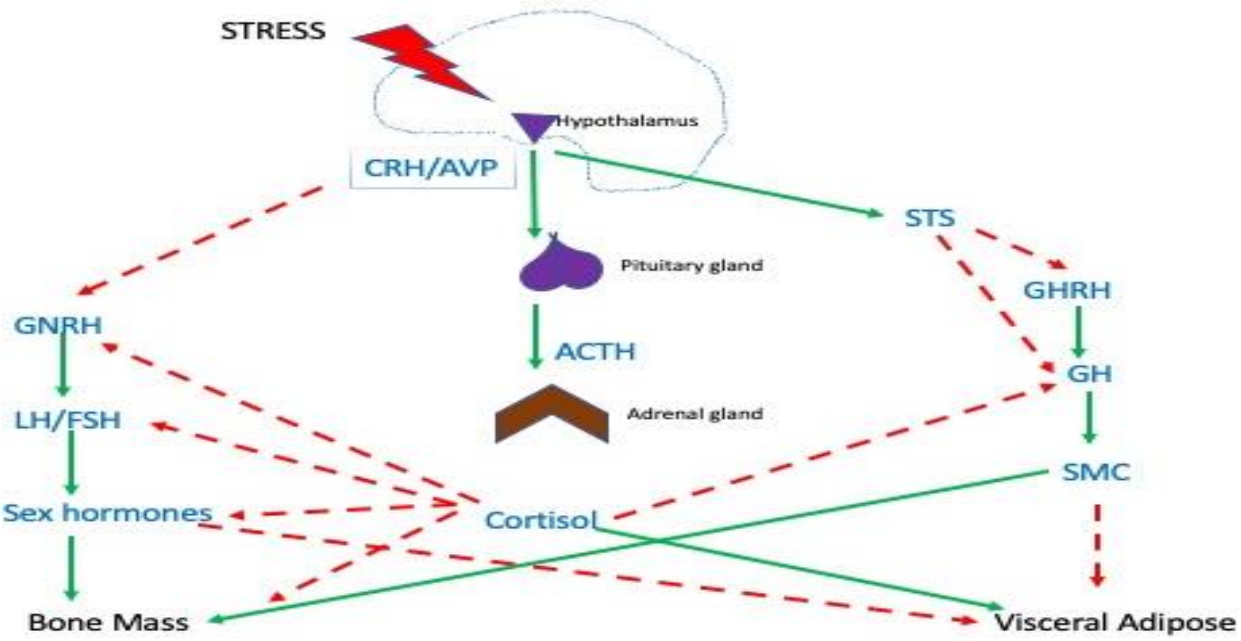

Figure 1: Stress Pathway: Green lines indicate activation and red dashed lines indicate inhibition. Adapted from Tsigos et al. 2020

In summation of the endocrinologic perspective of the adaptive stress response, it is piloted by PVN CRH-AVP, which triggers the ultimate production of the glucocorticoid cortisol, and the locus coeruleus (LC) and norepinephrine-synthesizing cell bodies (NE), which will ultimately trigger the production of catecholamines norepinephrine and epinephrine.

Characteristics of Toxic Stress

As mentioned in the above section, the body has calculated processes equipped for maintaining internal homeostasis and can employ compensatory mechanisms to oppose instability. As Tsigos et al. (2020) points out, homeostasis can be interrupted by intrinsic or extrinsic stressors, real or perceived threats. These compensatory mechanisms constitute the adaptive stress response. Each individual's unique stress response is determined by a number of psycho-social-physical factors, which are composed of genetic, environmental, and developmental characteristics (Tsigos et al., 2020). The behavioral and physical adaptations that occur in response to adverse stimuli are calculated to help the individual survive the real or perceived threat to homeostasis. These adaptations are designed to act acutely through the concurrent stimulatory and inhibitory functions of the adaptive stress response; hence, the body is not designed to tolerate sustained stress levels and can become maladaptive and nonspecific. Emerging research continues to support the detrimental consequences of prolonged stress (mostly concerning cortisol than epinephrine and norepinephrine), termed toxic stress for its potent, potentially morbific, psycho-social-physical effects. Moreover, toxic stress exposure during embryonic/fetal periods of developmental sensitivity and plasticity can negatively impact the efficacy of the body's compensatory mechanisms (Tsigos et al., 2020).

To provide perspective on toxic stress, the body's tolerance of stress can be outlined in Han Seyle's three stages: alarm, resistance, and exhaustion. The resistance and exhaustion reaction stages show evidence of deficits related to toxic stress exposure (Chu et al., 2021). The alarm reaction stage describes the adaptive stress response and the acute physiologic modifications for survival. Aforementioned, the adaptations during this stage should subside and return to a basal state once the stressor disappears. Ideally, the serum cortisol levels and any

physiologic changes (blood pressure, cardiopulmonary effort, inhibition of digestion, etc.) should return to baseline. However, if activation of the adaptive stress response persists due to prolonged stimulation, the body will adapt to higher cortisol levels; this defines the resistance reaction stage. While this stage induces symptoms of confusion, irritability, or poor concentration (Chu et al., 2021), the body compensates enough to prevent mass system dysfunction and morbific consequences. During the exhaustion reaction stage, the body's compensatory mechanisms against sustained high stress levels fails, bringing widespread deficits to light. Systemic consequences of sustained toxic stress levels include reproductive inhibition, cognitive impairment, growth hormone suppression, thyroid axis inhibition, immune suppression, digestive alterations, metabolic syndromes, and so forth (Chu et al., 2021; Tsigos et al., 2020). It is important to note that toxic stress levels differ from excessive cortisol production related to a pathophysiologic issue with the endocrine system (Cushing's etc.).

Chapter 3 : Cortisol's Relationship with Metabolic Syndromes and Cardiac Stress

It is understood that the adaptive stress response catalyzes physiological changes adept for survival, and as briefly discussed in the previous chapter, these changes can include changes in metabolism, such as digestive inhibition or gluconeogenesis, or in cardiopulmonary effort. This can acutely manifest as increases in heart rate, heart contractility/volume, blood pressure, blood coagulation, respiratory rate, serum glucose/cholesterol levels, blood coagulation, and oxygen/nutrient redistribution (Chu et al., 2021; Lob, E. & Steptoe, A., 2019; Tsigos et al., 2020). These physical adaptations are helpful for short-term survival in the face of a perceived threat; however, long-term continuance of these physical adaptations can eventually increase the individual's likelihood of developing CVDs, such as stroke and coronary heart disease (Chu et al., 2021; Lob, E. & Steptoe, A., 2019; Tsigos et al., 2020). Continuing research proposes a causal relationship between the development of CVD risk factors and lasting physical stress adaptations.

Furthermore, exposure to toxic stress for a prolonged period of time can prompt the development of a metabolic syndrome (MetS) (Chu et al., 2021; Lob, E. & Steptoe, A., 2019; Tenk et al., 2018; Tsigos et al., 2020). MetS is recognized as a group of metabolic comorbidities that exponentially increase an individual's risk of developing CVDs. While the precise diagnostic criteria for MetS varies across sources, most agree with the following parameters: increased obesity, increased serum glucose resistance/insulin resistance, hypertension, and dyslipidemia (McCracken et al., 2018; Tenk et al., 2018). Interestingly, many of the MetS characteristics are continuations of the acute physical adaptations that occur during the adaptive stress response. It is important to note that both stress and MetS are multicausal, which has made

conclusive correlational studies difficult to conduct. The following chapters will elaborate on the similarities between the adaptive stress response and characteristics of MetS.

Glucocorticoids increase serum glucose levels while countering the effects of insulin to maximize the amount of available energy (Lob, E. & Steptoe, A., 2019; Tsigos et al., 2020). Furthermore, glucocorticoids promote oxidative stress which has a role in insulin resistance (Tenk et al., 2018).

Amassing research shows that there may be a positive correlation between stress and increased blood pressures. Individuals exposed to chronic stress levels and have an increased sensitivity to glucocorticoids seem to exhibit higher blood pressures, a characteristic of metabolic syndromes; this could be directly linked to toxic stress levels or a secondary consequence to dyslipidemia or insulin dependence (Lob, E. & Steptoe, A., 2019; Tenk et al., 2018; Tsigos et al., 2020; Van de Valk et al., 2018).

Prolonged exposure to glucocorticoids shows an increase in visceral adipose tissue, or fat that accumulates in the abdominal cavity. Accumulation of fatty tissue can be attributed to many stress-related changes in fat storage, appetite satiety, hunger signals, and cravings (Tenk et al., 2018; Tsigos et al., 2020; Van de Valk et al., 2018). Van der Valk et al. (2018) discussed research that may link the endocrinological effects of glucocorticoids (thyroid/gonadal/hormonal imbalances) to the buildup of visceral fat and loss of muscle mass (See Figure 1). Additionally, current research acknowledges the role chronic stress levels occupy in the obesity pandemic.

Additionally, research conducted by Tenk et al. (2018) found significant positive correlation between stress and triglyceride levels ($p<0.05$), and a negative relationship between stress and high-density lipoproteins ($p=0.009$). A lipid profile like this has been conclusively related to atherosclerosis, a leading factor in CVDs.

Role of Dysfunction in Cardiovascular Disease (CVD)

The National Center for Chronic Disease Prevent and Health Promotion (2022) emphasize high blood pressure (hypertension), obesity, diabetes (insulin resistance and elevated serum glucose), and high cholesterol (dyslipidemia) as the leading risk factors for stroke and heart disease.

Interestingly, some researchers have also linked chronic stress to a sustained low-grade inflammatory state (Tenk et al., 2018; Van de Valk et al., 2018). And while the development of obesity, hypertension, and insulin resistance/increased serum glucose levels have been shown to increase cardiovascular stress, researchers are also finding that the increase in oxidative stress can be linked to incidence of CVDs (Rossi et al., 2021). As discussed earlier, oxidative stress is commonly associated with glucocorticoids (Tenk et al., 2018).

Figure 2: This infographic produced by the CDC (2013) outlines the risk factors associated with CVDs along with interventions to mediate the risk.

While the interventions in Figure 2 are suitable for the adult population without outstanding factors, this paper specially discusses the group that suffers an epigenetic predisposition to MetS or CVDs as a consequence of arguably teratogenic effects of excessive maternal cortisol production on embryonic/fetal development.

The focus of this paper is on cortisol in relation to fetal development and fetal outcomes. Fetal development is markedly chronological and intentional in its developmental course of tissue and organ specification/formation. The next chapter will explore how the disruption to maternal-fetal hormonal milieu can incite long-standing, irrevocable consequences on development that will impact the offspring's adult life.

Chapter 4 : Development from Conception into Adulthood

Table 1: Based on information from the Embryology textbook (Hill, M.A., 2022)

Week 1	Fertilization of the ovum with the spermatozoa
Week 2	Implantation of the ovum onto the uterine wall
Week 3	Gastrulation (when the embryonic cell transforms from a 1D layer of cells to a 3D multilayered structure) and notochord (key to helping with cell ectoderm and mesoderm differentiation) formation - **Ectoderm** - **Mesoderm** - **Endoderm**
Week 4	Beginning of organogenesis - Differentiation of the spinal cord and components of the brain begins components of sense of smell form - The heart begins to pump, first functioning organ - Portions of the endocrine system begin to form thyroid, pituitary - The liver begins to develop - Simple structure of skin begins to form
Week 5	Continuation of organogenesis - Continuation of pituitary, heart, liver, and brain/cord formation - Respiratory system starts to develop - Components of the system responsible for hearing/sight begin to develop

	- Budding limbs can be visualized
Weeks 3-8	Described as the **embryonic period** The embryo will conduct most of the foundational development, making it most sensitive to external stimuli.
Weeks 9-birth	Described as the **fetal period** These weeks involve the complexification of the organ systems that were established within the embryonic period of development. Development of the neural system remains active during the fetal period, making it susceptible to defects or maladaptive changes for the majority of the pregnancy.

Sequential Milestones in Embryonic and Fetal Development

Embryonic development following fertilization of the ovum/oocyte by the spermatozoa, forming a zygote, can be categorized into periods of coordinated body system development dictated by genes and various other growth factors.

The first two weeks following fertilization are considered pre-embryonic development. During this time, the zygotic cells will multiple as it travels towards the uterus, where it will ideally implant into the endometrium (inner uterine wall) (Biga et al., 2019). Between the third and eighth week of embryonic development, the crude body systems and structure of the embryo will begin to take form. Research has found that organogenesis begins within the third or fourth week, with elementary CNS development occurring around the fourth and fifth week (Biga et al., 2019). After eight weeks gestation, the embryo will be considered a fetus and transition into fetal

development. Ultimately, the first eight weeks build the foundations for the neurosensory system, musculoskeletal system, digestive system, and other organs that will mostly complexify during fetal development. Development of the neural system remains dynamic during the fetal period, making it susceptible to defects or maladaptive changes for the majority of the pregnancy (see Figure 3). From the ninth week until the thirty-first week, developmental focus shifts to building upon embryonic foundations and preparing for extrauterine life (Biga et al., 2019).

Though this paper will briefly review the developmental phenomenon that occur during the fetal period, the primary focus will be the neuroendocrine and cardiac systems as they relate most directly to CVDs. After the sensitive windows of development, systems are refined, and maturational energy is directed towards preparation for birth and extrauterine survival.

During the fetal period, the skin differentiates the epidural and dermal layers, and pigment/ridges become more apparent in the dermis (Arey, L. B., Rogers, K., & Sapunar, D., 2012). Early ossification can arise during this period and bone marrow begins to produce erythrocytes, a role that was solely occupied by the liver (Biga et al., 2019). Around the tenth week, the fetus exercises the musculoskeletal system through movement experienced by the mother as “quickening” (Arey, L. B., Rogers, K., & Sapunar, D., 2012).

The cardiovascular system morphs throughout embryonic, fetal, and neonatal stages to meet the offspring’s needs accordingly (Arey, L. B., Rogers, K., & Sapunar, D., 2012; Miranda et al., 2017). While the heart undergoes constant changes, the ability to perform adequately is determined by four major components: preload (ventricular volume at the end of diastole), afterload (ventricular volume at the end of systole), contractility (force/strength of the contraction), and heart rate (Miranda et al., 2017); to gauge cardiac performance, function must remain intact throughout gestational development. It must be acknowledged that the fetal cardiac

system is historically difficult to assess due to limits in diagnostic tests and fetal disposition; however, recent years have introduced new assessment methods, and this should positively impact the quality and quantity of research produced.

As suggested by the Figure 3, the dark blue window of critical neural development continues into the fetal period and has the longest sensitive window of all the systems. The central nervous system (CNS) stems from the ectoderm (derived from the notochord) during the third week of embryonic development (Arey, L. B., Rogers, K., & Sapunar, D., 2012; Hill, M.A., 2022). During the fourth week, primitive brain structures form, known as the prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain). By the fifth week, further specification occurs—the forebrain bifurcates into the telencephalon and diencephalon, and the hindbrain into the metencephalon and myelencephalon. The telencephalon of the forebrain develop into the hemispheres while the diencephalon gives form to the pineal gland (important for circadian rhythm) and part of the pituitary gland (Arey, L. B., Rogers, K., & Sapunar, D., 2012). For this paper, it is important to note that in the adult brain, the telencephalon founds the amygdala, hippocampus, cerebrum, hypothalamus, and pituitary, all of which are essential in understanding the stress system discussed in the previous chapter. The hindbrain's metencephalon establishes the cerebellum (balance) and the myelencephalon will form the medulla (autonomic regulation) (Hill, M.A., 2022). The peripheral nervous system (PNS) develops alongside the CNS, originating from the neural crest of the ectoderm (Hill, M.A., 2022); the PNS is divided into the somatic nervous system and the ANS (PSNS/SNS). During neural development, the ANS is derived from neural crest cells that migrate and specify

to fit system needs (Arey, L. B., Rogers, K., & Sapunar, D., 2012). Senses most remarkably develop later during the thirteenth and sixteenth weeks (Biga et al., 2019).

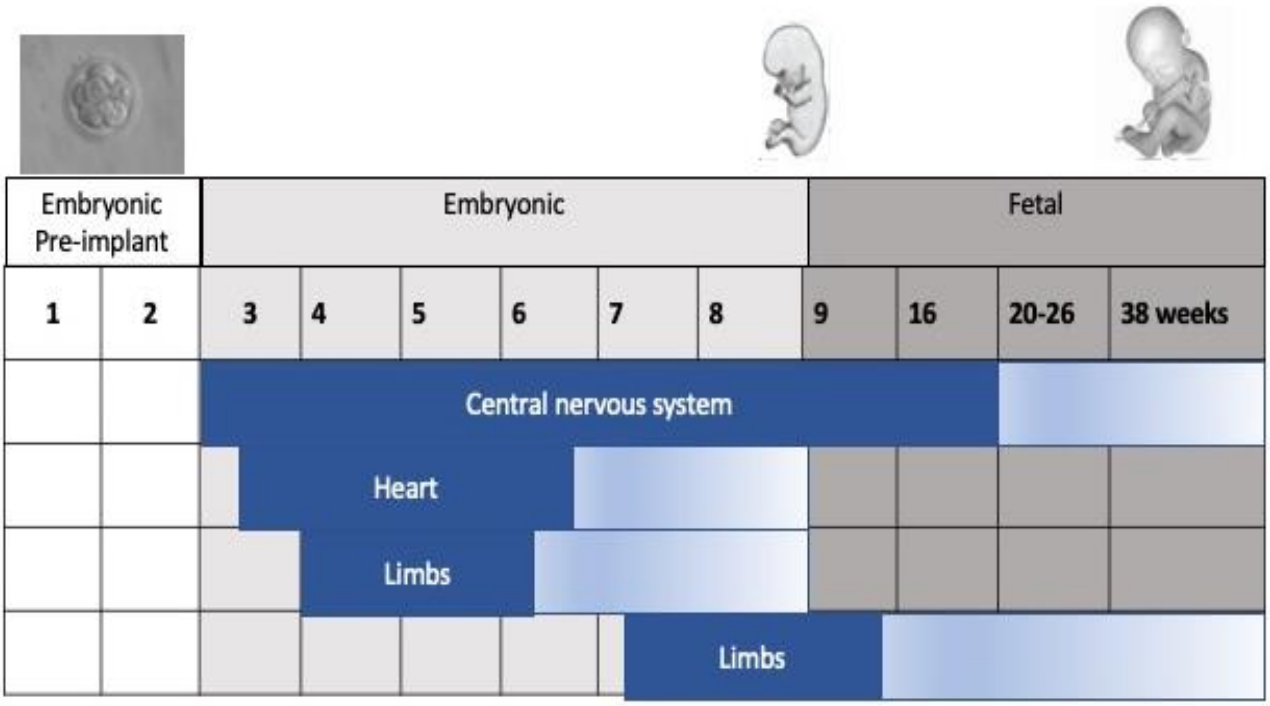

Figure 3: Development by gestation with periods of sensitivity towards abnormalities via toxins/teratogens. Dark blue indicates risk for major defects, light blue indicates minor risk. Adapted from Gilbert, S. F.

Fetal Sensitivity to Maternal Condition During Pregnancy

The nature of pregnancy innately links the maternal and fetal experience, with the maternal experience ultimately influencing the offspring's foundational development. Plainly, through this connection, the developing embryo/fetus interprets the maternal environment through physiologic cues and adapts accordingly to increase chances of survival. This section will review the genetic and visceral implications for offspring that are exposed to abnormal maternal stress levels.

The mother supplies the developing embryo with nutrients, oxygen, endocrinologic support, and other products through the placenta. Unification of the fetal circulation with the placenta through the umbilical cord is fixed within the embryonic stage and persists until severance during the postpartum period. While acting as the primary source of nourishment for the developing embryo/fetus, the placenta also prepares the developing offspring for the extrauterine environment through maternal cues. Hence, maternal stress levels, intake, health, and so forth are all reflected in embryonic/fetal development. With this understanding, research supports the adaptive effects that the embryo/fetus sustains in response to maternal condition during pregnancy.

To buffer exposure to potential threats or teratogens (agents that are toxic to a developing fetus), the blood-placenta barrier (BPB) acts as a primary defense and regulatory hurdle to promote optimal fetal maturation. However, the scope of the (BPB) can be limited, so the highly sensitive and selective fetal blood-brain barrier (BBB) acts as another obstacle protecting impressionable neural parenchyma (Goasdoué et al., 2017). As Goasdoué et al. (2017) discuss in their research, the BBB's specificity is effective against large, lipophobic, and/or receptor-

dependent drugs/toxin, making it more pertinent when discussing drugs. For the purposes of this paper, the discussion will explore glucocorticoid interaction within maternal-fetal circulation in more detail. To preface the below research studies and conclusions about the relationship between cortisol exposure and development, it must be understood that cortisol is integral to normal development; however, at abnormally high levels, it can arouse unfavorable epigenetic imprints on developmental trajectory. Moreover, it cannot be considered a classic teratogen but rather a modulator for development; maturation will appear generally unremarkable but there will be insidious epigenetic faults that can determine quality of life later. Inherited genetic expression can compound with acquired lifestyle risks factors for MetS and CVDs. It is the mission of this paper and further research to investigate the impact of excessive cortisol and how timing/levels may determine the repercussions for later life (increased HPA-axis reactivity, risk for CVDs/MetS, etc.).

Starting with the glucocorticoid hypothesis proposed in the early 1990s, researchers continue to suspect that fetal exposure to excess glucocorticoids may explain aspects of fetal programming which can predict growth and health outcomes (Reynolds, R.M., 2012). To attenuate glucocorticoid potency and rectify the high glucocorticoid permeability of the BPB/BBB, there is a placental enzyme recognized as 11 beta-hydroxysteroid dehydrogenase (HSD2) that metabolizes cortisol into the inactive product cortisone. Due to glucocorticoid's relevance in growth and system maturation, HSD2 does not absolutely impede glucocorticoid reception at GR/MR sites in the fetus, placenta, and fetal membranes. Ideally, HSD2 production rises throughout gestation to offset the innate surge in maternal glucocorticoids. However, increasing research has found that the efficacy of HSD2 can be diminished by poor intake, infection, inflammation, hypoxia, and/or stress (Reynolds, R.M., 2012). Moreover, as discussed

in the previous sections, toxic stress can also impact intake or incite a low-grade state of inflammation. Should maternal cortisol levels exceed HSD2 coverage, cortisol can bypass BPB/BBB and impact development, especially during critical periods. Nazzari et al. (2019) suggest that HSD2 gene expression can be downregulated when exposed to SNS catecholamines, which further supports the association between maternal stress and fetal subjection to hazardous glucocorticoid levels.

Excess glucocorticoids with insufficient HSD2 response can provoke visceral developmental deviations that can prove maladaptive in adulthood. While there are many systems susceptible to the adverse effects of excess glucocorticoid exposure, this paper will outline the adaptations pertinent to stress reactivity and CVDs. The theories presented thus far are fairly well established and can provide important context for the following research. It is crucial to consider the methodology and how minute factors can bias the results, effectively altering the study's conclusions. Some important variables include the researcher's definition and quantification of stress, sample heterogeneity, age/gestation of subject, pre-existing conditions, and so forth. Without a consistent methodology, a clear hypothesis cannot be made, and comparison is futile. Furthermore, researchers seem to unanimously agree that research will be stunted so long as there is a failure to reach a consensus regarding the definition of stress, how to quantify it, and how to classify it as normal or toxic (not including a clinical diagnosis). With this in mind, the research will acknowledge the spectrum of abnormal glucocorticoid level measurements with an analysis into how the variations may affect the results.

Proper fetal maturation necessitates circulating glucorticoids, but development can suffer under adverse levels of exposure (Reynolds, R.M., 2012; Miranda et al., 2017; Stoye et al., 2020). As discussed earlier, glucocorticoid levels linearly rise as the pregnancy continues in

preparation for birth and to settle developmental details. It is when these levels are inappropriate in potency or timing that can cause detriments. A study conducted by Stoye et al. (2020) set out to track the relationship between serum cortisol levels and neonatal birth weight. Using a sample of 151 pregnant women at clinics across Texas, Pennsylvania, and Illinois, researchers collected urine and serum samples (to detect active and inactive glucocorticoid metabolites) during the second and third trimesters. After controlling for confounding variables such as smoking, BMI, maternal age, gestation, gravidity, hypertension, and so on, researchers were able to track excretory versus serum metabolite trends and draw physiologic conclusions regarding glucocorticoid and enzymatic levels. During the second trimester, there was no association between glucocorticoid excretion and serum cortisol levels; meanwhile, during the third trimester, the serum levels were higher than excretory levels. These results suggest that individual differences in glucocorticoid metabolism and HPA-axis responsiveness to the negative feedback system (Stoye et al., 2020). Furthermore, researchers found a positive correlation between glucocorticoid excretion and birth weight.

Another study piloted by Entringer et al. (2017), investigated the potential relationship between maternal cortisol production and fetal adiposity at different gestational stages up until six months postpartum. With a smaller sample of 67 pregnant singleton women, researchers had the women collect five saliva specimens daily for a total of twelve days scattered within the three gestational periods. The frequency differs from some of the other studies, and it arguably respects the variations in maternal cortisol and fetal adiposity that may arise across gestational development. The results found a positive correlation between maternal cortisol levels in late gestation and fetal body fat percentage during the six-month postpartum period. Moreover, researchers suggest that fetal exposure to maternal cortisol levels could determine glucose

concentration and fat storage in offspring through fetal programming of adipose tissue. (Entringer et al., 2017). Reflecting on the previous chapters, it is completely plausible seeing that chronically elevated levels of cortisol impact visceral adiposity and serum glucose levels (see Figures 1 and 2). Entringer et al. (2017) continue on to specify that the correlation between late gestation cortisol exposure and adiposity could be attributed to the fetus' augmented sensitivity to adipose programming. This conclusion can be supported by the understanding that the third trimester is important for the preparation of extrauterine life and much of infant adipose tissue is generated during this time.

The results of these studies seemingly oppose the faction of researchers that have emphasized a connection between low birth weight (as a consequence of elevated glucocorticoid exposure) and gene expression affecting cardiac function, insinuating that the negative impact on cardiac function increases the offspring's risk for developing a CVD in later life (Miranda et al., 2017; Reynolds, R.M., 2012). It's important to mention that these sources did consider fetal growth restriction when discussing the correlation between low birth weight and cardiovascular consequences. Though both sides agree about the relation between excess maternal glucocorticoid exposure and an increased risk for CVD in exposed offspring, they are approaching the cause from different angles with different methodologies. Perhaps low fetal birth weight and stress are related through circulatory/sustenance shunting that occurs during the stress response, or it could be a matter of gestation at the time of exposure. Regardless, the discrepancy could be amended through increasing the rigidity of methodology and boosting research that will investigate the mechanisms underlying these effects in a range of fetal populations (a shortcoming that all sources recognized).

As stated previously, the neural system has the longest critical window which increases the risk for foundational maladaptation. Maternal and fetal CRH/glucocorticoid production plays a vital role in the neural system's maturational course because it helps to develop fetal systems and communicate maternal cues to the fetus. Recent research investigating the impact of maternal cortisol on neural development appears to be accounting for gender-specific differences, which presents a more detailed perspective into why some individuals may be more prone to disease processes. Cowell et al., (2020) orchestrated a study to identify the relationship between maternal cortisol output and associated deviation in PNS/cardiac function. The study pulled 204 singleton early pregnant women from cohort enrolled in a program to study the role of stress and development. It's relevant to consider the possible bias of this group related to homogeneity of the sample. For three days, five daily cortisol saliva samples during mid gestation were collected, and during the third trimester, a hair specimen was collected to assess longstanding cortisol levels. At six months of age, the offspring of these women endured Repeated Still Face Experiments and were assessed for their responsive respiratory/cardiac (respiratory sinus arrythmia test, RSA), emotional, and activity. Results found that both genders (especially in male offspring) born to mothers with high prenatal cortisol levels had maladaptive PNS responses with the Repeated Still Face Experiments. Researchers did recognize that the timing for collection of cortisol samples and their attempts to control for natural cortisol increases may have been inappropriate, thus impacting the results (Cowell et al., 2020). Many in the field acknowledge the challenge of associating HPA-axis function and abnormal stress, let alone impacts on infant ANS activity; however, research continues to support an increased stress reactivity in offspring born to mothers that report stressful instances (Cowell et al., 2020). It is

feasible that more stringent definitions/quantifications of maternal/neonatal stress and gestationally-mindful specimen collection periods could yield more compelling results.

Programmed Stress Reactivity in a Developing Fetus

Whilst in utero, the embryo/fetus utilizes maternal indications of extrauterine life to adjust their unique developmental trajectory to maximize chances of survival. In most circumstances, this is a valuable adaptation; however, this process can establish maladaptive outcomes if the maternal signals are an inaccurate depiction of the outside environment. This balance is recognized in fetal programming (Irwin et al., 2021).

Aforementioned, cortisol is an important product of the HPA-axis that is required for healthy embryonic/fetal development but can prove detrimental for the offspring under sustained or high levels. Said repercussions can manifest in an assortment of body systems to any extent depending on gestational time of exposure and potency, making the fallout abysmal. Fittingly, maternal stress reactivity is hypothesized to program offspring stress reactivity, denoting that maternal cortisol levels can moderately dictate the stress system and reactivity of the offspring. Consequently, numerous studies support the maladaptive relationship between disproportionate maternal stress levels and subsequent fetal HPA-axis functionality/stress reactivity (Cao-Lei et al., 2020). Justly, fetal stress reactivity would increase and the HPA stimulatory threshold would decrease if maternal cues warned of a perpetually unsafe environment, with the logic being that constant hypervigilance is vital to survive these conditions.

Research evaluating the influence of fetal programming on HPA-axis functionality across animal and human studies suggests a link between maternal stress and infant cortisol regulation. Predictably, Irwin et al. (2021) report that there is a deficiency in studies directly examining the link, and they note a dilemma to then draw comparisons as a consequence of irregular methodologies and varying gestational periods during study. In their study, Irwin et al. (2021)

aimed to evaluate their claims that elevated levels of maternal cortisol would be reflected in the elevated infant cortisol response to painful stimuli. In addition, they hoped to expose any sex-based differences that some studies were reporting. In a sample of 152 singleton pregnant women from clinics in Southern California, researchers collected five different salivary cortisol samples during medical interviews throughout the course of the pregnancy. Then, at six and twelve months postpartum, they collected salivary cortisol samples from the offspring before and after inoculation. In addition, Irwin et al. did account for sociodemographic covariates during analysis. Results of the study revealed a correlation between prenatal exposure to high maternal cortisol levels and heightened infant cortisol reactivity without evidence of sex-based differences (Irwin et al., 2021), suggesting that maternal cues affected fetal programming of the HPA-axis. The discussion goes on to consider the mechanisms behind this correlation, most of which will be discussed in the next chapter on epigenetics, which include DNA methylation of genes related to the HPA-axis, greater proportion of cortisol response to stimulus, and an inhibition in the growth of key systems as a consequence of prenatal exposure (Irwin et al., 2021). The evidence of this study could support the claim that affected offspring are more likely to experience persistent stress levels in life thus increasing their risk for CVDs; however, more research is necessary to establish a firm parallel.

Though many researchers agree that abnormal maternal stress levels affect fetal outcomes, there is debate on the influence of maternal psychosocial stress on offspring stress reactivity and the HPA-axis. The controversy could stem from inadequate methods of quantifying psychosocial stress, making it difficult to account for in analyses of maternal stress. Ping et al. (2020) offer a unique longitudinal study of maternal stress and the impact on sex-specific HPA-axis reactivity in offspring through measuring subjective stress evoked by an

objectively distressing ice storm in Quebec. The sample was composed of women that were pregnant or became pregnant within three months of the storm, equating to a final sample size of 45 pairs. Mothers were provided with a questionnaire assessing for their perceptions of the disaster and the psychological consequence(s) they may have experienced (in addition to questions controlling for sociodemographic factors). To account for fetal gestation, researchers estimated time of exposure to be within conception and the documented peak of the disaster where the greater the number equated to later gestational exposure. Then, thirteen years postpartum, the offspring endured a three-hour stress-inducing test (Trier Social Stress Test) with seven salivary cortisol specimens: 1) prior to the start of total experience, 2) five minutes before the Trier Social Stress Test, 3) immediately after stress test, and 4) fifteen-minute intervals of an hour post stress test. After controlling for offspring puberty/behavior and maternal characteristics, results concluded that there is an association between increased maternal stress and reactive cortisol levels in offspring, especially those exposed mid to late gestation (Ping et al., 2020). Additionally, data showed that offspring exposed to greater levels of maternal stress late in gestation had higher pre-stressor (baseline) cortisol levels, with higher baseline cortisol levels in female offspring over male. In retrospect, the researcher could have established a more reliable baseline if the first cortisol sample was a hair specimen (Romero-Gonzalez et al., 2018). Likewise, Ping et al. (2020) report unreliable results with the subjective measures of stress in the mothers; meanwhile, they reported that their subjective stress assessment was preferential to post traumatic stress manifestations. Perhaps adopting a more non-specific stress assessment could have modified the results.

Though the results of these studies cannot directly support a causal relationship (much like the other studies), it can point to the impact maternal stress levels have on stress reactivity to various stimuli and differences in offspring exposed to heightened levels of prenatal stress.

Chapter 5 : Fetal Exposure to Cortisol and the Epigenetic Impact in Later Life

This chapter will delve into the discipline of epigenetics/fetal programming as alluded to in previous chapters and consider its role in fetal development that has been subject to extreme levels of maternal stress. Moreover, the research proposed in this chapter will aim to reinforce the impact of prenatal stress on later quality of life.

Epigenetics delineates the field of study dedicated to exploring genetic variations in phenotype based on an individual's environment or generational genetic heirlooms. Currently, there are three primary mechanisms behind epigenetics: DNA methylation, histone modification, and microRNA (Cao-Lei et al., 2020). DNA methylation can be understood as a shift in genomic activity without a mutation to the DNA sequence (Stratton, M.S., Farina, F.M., & Elia, L., 2019). Histones function as the "gatekeepers" of gene expression by aiding or disrupting transcription (Gilbert, S.F. & Barresi, M.J., 2016). Finally, microRNA is a type of RNA that works to repress gene transcription (Stratton, M.S., Farina, F.M., & Elia, L., 2019). In respect to this paper, these epigenetic mechanisms could demonstrate the heritability and susceptibility to stress programming and reactivity (Cao-Lei et al., 2020). It deduces that epigenetic mechanisms can alter the upregulation and downregulation of particular genes (like those receptive to glucocorticoids) through precise coordination of silencing select promoter activity via binding to transcription factors and/or chromatin inactivation (Cao-Lei et al., 2020; Conradt et al., 2018). Sensibly, the environment dictates an individual's unique gene expression throughout the course of their life. With that, the epigenetic modifications that occur in utero are stable changes that persist long after exposure. Expression does not oscillate with peaks of cortisol, rather these

irrevocable changes to gene expression will persist through the life of the offspring and possibly thereafter. Consequently, an individual's epigenetic profile may divulge the origins of their unique stress reactivity, and in turn, revealing their risk for associated disease processes.

Through epigenetic mechanisms, in utero conditions can impact fetal programming of body systems to best adapt to the environment. If maternal cues frame the extrauterine environment as threating, the fetal phenotype and upregulation of genes related to the stress response will be reflective of sustained prenatal stress (Tsigos et al., 2020). This theory has been reiterated throughout this paper with this chapter suggesting an epigenetic element. For example, in the study evaluating the stress response of offspring born to mothers that endured a disastrous ice storm (Ping et al., 2020), there may have been an overlooked element of fetal programming that attributed to elevated stress levels at baseline and reactivity in offspring. Since the physical qualities of the maternal environment have been thoroughly analyzed within this paper and otherwise, this section will investigate maternal perceptions related to the social environment and the potential impacts on offspring stress reactivity phenotype.

Most of the studies above discount for socioeconomic status (SES) covariables to avoid introducing potential bias. While this may be essential in some studies, it would be negligent to completely omit the role SES plays in the epigenetics of stress system reactivity and the associated risk for CVDs. Bush et al. (2017) acknowledge that this deficient is especially alarming because low SES groups are typically at a greater risk of prenatal adverse exposure. Hence, they introduce a study that accounts for stress reactivity profiles of low SES mothers-infants through examining objective instances of stressful life events (SLE) and perceived stress (PS) in low- to middle-income pregnant mothers, then assessing offspring stress reactivity and

regulation. A sample total of 151 singleton mothers with a household income below 500% of the federal poverty level were recruited from hospital clinics, community health centers, WIC program, organizations that direct programs towards pregnant women, and online advertisements (Bush et al., 2017). Mothers completed PS questionnaires during mid to late gestation and PS/SLE (via CDC's PRAMS survey and PS self-report) questionnaires at six months postpartum with the infant stress test also completed in-person during the six-month postpartum appointment. At the six-month appointment, infant stress reactivity/regulation was assessed using parent reports of temperament (via Infant Behavior Questionnaire), Still Face experiments, and responsive respiratory/cardiac activity (via RSA). Researchers found that the results varied but there was a link between high maternal reports of prenatal/postnatal stress and reports of infant with lower stress-regulatory capabilities. Such results could propose that offspring will reflect the stress profile of their mother's environment despite never enduring it within their extrauterine life. Similar to Ping et al. (2020), Bush et al. (2017) found that maternal perceptions of subjective stress were more difficult to quantify and apply than objective measures of stress. Perhaps the great variations in the perceptions of stressful events makes this measure highly incalculable for now. There is a need for more research investigating the epigenetic presence of hereditary stress reactivity in multiple generations subject to subsequent adverse environments, particularly considering the cyclic nature of poverty; this could be achieved through longitudinal studies tracking stress reactivity phenotypes across generations. Nonetheless, these results do not support a solely causal relationship between SES and risk for CVD in offspring as there are many components contributing to an individual's cellular and bodily health. Finally, this study could have benefited from salivary or hair cortisol specimens to strengthen their assessment of offspring stress reactivity.

Conversely, there are few studies exploring the positive outcomes for offspring born to mothers with perceived psychosocially favorable pregnancies. Thomas et al. (2017) orchestrated a study evaluating the impact of prenatal maternal social supports and the consequential relationship between offspring and mother in conjunction with offspring cortisol reactivity. The researchers chose to examine social environment because they felt that infant and adult HPA-axis activity is sensitive to social situation. A total sample of 272 singleton women with less than twenty-two-week gestational pregnancies was pulled from prenatal clinics. To quantify perceptions of maternal social supports (both negative and positive) and maternal emotional wellbeing, researchers administered the Social Support Effectiveness Questionnaire and the Edinburgh Depression Scale at three points in time: 1) mid gestation, 2) late gestation, and 3) six months postpartum. Additionally, mother/infant interaction was observed (via the Parent Child Interaction Teaching scale) six months postpartum with infant salivary cortisol specimens extracted at baseline and twenty minutes after a standardized stressor (toy retraction/obstacle and restraint). After controlling for confounding variables such as family characteristics and the innate cortisol diurnal pattern, the results reflected decreased infant cortisol levels at baseline/post-stressor and higher quality interactions in mother-infant pairs that reported ample prenatal social support. Likewise, mothers that reported greater social support demonstrated higher quality interaction and disclosed fewer prenatal depressive symptoms (Thomas et al., 2017). Inclusion of this study illustrates the potentially positive outcomes of fetal programming when the extrauterine environment is beneficially stimulating. Future studies could insinuate that offspring stress reactivity phenotype is reflective of a non-threatening environment as communicated by maternal cues during pregnancy; however, more research is necessary to strengthen our understanding of this exchange.

Chapter 6 : Conclusions to Research and Further Research

If the epigenetic mutations induced by excessive intrauterine cortisol are as potent as the research suggests, then typical interventions to ward off MetS and CVDs may prove inadequate and warrant adaptations in management and treatment. Additionally, as science reveals epigenetic ties, the clinical setting may uncover revelations with patients that are unaffected by typical MetS/CVD intervention because their phenotype is independent of their lived experiences.

Through source appraisal and analysis, there were several shortcomings in research that stunted progress. Withal, the topics outlined in this paper warrant longitudinal research to accurately track the association between prenatal stress exposure during critical periods of development and the likelihood of developing CVD later in life. Currently, longitudinal research is scarce. Some researchers alluded to the deficit, acknowledging that the limited amount of longitudinal research restricts conclusions because offspring with an increased reactivity who likely remain in stressful conditions may not show that until significantly later. To truly grasp the gravity of the relationship, offspring should be followed for the duration of their life. In doing so, researchers may be able to validate or dismiss the relationship between the development of metabolic syndromes and chronic stress exposure coupled with increased glucocorticoid sensitivity. Additionally, many of the sources above drew overarching conclusions from data that was limited to gestational milestones using methods that impacted the results. Uniquely, research into intrauterine conditions is highly impressionable by the gestation. It is obtuse to assume the results from one snapshot of gestation apply to the entirety of intrauterine maturation and the

subsequent profile of the offspring. Moreover, how stress is understood and quantified by researchers varies which is producing inconsistent results. For context, some of the studies above used observational means and relied on salivary cortisol samples (Entringer et al., 2017; Irwin et al., 2021; Ping et al., 2020; Thomas et al., 2017), some on mixed hair/saliva specimens (Cowell et al., 2020), and did not collect specimens (Bush et al., 2017). With more rigorous methodology, a general consensus could be more possible. It is important to note that hair specimens are a more accurate depiction of sustained cortisol levels while salivary samples are short-term measurements (Cowell et al., 2020).

Research in this field is continuing to suggest that attempts to curb the evolution of MetS and CVDs in adulthood may be inept in populations that developed in unfavorable intrauterine environments. Seeing as prenatal maternal stress is nondiscriminatory, it is paramount that resources are universally allocated to the early identification of prenatal maternal stress and administering the appropriate interventions (Romero-Gonzalez et al., 2018). For example, with more research into normal and abnormal stress during pregnancy, prenatal appointments may benefit from the inclusion of routine stress (cortisol) assessments to aid in timely intervention.

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ACADEMIC VITA

Education

PENNSYLVANIA STATE UNIVERSITY……*Anticipated Graduation: May 2022*
Bachelor of Science in Nursing with an academic minor in Human Development and Family Studies

- *Schreyer Honors College and Altoona Honors College*
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- *Student Nurses' Association of Pennsylvania, Vice President*

Clinical Experience……..……*720 Total Hours*
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- Completed clinical courses on: Stroke, Neuro/Ortho Trauma, L&D/Postpartum, Cardiac units, MICU, STICU, SPCU, CTICU, NVICU
- Nursing responsibilities performed under RN supervision include: administering medication, performing assessments, assisting in medical/nursing treatment, educating about plan of care, documenting necessary information
- Further developed time management, prioritization, communication, and patient teaching skills

Clinical Practicum/Preceptorship……..……90 Total Hours
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- Altoona Honors College Scholar
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Certifications and Awards

- Certified Mandated Reporter the University of Pittsburgh - *Renewal Date: August 2023*
- AHA BLS (CPR-AED) - *Renewal Date: May 2023*
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