University Honors Capstone Research Project

# How Does Maternal Psychological Distress Affect Fetal Immunity?

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## Introduction

Postpartum depression, defined as a mood disorder occurring after childbirth characterized by persistent sadness, anxiety, and fatigue, is a term recognizable to the general public, with the words immediately bringing up some kind of emotion or memory. Acquaintance with the term may result from observation of a close friend or family member, or a familiar public figure. This overwhelming and all-encompassing mental illness can have effects on not only the mother but her offspring as well. However, concerns are not limited to depression during the postpartum period. Maternal depression, stress, and anxiety can also have overarching negative outcomes on both the mother and fetus in the prenatal period, which occurs during pregnancy. A wide array of evidence suggests that maternal prenatal depression and anxiety can also have negative effects on the immune system of offspring. Reduced immunoglobulin levels and increased amounts of atopic disease are often associated with maternal distress (Entringer et al., 2015). There are a few suggested physiological reasons for these outcomes. This may include effects on the maternal hypothalamic-pituitary-adrenal (HPA) axis—a complex system involving the hypothalamus, pituitary gland, and adrenal glands that regulates stress response—resulting in a decreased immune response and reduced production of secretory immunoglobulin A (SIgA), an antibody that protects mucosal surfaces, by the mother, both of which may lead to a reduced infant response to immune distress (Kang et al., 2018).

Depression, which is found to affect 7-12% of women during pregnancy, has overarching effects on both mothers and offspring (Kang et al., 2018). From observing only the mother, one would notice appetite changes, altered sleep patterns, melancholy, and increased sadness and anxiety (Kang et al., 2018). As a result of symptoms, the mother may have less interaction with their infant, reduced breastfeeding, increased smoking, and increased selective serotonin

reuptake inhibitor (SSRI) consumption (Kang et al., 2018). These factors affect the fetal environment via the HPA axis, which responds to stress in a negative feedback loop. This stress is not limited to depression. Anxiety, anger, and fatigue may all affect the fetal environment.

The hypothalamic-pituitary-adrenal (HPA) axis is made up of the hypothalamus, pituitary gland, and adrenal glands. This system is responsible for regulating the body's central response to stress, which is defined here as any threat to psychological or physiological homeostasis that challenges an organism’s well-being. To restore homeostasis, the endocrine, nervous, and immune systems respond to create what is known as the 'stress response' (Joseph and Whirledge, 2017).

In the face of stress, survival is the highest priority. Growth, reproduction, and immune function are all seen as less essential. Following activation of the HPA axis by a stressor, neurons in the paraventricular nucleus of the hypothalamus release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), stimulating the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH induces the synthesis and secretion of glucocorticoids (cortisol), mineralocorticoids (aldosterone), and adrenal androgens, which are then released into the blood from the adrenal cortex. Higher cortisol levels, often used to measure stress, inhibit the release of CRH and ACTH through a negative feedback loop, allowing the HPA axis to return to its physiological state after activation (Entringer et al., 2015). Following CRH secretion, cytokine production is decreased. This may lead to decreased T-cell activity, lower natural killer cell levels, and an overall diminished immune response (Kawano & Emori, 2015). For this reason, the HPA axis is often thought of as a bridge connecting psychological and immune states.

When a pregnant mother becomes stressed, her intrauterine environment is altered. This activates the HPA axis, affecting the fetal autonomic nervous and immune systems. This may be due to transplacental transfer of stress mediators and activation of transmitters in the fetus. Parts of the immune system, such as T-cell differentiation, develop prenatally and are susceptible to maternal hardship. This may lead to long-term alterations to the immune system, affecting the HPA negative feedback loop. Such effects may include modified maternal stress hormones that influence the fetal immune response. Reduced fetal immune function could result in changes to the infant microbiota (Andersson et al., 2015).

Immunoglobulin A (IgA) is an essential antibody in humans of all ages, playing a role in immune-related functions of mucous membranes. More specifically, IgA prevents pathogens from entering the gut mucosa, allowing for an oral tolerance to environmental toxins known as antigens. Infants are exposed to a variety of bacteria after birth, with some being dangerous and others beneficial. While the exact reason some infants do not smoothly transition from womb to world is yet to be determined, there is evidence that SIgA, the secretory form of Immunoglobulin A, plays an important role in this passage (Kang et al., 2018). In the first few weeks of life, SIgA is supplied through breast milk. It is protective against infection in the first few weeks of life, until the infant's gut begins to produce its own endogenous SIgA. Thus, SIgA has a key role in establishing the newborn gut microbiota. Several studies have shown that infants who are not breastfed have significantly lower SIgA levels in the first year of life (Bridgman et al., 2016). Deficiencies of this protein are often associated with respiratory or gastrointestinal infections and allergic disorders, and delayed immune maturation and SIgA production in infants can have similar effects. According to some studies, this may manifest in many ways, including atopic diseases, asthma, rhinoconjunctivitis, gut dysbiosis, dermatitis, and more (Entringer et al., 2015).

Through the HPA axis and SIgA deficiencies, maternal perinatal stress directly affects the uterine environment and negatively impacts the fetal immune system. This often leads to further negative outcomes. This review will discuss the effects of maternal perinatal psychological distress on fetal immunity through the lens of primary literature. In this review, three studies on the correlation between maternal psychological distress and reduced immune function will be covered. These studies differ in several areas, including the specific psychological factors assessed, the methods of collection, and the measurement used to assess immune functioning. Two studies measured SIgA in infant feces or breast milk, while the other examined the prevalence of infectious and noninfectious illnesses in infants.

**Effects of Maternal Psychological Distress on Maternal SIgA (Breast Milk)**

The first study examined the correlation between maternal postpartum psychological state and concentration of SIgA in breast milk (Kawano & Emori, 2015). According to this study, high SIgA levels can prevent bacterial or viral infections by neutralizing toxins and enzymes produced by pathogens. For this reason, an increase in SIgA levels typically is a sign that the immune system is reacting to physical stress. The concentration of SIgA can also be used as a marker for mental stress (Kawano & Emori, 2015). However, most previous studies used serum or saliva samples to measure SIgA. Kawano and Emori's study was one of the first to use breast milk as a specimen. Breastfeeding is known to have many benefits for both infants and mothers, including but not limited to nutrition, infant-mother bonding, reduced risk of sudden infant death syndrome, and a heightened maternal recovery after birth. Another important benefit of breastfeeding is the transfer of immune mediators, with secretory Immunoglobulin A being the primary focus.  As mentioned previously, when a patient experiences stress, the HPA axis

secretes corticotropin-releasing hormones, simultaneously increasing plasma cortisol levels and decreasing cytokine production. This leads to an accordingly reduced immune response.

The study by Kawano and Emori was conducted with 81 mothers in Tokyo, Japan. Candidates were selected based on many factors that included a healthy BMI, lack of tobacco use, and sole reliance on breast milk for their children's sustenance. Breast milk SIgA levels were measured two weeks after delivery, and 10-15 milliliters of breast milk were manually collected immediately after breastfeeding and stored at - 30° C. These samples were thawed and centrifuged, and SIgA levels were analyzed using an enzyme immunoassay and DU640 spectrophotometer.

Psychological states were assessed concurrently using several different surveys. The Profile of Mood States (POMS) questionnaire measured mood states over the previous week. This questionnaire includes criteria of tension-anxiety, depression-dejection, anger-hostility, vigor, fatigue, and confusion. The General Health Questionnaire (GHQ), which is commonly used on postpartum women, was intended to detect the magnitude of stress and neurological symptoms, including categories such as physical symptoms, anxiety, sleeplessness, social life, disabilities, and depressive tendencies. Lastly, the State-Trait Anxiety Inventory (STAI) scales were used to distinguish between anxious state at the time of assessment and anxious personality traits.

To determine the associations between maternal characteristics and breast milk SIgA levels, t-tests were used with the Mann-Whitney *U* test to analyze differences in the effects of all three tests on SIgA in breast milk. Spearman's Rank Correlation (*r*) was used to observe the correlation level between breast milk SIgA levels and the psychological states measured by each survey. After running statistical tests on correlations between SIgA levels and psychological

scores on the three tests described, breast milk SIgA levels were found to be negatively correlated with negative POMS traits. Negative traits included tension-anxiety, depression-dejection, anger-hostility, fatigue, and confusion. No correlation was observed with the positive state (vigor), supporting the idea that negative psychological conditions have more influence on breast milk SIgA levels. A weak negative correlation was observed between breast milk SIgA level and STAI state anxiety score ($r$ = -.334, $p$ = .004). The negative correlation between GHQ score and SIgA levels was found to be strong ($r$ = -.625, $p$ = .000).

While it has already been established in other studies that reduced breast milk SIgA levels are correlated with anxiety and fatigue in mothers after delivery (Groer et al., 2005), Kawano & Emori's study found that anger can also be associated with lower SIgA levels. All mentioned studies were in agreement that negative psychological traits during and directly following pregnancy are negatively correlated with breast milk SIgA.

The results of this study suggest that a low-stress peripartum period results in increased passive immunity transmitted to the infant via breast milk. From this conclusion, the importance of mothers' psychological health during the perinatal period is emphasized. There are many external factors that may alter results, such as the support of other family members for each mother and her financial status. Furthermore, the study did not extend beyond one week postpartum, leaving a substantial unstudied window in the postpartum period. Future research could examine the effects of stress on breast milk SIgA over a longer period following birth.

**Effects of Maternal Psychological Distress on Infant SIgA**

Another study summarized the possible correlation between maternal depressive symptoms and reduced fecal SIgA (Kang et al., 2018). The goal of this study was to measure the levels of SIgA in infants and determine how they may be related to maternal depression both in

the prenatal and postpartum period. Reduced levels of SIgA early in life may increase the risk of Immunoglobulin E-related allergic diseases, *Clostridium difficile infection*, and atopic diseases (Kang et al., 2018). The study by Kang et al., 2018 highlights the important role SIgA plays in establishing newborn gut microbiota composition. According to previous studies, exposure to maternal stress in the third trimester changed the gut microbiota of month-old infants such that fewer lactic acid bacteria were found to be present (Kang et al., 2020). This study builds on Kawano and Emori's work, which measured breast milk SIgA levels in relation to maternal psychological state. As they were found to be negatively correlated, the study done by Kang et al., 2018 goes a step further by measuring infant SIgA levels. Maternal depression, one presentation of psychological distress, was chosen as the mode of comparison.

In the second study, pregnant women aged 18 and older from the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort were selected. Maternal depression, which was self-reported, was assessed at recruitment (which was a mean of 27 weeks of gestation), 36 weeks of gestation, and 6 and 12 months postpartum. Prenatal and postpartum depression were determined using the Center for Epidemiologic Studies Depression (CES-D) Scale. Depression was measured through the frequency of experience of depressive behaviors, from zero to three times a week. The infants themselves were assessed at birth and three months of age. Stool samples were collected during the three-month home visits from a freshly soiled diaper using a spatula and then divided into aliquots. The fecal SIgA levels were measured in milligrams per gram of feces, with SIgA Immunodiagnostik ELISA used for measurement.

Covariates were selected from the data, which included a history of depression, maternal asthma or allergy status, consumption of SSRIs, delivery mode, exposure to antibiotics, small gestational age, breastfeeding status at the time of stool collection, number of children and pets

living in the home, prenatal and postnatal smoke exposure, and infant allergic eczema. All of these factors are individually known to reduce SIgA levels. 12% of women in the sample had clinically significant depressive symptoms only in the prenatal phase, 8.7%  only postpartum, and 9.2% in both periods. The mean SIgA concentration in infants was 3.79 mg/g feces. Fecal SIgA concentration declined with infant age and was higher in breastfed infants. Infants breastfed for four to eight months had a mean of 8.9 mg/g feces. Mothers who experienced antepartum depressive symptoms were 2.3 times more likely to have fecal SIgA concentrations in the lowest quartile than mothers without, and had lower concentrations overall. Four to eight months of infant age is when maternal antepartum depression symptoms are most correlated with low fecal SIgA concentration.

In summary, fecal SIgA concentrations in the lowest quartile were twice as likely to occur in mothers with antepartum or persistent depression. Even when maternal mood improved postpartum, mothers with antepartum depression delivered offspring with low fecal SIgA. Lowered SIgA concentration had the largest effect on infants aged four to eight months in both breastfed and non-breastfed groups, suggesting later infancy is when antepartum depression has the most effect on SIgA levels. This study suggests that while maternal psychological health in the postpartum period should be closely monitored, the prenatal period must be intently observed as well. Depression during this period may have greater effects on the infant's immune system, leading to heightened risk for atopic disease later in life.

**Effects of Maternal Psychological Distress on Infant Disease Diversity**

The final study discusses how maternal stress during pregnancy predicts infectious and noninfectious illnesses in infants (Bush et al., 2021). Previous studies show elevated maternal daily cortisol was associated with increased respiratory rates, skin infections, and general

illnesses in infants, as well as antibiotic use (Beijers et al., 2010). Elevated maternal cortisol is also associated with increased urgent care and emergency room visits for their infant (Phelan et al., 2015). While it is known that postnatal stress may affect brain function, prenatal exposure to stress also has potential for pervasive effects due to the sensitivity of the development of organs and systems functions during this time. The study by Bush et al. predicted that the outcome was strongly associated with the HPA axis and its effects on the fetal autonomic nervous system. The authors of this study noticed that most evidence on this front was from European samples of high socioeconomic status. Therefore, their experimental design focused on an ethnically diverse population of low-income pregnant women in the US, hypothesizing that offspring of mothers with higher stress levels would experience a higher diversity of illnesses in infancy.

The population used was the Stress, Eating, and Early Development (SEED) study, designed to identify the connection between prenatal stress and weight gain and child development. Mothers who were low-income, racially or ethnically diverse, and overweight with low medical risk pregnancies were recruited. Gestation ranged from 18 to 23 weeks. Mothers with any medical conditions or medications that may interfere with baseline weight or mood were excluded. Infant illness was assessed through medical record abstraction (MRA) of information related to diagnoses or medications prescribed at each visit in observation. Both primary care and emergency room visits in the first year of life were included. An infectious illness count was taken by summing diagnoses considered infectious. The total number of occurrences of each infection was reflected in the score.

Maternal stress was self-reported and retrospectively assessed by phone calls 12 months postpartum using situations from the Centers for Disease Control (CDC) and Prevention Pregnancy Risk Assessment Monitoring System postpartum survey. Participants were asked to

respond yes or no to experiences with hardship, such as the death of a loved one, major illness, etc. The Cohen Perceived Stress Scale (PSS) questionnaire was used to pinpoint the extent to which individuals view their lives as unpredictable or overloaded over the previous month. This was assessed during the second and third trimesters of pregnancy and again six months postpartum.

In Bush et al's study, perceived stress during pregnancy was positively correlated with all three illness outcomes during the first year of infant life. Each point above an average prenatal stress score was associated with a 38% increase in the number of infections, a 73% increase in noninfectious illness, and a 53% increase in illness diversity. The number of stressful events during pregnancy was not significantly related to illness prevalence. Postnatal perceived stress was not related to infant illness outcomes. The study also supported the idea that offspring from a lower socioeconomic status may be more at risk for illness.

To summarize the conclusions of the third study, maternal prenatal stress, especially late in pregnancy, leads to higher amounts of both infectious and noninfectious illness, as well as illness diversity. Although the immune system develops in the first trimester, maternal antibodies begin transplacental passage at 16 weeks of gestation, and the majority of IgG flows during the final 4 weeks of pregnancy. This provides protection against illness in the first few months of life. Further studies are required for confirmation, but it is strongly suggested that the final trimester is imperative to a developed immune response in infants.

**Conclusion**

Each of these three studies displays that maternal psychological distress leads to a decreased immune response, which then leads to increased levels of illness in infants. Exposure to stress during and after pregnancy may reduce SIgA in breast milk, which in turn may result in

decreased infant SIgA levels after delivery, as observed by decreased fecal SIgA levels in infants. In response to decreased SIgA levels, as the above studies indicate, infants have a diverse range of diseases. Collectively, the three studies provide further evidence of the idea that mental health is strongly connected to physical health and should be prioritized in mothers who are in the emotionally turbulent period of pregnancy and postpartum.

While the effects of maternal psychological distress have been widely studied, there are still many knowledge gaps when it comes to the impacts on the infant's immune system. To validate the hypotheses discussed in this review, further research is needed for each study. Regarding the study done by Kawano and Emori, which observed the effect of maternal psychological state on immune factors in breast milk, subjects were of the same nationality (Japanese) and were recruited from the same hospital. This is true for many studies of this kind, which is important to keep in mind when considering a wider population. This study also excluded patients with allergic or immunological diseases. The difference between the effects of negative feelings on mothers with and without these diseases could be observed in a future study. There is also a lack of research on the mental state after the first week postpartum, as these mothers were only observed in the first week. This is another area where further research may be needed.

In the second study discussed (Kang et al., 2020), which observed the effects of maternal psychological distress on infant fecal SIgA levels, a larger and more diverse sample of mothers was used. However, there were far more confounding variables, such as mothers on SSRIs and a lack of assessment of the effect of maternal anxiety on fecal SIgA levels. Fecal SIgA levels seemed to be reduced more by maternal anxiety than depression, meaning more research on this specifically could be highly beneficial.

The final study (Bush et al., 2021), which focused on how maternal stress in pregnancy predicts infectious and noninfectious illness in infants, focused on low-income women from diverse backgrounds. Because of this, the sample type may not be easily generalized to other populations. Many mothers targeted by this study may be less likely to seek medical attention, and because this study was restricted to people with six documented medical visits, many women targeted by the study may have been missed. This study was also unable to adjust for infant postnatal exposure to household smoking, which may have altered results. The last limitation of this study was the variance in charting, which may affect illness counts. In the future, larger samples could be used, and the HPA axis could be further observed. In addition, the effects of maternal stress reduction techniques on illness levels could be studied.

Of the future study possibilities mentioned in each paper, a few were of higher importance. Larger and more diverse samples would further show the effect of maternal stress on infant immune function. To detect feasible solutions for this issue, the effectiveness of different maternal stress-reduction techniques during pregnancy could be studied in relation to the infant's immune state. By fine-tuning reduction techniques for maternal stress, the infant benefits just as much as the mother, and progress is made toward a healthier world.

**Contextualization of Work**

Research relating maternal distress to fetal immunity is incredibly important in both the medical field and the scientific space relating to the peripartum period. Historically, women's health is an area that is often underresearched and overlooked. Mental health is another aspect of society that is regularly ignored, with symptoms pushed aside for more prominent health issues. A review highlighting just how important the mental health of pregnant mothers is to not only the mother, but the offspring's immunity through SIgA levels for years to come, is just another

reminder of why both women's health and mental health need to be prioritized. Giving exact statistics showing that maternal distress leads to reduced fetal immune function makes the truth impossible to ignore. This is true within academia, medicine, and society as a whole. Mental and physical health are deeply intertwined. The more spotlight shone on both mental health and women's health in medicine, the more that can be done to make changes for the better. For example, more medical protocols may be put in place to monitor and improve the mental health of pregnant and postpartum mothers, ensuring the presence of a support system and helping remove external stressors. This change can also be made by society. Anyone who knows a pregnant or recently postpartum mother can help out by checking in and offering support during this delicate time. The more understudied areas are researched, the more attention they will receive.

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