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The Genetic Link to Postpartum Depression

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Abstract

Postpartum depression affects an estimated 12% of women following delivery and it is believed that 50% of those women will go undiagnosed. It is well accepted in the scientific community that genetics play a role in the development of many mental health disorders. Recent research has demonstrated that this may also be the case with postpartum depression. There is a 50% incidence rate among women who have a first-degree relative diagnosed with postpartum depression (Guintivano et al., 2018). A literature review was conducted focusing on the research of epigenetics within the last five years, specifically investigating DNA methylation and single nucleotide polymorphisms. Sixteen articles met the inclusion criteria from PubMed and APA PsycInfo. The most promising research is related to DNA methylation at the TTC9B and HP1BP3 genes. Although it is still early in the research process, researchers have been able to use this information to accurately predict the development of postpartum depression in women with over 70% accuracy (Payne et al., 2020). Other areas of interest include DNA methylation at the oxytocin receptor and single nucleotide polymorphisms found in the genes 5HTT, COMT/MAO, and Beta-11. Although the research into these areas is relatively new and further confirmatory research is needed, this has established a good basis for investigating the genetic involvement in postpartum depression. This can result in better postpartum care for women, develop potential screening mechanisms, and lead to better outcomes for women and their children.

Key words: postpartum depression, genetics, DNA methylation, single nucleotide polymorphism

The Genetic Link to Postpartum Depression

The CDC estimates that 1 in 8 women will experience postpartum depression symptoms following the birth of their child. Assisting and aiding in family planning is a common request seen in primary care. Primary care is also involved with the follow-up care of postpartum mothers and establishing care for infants. Additional research on this topic may help new mothers and their providers successfully navigate the occurrences of postpartum depression. By understanding the genetics related to the development of postpartum depression, it could lead to better screening and treatment outcomes for both.

Statement of the Problem

Postpartum depression not only affects women post-delivery, but it can have a negative impact on infants. Postpartum depression can cause mother/infant bonding and attachment problems, which may result in an increased risk to the infant of emotional, social, and behavioral developmental impairments. There is a 50% incidence rate among women who have a first-degree relative diagnosed with postpartum depression, showing there may be a possible genetic link. It is estimated that 50% of women suffering from postpartum depression are never diagnosed (Guintivano et al., 2018). A better understanding of the genetic relationship to postpartum depression will not only benefit mothers by potentially providing better screening and treatment options, but also lead to better outcomes overall for mothers and their children.

Research Question

Postpartum depression is a serious condition that not only affects the life of postpartum women, but their newborn infant. It has the potential to influence infant growth, development, and mother-child bonding. It is important to identify potential biomarkers that may assist in identifying women who are at an increased risk. These problems led to the research question: Is

there a genetic link to the development of postpartum depression? Due to genetics being such a broad term, the focus will be on DNA epigenetic changes and DNA polymorphisms.

Methods

A review of literature shows there may be some underlying genetics involved with the development of postpartum depression in women, with a specific focus on DNA epigenetic changes and DNA polymorphisms. DNA methylation has been strongly studied and shows a potential correlation.

A literature review was performed using electronic search databases PubMed and APA PsycInfo. Keywords and MeSH terms were used to set the parameters for literature examining "postpartum depression genetics," "postpartum depression epigenetics," and "postpartum depression polymorphism." This resulted in 376 sources meeting the parameters. Limits were further set to sources that were published within the last five years (2016), which reduced the total number of sources to 156. Many of the 156 remaining studies were excluded because they did not specifically address postpartum depression, but only focused on generalized major depression. Other exclusions looked at other postpartum psychological conditions and did not exclusively focus on postpartum depression. Many others were eliminated because they did not focus on genetic findings that related to postpartum depression. Due to lacking more recent research in the noradrenergic system, the parameters were extended to include within the last seven years. This led to sixteen sources meeting the final inclusion criteria.

Overview: Postpartum Depression

Postpartum depression has been added to the latest version of the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5). This book is used as a diagnostic guide for psychological conditions. Postpartum depression is found within the criteria for

diagnosing major depression with peripartum as a specifier. According to the diagnostic criteria, depression symptoms will appear within four weeks of delivery, but many other sources question this time period and state it should be increased to 6 or 12 months post-delivery. In order to have a diagnosis of postpartum depression, the patient must exhibit at least five of the following symptoms for two weeks, nearly every day. One of the symptoms must include a depressed mood or markedly decrease in interest or pleasure in most or all activities previously enjoyed. Other possible symptoms include change in appetite, insomnia or hypersomnia, agitation or retardation, fatigue or loss of energy, feeling worthless or excessive or inappropriate guilt, decreased ability to concentrate or think, indecisiveness, or recurrent thoughts of death or suicidal ideations (may or may not include a specific plan). Symptoms must result in significant distress or impairment in social, occupational, or other areas of function. Also, the symptoms cannot be from effects of substance abuse or another medical condition. Symptoms cannot be better explained by a schizophrenia disorder, other psychotic disorder, and there cannot be manic or hypomanic episodes (American Psychiatric Association, 2013).

The exact incidence is unknown, but estimates range from 10% to 20% of postpartum women suffer from postpartum depression. Suicide accounts for 20% of postpartum causes of death (Guintivano, Manuck, & Meltzer-Brody, 2018). There may be some evidence that suggests a higher incidence rate among lower to middle income families. The specific pathogenesis is an ongoing research question. Evidence has shown mothers who have a history of depression prior to pregnancy are at an increased risk of developing depression postpartum. Women who are diagnosed with postpartum depression have a 40% recurrence rate in subsequent pregnancies. 87% of women will be in remission two years after delivery (Stewart, & Vigod, 2016). There are recommendations for screening postpartum women, but there is not a solid consensus on the

most appropriate method. The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics recommend using a ten-item questionnaire, titled the Edinburgh Postnatal Depression Scale (EPDS). Using this questionnaire, clinicians are able to give a numeric value to potential depression. Thirty points are possible and a score of 14 or higher is considered a positive screen. In those incidences, treatment is recommended for postpartum depression. When looking at the potential causes for postpartum depression, genetics is high on list. At 50% the phenotypic variation is significantly higher in postpartum women with postpartum depression. In contrast, the phenotypic variation in individuals with major depression without the postpartum specifier was 32%. The focus for genetic involvement is linked to DNA methylation and polymorphism DNA changes (Guintivano et al., 2018; Stewart, & Vigod, 2016).

DNA methylation

As we move through life our DNA adapts and changes with us. These changes to the DNA, known as epigenetic variations, are extremely small. However, as we evolve these changes can add up. Environmental exposures and lifestyle choices all play a role in epigenetics. DNA methylation is a chemical modification to the underlying DNA structure where a methyl group (CH3) is added to a DNA strand. This is commonly found in cytosine guanine pairs (cystosine-phophate-guaine [CpG]) of a DNA strand. This modification can lead to changes in gene expression and stability. DNA methylation has been linked to the development of cancer and early mortality (Lapato et al., 2019). The research into DNA methylation to aid in diagnosis is relatively new. The Food and Drug Administration has recently approved a DNA methylation blood test as a diagnostic tool in colorectal cancer. As research continues to advance in the epigenetics of postpartum depression there is potential to use this information as part of prenatal care. Blood draws are a relatively noninvasive procedure and would not compromise the

pregnancy or fetus. It could give providers a snapshot into the epigenetic variations present and increase actions to prevent or reduce the severity of postpartum depression (Lapato, Wolf, Lancaster, Roberson-Nay, & York, 2021). There are three main genes that have emerged through research as potential areas of interest. These genes include the Oxytocin receptor, TTC9B, and HP1BP3.

Kimmel et al. (2016) investigated the effects of methylation of Oxytocin receptor genes. Oxytocin is known to be a big component of social bonding; it also has been found to be a major regulator of stress and anxiety. Their hypothesis was that the stress of giving birth reacted with an underlying genetic vulnerability which resulted in postpartum depression. In this study, human subjects were used and divided into three separate cohorts. The first cohort had a relatively small sample size of 93 pregnant women. These women entered the cohort in the first trimester and were followed until one month postpartum. Blood samples were collected in first, second, and third trimesters prior to delivery and then again at one week, one month, and three months postpartum. Ninety-nine percent of the participants had a history of major depressive disorder or bipolar disorder (Kimmel et al., 2016).

The second cohort of women consisted of 63 women with an average age of 33 years old. One hundred percent of the participants had a previous history of major depressive disorder or bipolar disorder. Diagnostic criteria was obtained from the DSM-5. Blood was drawn in the first and third trimesters of pregnancy and within the first seven weeks post-delivery. These women were also screened post-delivery using the Edinburgh Postnatal Depression Scale. Out of the 63 women, 17 had new onset postpartum depression, 18 were always depressed, and 28 were with no mood disturbance (Kimmel et al., 2016).

In the third cohort, 240 women with no previous history of a psychological disorder were used. Blood samples were obtained in the third trimester, 48-72 hours post-delivery, and 6-8 months post-delivery. Depression was assessed using the Hamilton Depression Rating Scale. Women who scored greater than 14 were followed for three years post-delivery (Kimmel et al., 2016).

In the statistical analysis this study considered any P value less than 0.05 to be clinically significant. BrainCloud tool was used to compare the genetic results. BrainCloud is a public database that has dataset of brain prefrontal cortical gene expression levels and DNA methylation levels that are commonly used to compare genetic variants. They found that individuals who were depressed prior to giving birth had less DNA methylation of the Oxytocin ERE gene while those that developed depression postpartum had more DNA methylation (P=0.035) (Kimmel et al., 2016). They then used the third cohort, which consisted of women with no previous history of a mental health diagnosis and compared those that were diagnosed with postpartum depression to those that did not develop it. They found that women with a score of greater than 14 on the Hamilton Depression Rating Scale had much lower DNA methylation at the Oxytocin ERE gene than those that scored lower (P=0.035). They looked further into what hormones could influence the Oxytocin ERE gene and found that estradiol interacts with DNA methylation. With a P value of 6.1×10^{-6}, decreased levels of estradiol are found with decreased Oxytocin ERE gene methylation (Kimmel et al., 2016).

Toepfer et al. (2019) also conducted a research study aimed at investigating epigenetic DNA methylation changes of the Oxytocin Receptor (OTR) gene. Oxytocin is known to be an important hormone during pregnancy, delivery, and interpersonal bonding. Methylation is important because it is a known silencer, repressing genetic expression. Kimmel et al. (2016) is

the only other study addressing oxytocin methylation, and their findings suggested OTR could be used as a predictor to developing postpartum depression or intrusive thoughts. Toepfer et al. (2019) attempted to replicate the results found by Kimmel et al. (2016) (Toepfer et al., 2019).

One hundred seven mothers were enrolled in the study. Each underwent a blood draw in the first, second, and third trimesters of pregnancy and again at six months postpartum. At the six month mark the women and their children were recorded in a 15-minute play situation to evaluate the mother/child interaction. All the women in the study had a single intrauterine fetus. Women were excluded from the study if they had a preterm birth, or the child was born with a congenital birth defect. The EZ DNA methylation kit was used to analyze all blood samples obtained from the participants (Toepfer et al., 2019).

The results demonstrated that OXT methylation decreased from the first trimester to the second with no change between the second and third trimester ($P < 0.01$). Mothers that had depressive (intrusive) thoughts had a decrease in DNA methylation in the early trimesters with an increase in late pregnancy ($P < 0.01$). Whereas women without depressive thoughts had a decrease in methylation during the first and second trimester with continued decrease in the third trimester ($P < 0.05$). The mothers with depressive thoughts had about 6% more DNA methylation compared to women with no mood changes ($P= 0.018$). At three months postpartum the DNA methylation did not show an association to depressive thoughts ($P > 0.05$), which leads to DNA methylation status in late pregnancy and can predict depressive thoughts in postpartum women ($P= 0.016$) (Toepfer et al., 2019).

Elwood et al. (2019) found for every 10% increase in methylation at the OXT gene there was a 2.63 times greater chance of developing postpartum depression. Interestingly, there was no association found in women who had depression prior to the postpartum period. This suggests

that this could be a specific indicator for postpartum depression. More research is needed to corroborate these results (Elwood et al., 2019).

Osborne et al. (2016) focused the epigenetic changes to genes HP1BP3 and TTC9B in women who were diagnosed with postpartum depression. They aimed to replicate previously published studies related to DNA methylation and hormone changes. Four cohorts of human participants were used. The first two cohorts consisted of women with a previous mental health diagnosis. They were known as the John Hopkins cohort and Prospective Gene Expression PPD cohort. The other two were women with no previous history of a mental health diagnosis. They were in the Franconian Maternal Health Evaluation Studies (FRAMES) cohort or The Generations of Recurrent Early Onset Depression (GenRED) cohort (Osborne et al., 2016).

The John Hopkins cohort consisted of 93 pregnant women who had a history of major depression or bipolar disorder prior to being pregnant. The average age was 30 years old with 70% of the women identifying as Caucasian. The women were evaluated once during each trimester during pregnancy and at one week, one month, and three months postpartum. At each of these visits, the women underwent a blood draw and had a psychiatric interview. The DSM-5 criteria was used as the basis to diagnose depression in the postpartum period (Osborne et al., 2016).

Prospective gene expression PPD cohort consisted of 61 women with an average age of 33 years old who had a previous diagnosis of major depression or bipolar disorder. Eighty-eight percent of the women identified themselves as Caucasian. The DSM-5 was used as the criteria for diagnosis. The women were assessed at the first and third trimester using the Hamilton Depression Rating Scale (HDRS) and the Edinburgh Postnatal Depression Scale (Osborne et al., 2016).

GenRED cohort was a retrospective study. Eighty-four non-menopausal women with the average age of 39.7 years old completed a single blood draw. The women were asked if in the postpartum period they believed they experienced depressive symptoms. The control subjects were based off women who experienced depressive symptoms antenatally and then were euthymic during the postpartum period (Osborne et al., 2016).

The FRAMES cohort consisted of 240 women with the average age of 32 years old. A DNA sample was obtained from each individual at one, two and three years postpartum. Women completed the HDRS in the third trimester, at 48-72 hours post-delivery, and 6-8 months post-delivery. A score of greater than 14 was used to classify women into the depressed category (Osborne et al., 2016).

All of the blood samples were collected using the usual standard precautions. The EZ DNA Methylation Gold Kit was used to analyze blood looking for DNA methylation. Blood that was used to evaluate hormone levels was centrifuged for 30 minutes, then frozen and stored at -80 degrees Celsius. PCR amplifications were used to evaluate gene expression. Sliding window analysis was used to account for age-related DNA methylation changes (Osborne et al., 2016).

Osborne et al. (2016) found that they were unable to replicate results that methylation at HP1BP3 was not a significant predictor of postpartum depression in women with a history of a previous mental health diagnosis ($P= 0.085$). In women with no previous psychiatric history HP1BP3 and TTC9B were a significant contributing factor. Researchers were able to predict high HDRS scores with an AUC of 81% of the time. Next, hormone levels were assessed for an association to HP1BP3 and TTC9B methylation. HP1BP3 and TTC9B was found to have no association to levels of estradiol ($P= > 0.05$).

Payne et al. (2020) aimed to replicate previous data that DNA methylation on genes TTC9B and HP1BP3 could predict postpartum depression with an 80% accuracy. Human subjects were used for this study and divided into four cohorts: John Hopkins Prospective PPD, Emory University, UC Irvine, and John Hopkins Neuroimaging. These cohorts came from previous studies, but this study aimed to reexamine the results and look at it from a different perspective. The Edinburgh Postnatal Depression Scale (EPDS) was used across all cohorts as an assessment scale. A score of greater than 13 out of a possible 30 was considered diagnostic of postpartum depression. The John Hopkins Prospective PPD was used as the control group. Each cohort had the participants take the EPDS in the first and third trimesters. The EPDS was also completed in the postpartum period, but it varied between cohorts of when the assessment was done. The John Hopkins Neuroimaging and UC Irvine had participants with and without a previous history of mental health disorders (Payne et al., 2020).

The blood samples were processed using the EZ DNA Methylation Gold Kit following the manufacture instructions. Standard PCR protocols were used to identify PCR amplification. The samples were all randomized and given an identifying number to remove any bias. Laboratory employees were unaware of EPDS scores of participants until after completion of the data inquiry (Payne et al., 2020). Each blood sample was run three times in the lab to check for consistency. Payne et al. (2020) confirmed that methylation at genes HP1BP3 and TTC9B resulted in an increased likelihood of the development of postpartum depression ($P= 6.27 \times 10^{-6}$) in women with no prior history of mental illness. They consistently found that those with methylation had EPDS scores of greater than 13 postpartum. If methylation was found at HP1BP3 or TTC9B there was no correlation to increased EPDS score ($P= 0.0025$). The predictive accuracy was over 70% for HP1BP3 and TTC9B gene methylation and an EPDS score

over 13. This is consistent to the results from the John Hopkins Prospective PPD that these results were compared to (Payne et al., 2020).

Elwood et al. (2019) conducted a literature review and had multiple studies that looked at DNA methylation of the genes HP1BP3 and TTC9B. These were found in mice who displayed postpartum depressive symptoms and pregnant women with preexisting mental health diagnosis. Methylation at these genes were predictive of postpartum depression with an AUC of 0.96. These results were repeated in another study and successfully predicted the development of postpartum depression with an AUC of 0.81 (Elwood et al., 2019).

Single Nucleotide Polymorphism

Single nucleotide polymorphism is a genetic mutation. It affects the DNA base pairs adenine, cytosine, guanine, and thymine. In single nucleotide polymorphisms one of the base pairs is substituted for a different one. For example, adenine is replaced by cytosine, which changes the entire sequence of DNA and all future replications of that sequence. Research has focused on three different specific areas of genes known as 5HTT, COMT/MAO, and Beta-11.

5HTT

5-HTTLPR gene is a serotonin transporter gene that is found on the presynaptic membrane. It is believed that a polymorphism at this gene affects the serotonin concentration in the synapse. Serotonin has a well-established influence on depressive symptoms and the treatment of those symptoms. 5HTT gene is growing as a major factor contributing to the risk of major depression, postpartum depression, and other mood disorders.

Hu et al. (2019) completed a study looking at a genetic polymorphism change at the 5-HTTLPR gene. Four hundred thirty-seven women between the ages of 18-45 were enrolled as participants in the study. All of the women received prenatal care starting in the first trimester

and postnatal follow up for six weeks. Blood samples were obtained in the third trimester (between 34-40 weeks gestation) and within the first week post-delivery. The participants' mood was assessed using the EPDS and Self-Rating Depression Scale (SDS) questionnaires. The questionnaires were administered at one week and six weeks postpartum. A score of greater than 10 on the EPDS and a score of greater than 50 on the SDS were considered clinically significant. PCR was used to measure the 5-HTTLPR polymorphism and classified into two groups based off the alleles SS and SL/LL (Hu et al., 2019).

Postpartum depression was diagnosed in 12.8% of women at one week postpartum and 15.6% of the participants were diagnosed at six weeks postpartum based off the questionnaire scores. Maternal age, number of pregnancies, type of delivery, and income did not appear to impact those that were diagnosed with postpartum depression compared to those who were not ($P > 0.05$). When comparing those that were diagnosed and those that were not with how they scored on the questionnaires, participants with postpartum depression scored significantly higher ($P < 0.001$). The women were divided into two groups based off of which allele was present at the 5-HTTLPR, SS or SL/LL. Participants with the SS allele (recessive) were more likely to develop postpartum depression ($P= 0.004$) than those with the SL/LL allele ($P > 0.05$). The results they were able to produce is consistent with another study looking into the 5-HTTLPR gene polymorphism (Hu et al., 2019).

Li et al. (2020) also completed research on polymorphism at the 5-HTTLPR gene and the risk of a diagnosis of postpartum depression. They performed a meta-analysis in electric databases of case-controlled studies. The databases used were PubMed, Web of Science, EMASE, and CNKI. Search terms consisted of "serotonin transporter gene-linked polymorphic region," "5HTTLPR," "polymorphism," "variant," "single nucleotide polymorphism,"

"postpartum depression," and "PPD." There was no year limitation, with the last day of inclusion being May 20, 2019. Inclusion criteria consisted of case-controlled studies, genotypes in case and control participants, and 5HTTLPR polymorphism and postpartum depression risk. The Newcastle-Ottawa Scale evaluated the quality of each study by assigning it a numeric value. Those that scored a six or greater were included in this study, and ultimately six studies were included. This resulted in 519 cases with 737 controls for a total of 1,256 participants. The dominant LL and LS polymorphism allele at 5HTTLPR were found to be lower in the postpartum participants than those in the control group ($P= 0.004$, $P= 0.0001$). There was no definitive evidence that the recessive polymorphism at 5HTTLPR showed postpartum depression susceptibility ($P > 0.05$). Next 5HTTLPR was evaluated with comparison to Asian ethnicity. The presence of 5HTTLPR L allele polymorphism and the dominant allele showed a decreased risk of postpartum depression in Asian women ($P= 0.0001$, $P= 0.003$) (Li et al., 2020).

Yang et al. (2017) completed a literature reviewing focusing on 5HTTLPR gene and the potential link to postpartum depression. Three studies were included in the review. Based off these studies they found that women with the SS allele may have an increased risk of developing postpartum depression when compared to other genetic combinations like LL or SL, but the results were not statistically conclusive. Women with the LL allele had a decreased rate of postpartum depression. This has led the researchers to believe that the LL allele is more protective when it comes to the later development of postpartum depression (Yang et al., 2017).

Noradrenergic System

Another area of research is noradrenergic system. The noradrenergic system is known to play an important role in the regulation of emotions. This is done through the release of different enzymes and hormones. Monoamine oxidase (MAO) and catechol oxygen methyltransferase

(COMT) are two enzymes that work to deactivate the synaptic cleft. MAO breaks down a range of different amines. Previous studies have demonstrated a single nucleotide polymorphism within the MAO gene can decrease the activity of it. COMT is an enzyme that breaks down catecholamine neurotransmitters like epinephrine, norepinephrine, and dopamine found within the body. A single nucleotide polymorphism on the COMT gene interferes with the metabolism of the neurotransmitters in the noradrenergic system, resulting in an increased breakdown of the neurotransmitters. This decreases the level within the synaptic cleft. This decrease can expose women at an increased risk of developing postpartum depression. COMT has been a large focus in the genetics of major depressive disorder. A polymorphism mutation here is believed to decrease its metabolic activity (Ma, Huang, Wang, Zheng & Duan, 2019).

It is becoming widely accepted that there is a heritability to major depression. Twin studies have shown a heritability of 37%. When focusing on major depression, recent research has shown that mice with a genetic mutation in the MAO and COMT genes can develop depression or other mood symptoms. Ma et al. (2019) researched participants of Chinese ethnicity who all gave birth through cesarean section. Other inclusion criteria included participants over the age of 18, gestational age at birth of greater than 28 weeks, and no previous history of other serious medical or mental health diagnosis. Blood was drawn from the participants during the prenatal phase. Five hundred thirty-nine women were evaluated and the EPDS was used to assess mood 42 days post-delivery. A score of greater than 10 was considered significant for a diagnosis of postpartum depression. One hundred seven participants developed postpartum depression, an incidence rate of 18.1%. Genetic polymorphisms in the COMT gene were found to have an increased incidence of postpartum depression ($P< 0.05$), while

polymorphisms within the MOA gene were found to be clinically significant without statistical significance (P= 0.258) (Ma et al., 2019).

McEvoy, Osborne, Nanavati, & Payne (2017) found mixed results when researching COMT and MAO polymorphisms. They attempted to replicate previous studies that found a potential link with a polymorphism on the COMT gene and the development of postpartum depression. When postpartum was defined at 6-8 weeks following delivery there was a positive association with the development of postpartum depression ($P<0.05$). When the postpartum period was extended to 3-6 months after delivery there was no statistically significant findings ($P>0.05$). Similar results were found with MAO polymorphisms. In the first 6-8 weeks after delivery, there was strong association with the single nucleotide polymorphism and postpartum depression. But when the window was extended to 3-6 months post-delivery it was not found to be statistically relevant (McEvoy et al., 2017).

Beta-11

There is a growing belief that altered levels of cortisol may play a significant role in major depression and postpartum depression. In the terms of postpartum depression, specific interest is in a genetic polymorphism of the hydroxysteroid 11-beta dehydrogenase 1 gene (HSD11B1). This gene is responsible for catalyzing inactivated cortisone to active cortisone (Iliadis et al., 2017). In uncomplicated pregnancies, baseline cortisol levels are known to increase. When compared to healthy, non-pregnant women, pregnant women will have increased cortisol levels that peak at least two times above non-pregnant levels (Skalkidou et al., 2019). The following studies aimed to address genetic polymorphism changes along the cortisol signaling pathway and their relationship to the development of postpartum depression.

Iliadis et al. (2017) had a specific interest in the effect altered levels of cortisol play which led them to investigating the HSD11B1 gene. They reference other studies from 2015 and 2012 that brought attention to HSD11B1 and proposed that it was involved in depression susceptibility. In order to conduct their study, participants were taken from a larger study known as the BASIC-project. The EPDS was completed by participants during pregnancy at 17 weeks, 32 weeks, and then again at 6 weeks postpartum. Blood samples were also collected between pregnancy week 17 and 8 weeks postpartum. Scoring of a 12 or higher on the EPDS was considered clinically significant, which is 72-77% sensitive and 88-92.5% specific. A personality assessment was also administered at 32 weeks gestation (Iliadis et al., 2017).

There were a total of 769 women enrolled in this study. Genetic analysis was completed using the Hardy-Weinberg Equilibrium specifically looking for single nucleotide polymorphism on the HSD11B1 gene. Statistical analysis included linear regression models with the EPDS score as the dependent variable. Structural Equation Modelling was used to compare independent and dependent variables. In 84.5% of the participants a polymorphism was discovered at the HSD11B1 gene. The researchers believe this may be a common genetic variant. 8.6% of participants reported postpartum depression symptoms on the EPDS with a score of 12 or higher. Those with the genetic mutation scored higher on the EPDS with an average score of five compared to those with no mutation scoring a four ($P= 0.022$). Other factors that could contribute to the development of postpartum depression were not included in the research. Stress, negative life events, and family support are examples of this (Iliadis et al., 2017).

Skalkidou et al. (2019) also aimed to address genetic polymorphism changes along the cortisol signaling pathway and their relationship to each other. Participants were enrolled at 16-18 weeks gestation. Individuals were included if they were over the age of 18, attended routine

prenatal care appointments, and had no major health concerns. This resulted in 1,629 women being enrolled; 692 of the women had no previous mental health history. Participants completed the EPDS during the prenatal phase of 17 and 32 weeks gestation and again at six weeks and six months postpartum. Women that were found to be depressed during the prenatal phase were excluded. Blood samples were obtained at the time of delivery. The blood samples were evaluated using the silica-based Kleargene XL nucleic acid extraction kit. Sixteen genes involved in the stress-response were chosen. Genetic mutations were assessed using PCR and Kbioscience Allele-Specific Polymorphism assay (KASP). Cortisol levels were also measured. Depressive symptoms were assessed using the EPDS and considered clinically significant if there was a score of 12 or greater. The Kernel Association Test was used to evaluate the relationship between depressive symptoms and cortisol levels (Skalkidou et al., 2019).

Of the 1,629 participants, 9.5-11.5% of them reported depressive symptoms during the postpartum period. A genetic polymorphism on the HSD11B1 gene correlated with increased risk of developing postpartum depression (P= 0.00625). The researchers believed this mutation also had a relation to the amount of stress hormone released and suggested further research in this area. This study reports a drawback to using the EPDS as a scale for depressive symptoms. The participants all self-reported their scores and those that scored in the postpartum depression range were sent to meet with a psychologist. Ultimately, not all of the women were diagnosed with postpartum depression. This study also did not take into account other known risk factors that can lead to a postpartum depression diagnosis (Skalkidou et al., 2019).

Discussion

DNA Methylation

There is significant evidence presented by Kimmel et al. (2016) about the genetic link to postpartum depression. They were able to demonstrate in multiple different ways that with shorter DNA methylation at the Oxytocin ERE gene there is a stronger correlation to the development of depression postpartum. This study was one of the first looking into the Oxytocin gene methylation. Because of this, more studies are needed to replicate the data found.

Kimmel et al. (2016) had a range of women who were enrolled in the study, but each cohort had a small sample size. This can make it difficult to replicate the results. It also is impossible to generalize the findings across a larger population due to the small sample size.

Toepfer et al. (2019) were able to identify genetic changes at the Oxytocin receptor site that may be happening during pregnancy and used them to predict susceptibility to the development of postpartum depression. There is a potential downfall to this study; the depressive thoughts that women reported were not controlled on a standardized and publicly accepted scale. This research does not fully replicate Kimmel et al. (2016) findings but can be used as a resource to guide further research into the OXT gene and DNA methylation.

Osborne et al. (2016) was one of the few studies that looked at women with a history of depression prior to the postpartum period and women with no previous mental health history. Their goal was to replicate a previous study looking at DNA methylation, while also presenting new possible data in women with a history of a previous mental health diagnosis. They were able to successfully replicate previous findings by predicting postpartum depression based on methylations at HP1BP3 and TTC9B in women with no prior history of mental health disorders. When looking at women with a previous mental health history the results were not as successful.

This may suggest that DNA methylation may not be an appropriate choice to screen women with a prior mental health history for developing postpartum depression. This may be a reliable option to assess women with no previous mental health history for risk of developing postpartum depression.

Payne et al. (2020) set out to replicate the results published by Osborne et al. (2016). They focused on results that showed DNA methylation at HP1BP3 and TTC9B could predict postpartum depression on women with no prior mental health history. They were able to successfully replicate previous studies and predict postpartum depression accurately over 70% of the time. There were some potential downfalls in this publication. There was information lacking on the sample sizes used in each cohort. The timing of when the blood was drawn from participants was not consistent within the cohorts. These few downfalls do not appear to have a major effect on the results that were found, but it could help future researchers ensure consistent and accurate results.

The literature review by Elwood et al. (2019) was also able to confirm and replicate the results of Osborne et al. (2016). They were able to accurately predict postpartum depression 81% of the time. They were also able to replicate their results a second time. This is further proof that there is a high likelihood that DNA methylation has a strong impact on women who develop postpartum depression.

Due to the number of studies published on this topic, there is starting to become a growing body of body evidence that DNA methylation at HP1BP3 and TTC9B could be a potentially accurate screening tool in pregnant or postpartum women. There were multiple studies published prior to the window of inclusion for this literature review. These studies provided the groundwork for future researchers to base their hypotheses. Many of these

researchers conducted the studies analyzed in this literature review. All of them were successful at replicating the previous data. Before one can use this as a diagnostic and screening tool, more research needs to be completed to replicate the DNA methylation findings in larger studies to ensure sure the results are able to be generalizable and can be applied to a larger population set.

Single Nucleotide Polymorphism

5HTT

Hu et al. (2019) looked at single nucleotide polymorphism changes at the 5-HTTLPR gene. Their sample size was one of the larger ones researched, with over 400 participants. Their goal was to replicate another study that was previously done. Through their research they were able to corroborate previous research that SS allele at the 5-HTTLPR gene can be predictive of postpartum depression. The participants were only followed for a short period of time; follow up was discontinued after six weeks postpartum.

Li et al. (2020) preformed a meta-analysis of the 5-HTTLPR gene and the alleles SS SL and LL. They were able to include over 1,000 individuals from six separate studies. Ultimately, they were not able to replicate all the data that Hu et al. (2019) published. They did not find that the SS allele led to increased scores on screening questionnaires, which leads to the diagnosis of postpartum depression. They were able to confirm that women with the LL allele may have increased protection from developing postpartum depression.

The consistency of the results of 5HTTLPR gene and development of postpartum depression is lacking; however, there is evidence that having the LL or dominant allele shows a decreased susceptibility to the development of postpartum depression. This needs to be repeated on a larger scale before definitive conclusions can be drawn about the protective effect of a polymorphism at the 5HTTLPR gene.

Noradrenergic System

Ma et al. (2019) focused on polymorphism at COMT and MAO genes. Through their research they were able to establish a link between a polymorphism on the COMT gene that led to an increased incidence of postpartum depression. Their participants were ethnically limited to only Chinese women. Also, their standard for postpartum depression on the EPDS questionnaire was about three points lower than most other studies that used that as a guide. This could potentially mean their results are not accurate when compared to other studies using the same questionnaire. They were not able to conclusively prove a link to postpartum depression and a genetic mutation on the MAO gene.

McEvoy et al (2017) set out to replicate previous publications on COMT and MAO gene polymorphisms. Their results were to replicate the findings of previous studies but only within the first six to eight weeks postpartum. They followed the women for six months postpartum and found that after women who were depressed after the first eight weeks were not statistically significant.

This means that COMT and MAO gene polymorphisms may not be a useful tool outside of the first eight weeks. Ma et al. (2019) did not follow their participants outside of the six to eight week window so they are unable to confirm or disprove McEvoy et al. (2016) findings. Due the lack of corroborating research in this area, more research is needed. The researchers will also need to follow the participants for an extended period time in the postpartum period to assess the applicability of this research.

Beta-11

Iliadis et al. (2017) had a specific interest in a genetic polymorphism of the HSD11B1 gene. They found that a polymorphism mutation at the HSD11B1 gene was relatively common; it was found in 84.5% of participants. Those that had the mutation scored on average one point higher on the EPDS than those with no mutation. Only 8% of the participants with the polymorphism were found to have postpartum depression. This was one of the first studies in this area and more research is needed to replicate this data.

Skalkidou et al. (2019) also completed research at the HSD11B1 gene. They were able to find similar findings as Iliadis et al. (2017). There was an increased incidence of postpartum depression in individuals with a polymorphism at HSD11B1 gene. This study did not address that or investigate the potential commonality of the mutation. It does demonstrate a link between HSD11B1 gene and postpartum depression. However, the applicability of the information is lacking if the mutation is found to be common within the general population.

The participants in the majority of these studies all self-reported their scores on the questionnaires. This can lead to different biases among the participants. In addition, some of the questionnaires were completed retrospectively. This can lead to individuals downplaying what their actual responses may have been in the moment. Many of the studies used the same EPDS questionnaire, but were not consistent. In the future to further corroborate data and draw conclusions, a standardized scale that is specific and sensitive could improve research outcomes.

The study of genetics and postpartum depression is relatively new. Many of the studies that have been published with potential evidence have not been replicated or have not been performed on a large sample size. The groundwork is being laid, but more research is needed to corroborate results and draw definitive conclusions.

Applicability to Clinical Practice

The information provided in this literature review can help raise awareness within the clinical community of the possible genetic differences in women diagnosed with postpartum depression. Most of the tests conducted in these studies were based off a simple blood draw that is considered noninvasive. Blood work is already commonly used in the primary care setting to screen for different diseases and medical conditions. This could lead to better screening and treatment options which may ultimately improve the health and wellbeing of postpartum women, the family unit, and infants born to mothers suffering from postpartum depression.

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