BIOLOGICAL AND PSYCHOLOGICAL PREDICTORS OF PERINATAL ANXIETY EXACERBATION

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Lay Abstract

Anxiety disorders occurring during pregnancy and the postpartum period are highly prevalent, resulting in various negative effects to the mother, her infant, and family. Women with pre-existing anxiety disorders are more vulnerable during this time than those women without any mental health disorders. Although these women are at increased risk of experiencing a relapse or worsening of their pre-existing anxiety symptoms during the postpartum period, very little is known regarding what characteristics and factors increases a woman's risk. The goal of this thesis was to thoroughly investigate the risk factors that predict worsening of anxiety symptoms postpartum and how they can provide valuable information to aid in early detection of symptoms.

Abstract

This thesis presents research investigating the association between numerous sociodemographic, obstetrical and delivery, psychological, and biological factors with postpartum anxiety worsening in women with pre-existing anxiety disorders. First, a systematic review and meta-analysis investigating the risk factors associated with perinatal anxiety in women with and without pre-existing anxiety disorders was conducted. This investigation highlighted the lack of information pertaining to risk factors of anxiety occurring during the perinatal period, specifically in women with pre-existing anxiety disorders who are at increased risk of symptom worsening. Next, we conducted a study in which risk factors of postpartum anxiety worsening were assessed, specifically in women with pre-existing anxiety disorders. In this study, numerous sociodemographic, obstetrical and delivery, psychological, and biological factors were examined. We demonstrate that psychological factors, particularly intolerance of uncertainty, depressive symptom severity, and obsessive compulsive disorder symptoms, are significantly associated to postpartum anxiety worsening. That is, women with pre-existing anxiety disorders who exhibit heightened levels of these psychological domains during their third trimester of pregnancy are at increased risk of experiencing a relapse, or worsening, of their pre-existing anxiety symptoms during the postpartum period. This study provides a basis for future research to be conducted at investigating the associations between these risk factors and postpartum anxiety worsening. Study replication and continued research investigating the risk factors of postpartum anxiety worsening has the potential to provide valuable information in determining which women are at increased risk of worsening postpartum, with the hopes of decreasing the associated negative effects with postpartum anxiety.

Keywords: anxiety; perinatal; pregnancy; postpartum; risk factor

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List of Abbreviations

ACTH: Adrenocorticotropic hormone
AVP: Arginine vasopressin
CIDI: Composite international diagnostic interview
CPQ: Clinical Perfectionism Questionnaire
CRH: Corticotropin releasing hormone
CRP: C-reactive protein
CTQ: Childhood Trauma Questionnaire
DALYs: Disability adjusted life years
DSM: Diagnostic and Statistical Manual of Mental Disorders
ELISA: Enzyme-linked immunosorbent assay
EPDS: Edinburgh Postnatal Depression Scale
FHS: Family History Screen
GAD: Generalized Anxiety Disorder
GAD-7: Generalized Anxiety Disorder Scale—7 Items
HAM-A: Hamilton Anxiety Rating Scale
HPA: Hypothalamic-pituitary-adrenal
ICD: International classification of diseases
IES-R: Impact of Events Scale—Revised
IL: Interleukin
ISI: Insomnia Severity Index
IUS: Intolerance of Uncertainty Scale
MINI: Mini International Neuropsychiatric Interview
MOOSE: Meta-analysis of observational studies in epidemiology
MSPSS: Multidimensional Scale of Perceived Social Support
NOS: Newcastle-Ottawa Scale
OCD: Obsessive compulsive disorder
OCI-R: Obsessive Compulsive Inventory—Revised
PBI: Parental Bonding Instrument
PRISMA: Preferred reporting items for systematic reviews and meta-analyses
PSQI: Pittsburgh Sleep Quality Index
PTSD: Posttraumatic stress disorder
SAD: Social Anxiety Disorder
SCID: Structured clinical interview for DSM
SIGH-A: Structured Interview Guide for the Hamilton Anxiety Scale
STAI: State-Trait Anxiety Inventory
TNF: Tumor necrosis factor
VPSQ: Vulnerable Personality Style Questionnaire
Y-BOCS: Yale-Brown obsessive compulsive scale

Declaration of Academic Achievement

This thesis consists of 5 chapters. Chapter 1 provides a general introduction and background on anxiety disorders, perinatal anxiety, the associated disruptions in underlying biological mechanisms, and currently known risk factors. Chapter 2 is a systematic review and meta-analysis of risk factors of perinatal anxiety, highlighting the lack of knowledge in this area, particularly in women with pre-existing anxiety disorders. Chapter 3 provides the framework of our primary study, outlining the study methodology of investigating numerous risk factors of postpartum anxiety worsening. Chapter 4 presents the results of this study, focusing on various sociodemographic, obstetrical and delivery-related, psychological, and biological risk factors. Chapter 5 is a discussion of the study findings, there implications, and directions for future study.

Data collection for our primary study occurred between April 2017 and June 2018, at the Women's Health Concerns Clinic at St. Joseph's Healthcare Hamilton. Participants were also recruited from the Mountain Midwifery Care Clinic in Hamilton. The study was conceived and designed by Dr. Benicio Frey, Dr. Ryan Van Lieshout, and myself. I oversaw all study related features, including REB submission and approval, participant recruitment, study coordination, study visits, data collection, and management. I received previous training in administering and scoring all interviewer-administered questionnaires, including the Mini International Neuropsychiatric Interview and Hamilton Anxiety Rating Scale from a licensed psychiatrist, in which I have had over 3 years of past experience in administering these interviews. I performed all statistical analyses. I completed training at St. Joseph's Healthcare Hamilton, in which I received a phlebotomy certificate to complete blood sample collection, as well as processing of samples. Biomarker assays were performed by lab technician Jodi Gilchrist at St. Joseph's Healthcare Hamilton. I am very thankful and grateful to all contributors.

Portions of this work were presented at the Anxiety and Depression Association of America Annual Conference 2018 in Washington, DC, and at the Society of Biological Psychiatry Annual Conference 2018 in New York, NY.

In addition to the work summarized in this thesis, I collaborated with Dr. Benicio Frey, Dr. Ryan Van Lieshout, Dr. Cheryl Chow, and Ms. Sawayra Owais, on a systematic review and meta-analysis of non-pharmacological interventions aimed at improving postpartum maternal sleep. This work is not included in this thesis, as it is outside the scope. The citation for this publication is listed below:

1. Owais S, Chow CHT, Furtado M, Frey BN, Van Lieshout RJ. 2018. Non-pharmacological interventions for improving postpartum maternal sleep: A systematic review and meta-analysis. Sleep Med Rev, [Epub ahead of print].

CHAPTER 1

General Introduction

Anxiety disorders are among the most debilitating mental disorders globally, and are characterized by one's excessive fear and anxiety of any real, perceived, or anticipated threat(s). Anxiety disorders can be categorized more specifically into Generalized Anxiety Disorder, Social Anxiety Disorder, Panic Disorder, Agoraphobia, Separation Anxiety Disorder, and Specific Phobia, each with their individual diagnostic characteristics, as well as the experience of significant distress and/or impaired functioning. During the perinatal period, women are at increased risk of experiencing anxiety, which can result in adverse effects for the mother, her infant, and family. However, little is known about the psychosocial and biological risk factors for postpartum anxiety, particularly in women who have pre-existing anxiety disorders. Identifying potential psychosocial and biological markers of postpartum anxiety has the potential to predict and lead to early detection, as well as intervention, and even preventive treatments for these women.

Given that postpartum anxiety is a relatively new field of study, this work seeks to identify the psychosocial and biological predictors of this phenomenon. Chapter 1 provides background information on anxiety disorders in general, perinatal anxiety, the associated disruptions in potential underlying biological mechanisms, specifically the hypothalamic-pituitary-adrenal axis, and currently known risk factors, highlighting the paucity of research in these areas. In Chapter 2, a systematic review and meta-analysis of risk factors of perinatal anxiety is presented, which further emphasizes the lack of knowledge in this area, particularly for women with pre-existing anxiety disorders. Chapter 3 provides the methodology of our primary study investigating the psychosocial and biological risk factors for postpartum anxiety

worsening. Chapter 4 presents the results of this study, focusing on numerous sociodemographic, obstetrical and delivery-related, psychological, and biological risk factors. Finally, a discussion of the study findings and directions for future study will be discussed in Chapter 5.

Anxiety Disorders

As many as 1 in 4 individuals worldwide suffer from an anxiety disorder at some point in their lifetime, with women being twice as likely than men to be diagnosed (Remes et al., 2016). In 2010, anxiety disorders were the sixth leading cause of disability worldwide, producing 26.8 million disability adjusted life years (DALYs), with women accounting for approximately 65% of those DALYs (Baxter et al., 2014; Whiteford et al., 2013). Further, it has been estimated that anxiety disorders, together with depression, result in an annual global cost of over US$1 trillion (Chisholm et al., 2016). In Canada alone, anxiety disorders are estimated to cost the economy $17.3 billion per year (Conference Board of Canada, 2016).

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM), anxiety disorders are defined by excessive worry and fear to any real, perceived, or anticipated threat, in which the fear is distressing and debilitating (American Psychiatric Association, 2013). These disorders are often characterized by hyperarousal of the sympathetic nervous system (i.e., fight-or-flight system), resulting in physical symptoms such as muscle tension, increased heart rate, fatigue, and sleep disturbances (American Psychiatric Association, 2013). The most commonly diagnosed anxiety disorders are Generalized Anxiety Disorder, Social Anxiety Disorder, Panic Disorder, and Agoraphobia.

Generalized Anxiety Disorder (GAD) is the most common type of anxiety disorder, with lifetime prevalence rates ranging between 5.1-11.9% (Kessler et al., 2008; Watterson et al.,

2017; Weisberg, 2009). Age of onset for GAD it typically later in life (mean age 35 years) (de Lijster et al., 2017), with women being more affected than men (Wittchen, 2002). Generalized Anxiety Disorder is characterized by excessive worry and anxiety to various events (e.g., work, relationships), occurring more days than not and persisting for a minimum of 6 months (American Psychiatric Association, 2013). Individuals with GAD experience difficulties in controlling their worry, resulting in significant distress and functioning impairments, and must have a minimum of 3 of 6 of the following diagnostic symptoms: restlessness, fatigue, concentration difficulties, irritability, muscle tension, and sleep disturbances (American Psychiatric Association, 2013).

Social Anxiety Disorder (SAD) is defined as one's persistent fear of social or performance-related situations that may result in potential scrutiny and humiliation (American Psychiatric Association, 2013). Individuals with SAD recognize that their fear and anxiety is unreasonable, but will engage in avoidance behaviours of any potential fear-inducing social situations and/or endure significant distress throughout the situation which will typically persist for 6 or more months (American Psychiatric Association, 2013). Approximately 4% of the global population experiences SAD in their lifetime, with onset typically occurring by mid-adolescence (Stein et al., 2017). Although men are more likely to seek treatment for SAD, it is estimated that women are 1.5 times more likely to meet diagnostic criteria (Asher et al., 2017).

Unexpected panic attacks are the distinguishing feature of Panic Disorder, in which one experiences intense fear and discomfort accompanied with a minimum of 4 of 13 characteristic symptoms (e.g., heart pounding, sweating, shortness of breath, nausea, derealisation, etc.) (American Psychiatric Association, 2013). In addition to the occurrence of unexpected panic attacks, individuals are persistently concerned for at least 1 month about any recurrence, in

addition to some change in behaviour (e.g., avoidance of unfamiliar situations) (American Psychiatric Association, 2013). Lifetime prevalence rates of panic disorder have been estimated to range between 1.7-5.1% (de Jonge et al., 2016; Government of Canada, 2006; Grant et al., 2006; Kessler et al., 2006), with onset typically beginning in young adulthood and with women being more likely to be diagnosed (OR 1.8, 95% CI 1.6-2.0, $p<0.05$) (de Jonge et al., 2016; Sheikh et al., 2002).

Agoraphobia, the fear and anxiety associated with any situation in which escape or getting help may be difficult (American Psychiatric Association, 2013), has estimated lifetime prevalence rates ranging between 1.4-4% (Carr & McNulty, 2016; Kessler et al., 2005, 2007). Similar to the other anxiety disorders, agoraphobia is more common in women and is typically diagnosed in early adulthood (Stevens & Rodin, 2011). According to DSM-5 criteria, one must have an intense fear in response to at least 2 of 5 situations, including using public transportation, being in open or enclosed spaces, standing in a line or being in a crowd, and/or being away from home alone, with this fear persisting for at least 6 months (American Psychiatric Association, 2013). Unlike previous DSM versions, the DSM-5 no longer requires the diagnosis of Panic Disorder to be made in order for an Agoraphobia diagnosis to be applied (American Psychiatric Association, 2013).

Anxiety disorders are often comorbid with other psychiatric conditions, particularly Major Depression, with prevalence rates as high as 60% (Kaufman & Charney, 2000). Due to overlapping symptomatology, this comorbidity often compromises early and accurate detection and in turn, results in poorer treatment outcomes. Most anxiety disorders typically appear by early adulthood, with symptoms frequently cycling over time. These are often dependent upon existing circumstances, which can include the perinatal period for women.

Perinatal Anxiety

The perinatal period, commonly defined as any time from pregnancy to 12 months postpartum (Goodman et al., 2016), is often a time of both joy and stress. As many as 20% of women will experience an anxiety disorder within the first postpartum year (Goodman et al., 2016), with less than 15% of these women receiving treatment (Smith et al., 2009). These anxiety symptoms may either be appearing for the first time, or in many instances, may represent a worsening of already existing anxiety symptoms (Ross & McLean, 2006). As is seen in non-puerperal populations, perinatal anxiety is often comorbid with depressive disorders, which presents a barrier to accurate diagnosis and treatment. Although the economic burden of perinatal anxiety is unknown due to the paucity of research conducted in this area, it may be comparable to that of postpartum depression, which is as high as $5.7 billion in the United States (Diaz & Chase, 2010). Women with perinatal anxiety experience significant suffering and increased stress (Brand & Brennan, 2009), resulting in negative effects for these women, their infants, and family.

The literature has shown that rates of obstetric complications are increased in women with anxiety disorders. These include higher rates of preeclampsia, a longer and more difficult labour and delivery, preterm birth, and low birth weight (Anniverno et al., 2013; Dole et al., 2003; Kramer et al., 2009; Littleton et al., 2007; Orr et al., 2007; Roesch et al., 2004). Women with perinatal anxiety also often have more physical complaints throughout their pregnancy, such as increased nausea, vomiting, muscle pain, and heartburn (Anniverno et al., 2013). These women make more frequent visits to their obstetrician due to worries about the health of their fetus, manifest fear and anticipatory anxiety related to childbirth (Andersson et al., 2004; Rubertsson et al., 2014), and have increased rates of leave from work (Anniverno et al., 2013).

Perinatal anxiety may also put the mother-infant bond at risk, as these women are more likely to report decreased perceived bonding with their child (Tietz et al., 2014). Additionally, perinatal anxiety can affect offspring development, such that infants of mothers who experience heightened levels of anxiety during pregnancy are at increased risk of experiencing deficits in cognitive and motor performance at 3 months of age (Davis & Sandman, 2010) and poor attention regulation at 3 to 8 months of age (Huizink et al., 2002). Anxiety occurring in pregnancy may also increase the likelihood of difficult infant temperament in the first year following birth (Brand & Brennan, 2009; Britton, 2011), as well as elevated levels of negative affect in children observed by 2 years of age (Blair et al., 2011).

These negative offspring outcomes are not restricted to infancy however, as studies suggest that anxiety during pregnancy is associated with worsened executive functioning later in life. Specifically, decreased gray matter density in the prefrontal cortex, an area associated with executive functioning, has been reported in children of mothers with perinatal anxiety between 6 and 9 years of age (Buss et al., 2010, 2011). Further, these children often experience increased levels of their own anxiety and catastrophizing beyond 7 years of age (Bernstein et al., 2005; Davis & Sandman, 2012; Capron et al., 2015; Moore et al., 2004). A more recent study (Capron et al., 2015) examining the effects of perinatal anxiety on offspring later in life, specifically at age 18, found that these children are at increased risk of comorbid anxiety and depression (adj. OR 1.39, 95% CI 1.06-1.82, p=0.02; n=3644).

Perinatal anxiety not only has negative neuropsychiatric repercussions for offspring, but can also effect physical health. A recent meta-analysis (Flanigan et al., 2018) of 30 studies indicated that offspring of women who experienced anxiety during pregnancy were at greater risk of eczema/dermatitis (OR 1.34, 95% CI 1.22-1.47), allergies (OR 1.30, 95% CI 1.04-1.62),

and asthma (OR 1.15, 95% CI 1.04-1.27), with anxiety occurring in the third trimester of pregnancy having the biggest effect.

The consequences of perinatal anxiety also have significant effects on one's romantic relationships. Women with postpartum anxiety disorders, particularly when they are comorbid with depressive symptoms, report poorer marital satisfaction compared to those without these disorders (Odinka et al., 2017). Biological changes that occur during pregnancy and the early postpartum period have been reported to be potentially associated with anxiety occurring during the perinatal period, and in turn its resulting negative effects.

Hypothalamic-Pituitary-Adrenal Axis and Perinatal Anxiety

The female body undergoes significant biological and physiological changes throughout pregnancy and the early postpartum period, including in the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis plays a significant role in the body's stress response, such that it is activated during stressful situations (e.g., pregnancy) in response to corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) secretion from the hypothalamic paraventricular nucleus (Faravelli et al., 2012; Mastorakos & Ilias, 2006). The secretion of CRH and AVP stimulate the release of adrenocorticotropic hormone (ACTH), which in turn triggers the release of glucocorticoids, specifically cortisol (Faravelli et al., 2012). Cortisol, considered to be the most important glucocorticoid in humans, plays a critical role in a variety of biological changes, with roles in regulating inflammation, the immune and cardiovascular systems, as well as affective processes, among others (Faravelli et al., 2012; Kudielka & Kirschbaum, 2004).

During pregnancy, from implantation to approximately the second trimester, the body requires a strong inflammatory response, such that this is a time in which there are invading

cells, cells that are being repaired, and those that are dying off (Abrahams et al., 2004; Mor et al., 2011). Consequently, these early stages of pregnancy are often when the mother feels the most physically ill (i.e., "morning sickness"), requiring a pro-inflammatory response (Mor et al., 2007, 2011). Specifically, there are increased levels of pro-inflammatory T-helper cells and subsequent cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which play a role in mediating between the peripheral immune system and central nervous system (Kasper et al., 2003). In addition to their mediation role, these cytokines also have the ability to stimulate the HPA axis, as well as the release of other inflammatory markers, such as C-reactive protein (CRP) (Kasper et al., 2003). By the third trimester of pregnancy, circulating cortisol levels will rise threefold (Jung et al., 2011). This is in part due to the fact that the placenta also secretes increased CRH into the maternal bloodstream beginning in the second trimester of pregnancy (Thomson, 2013), in turn stimulating the inflammatory cascade that results in increased cortisol levels (see Figure 1.1). Following delivery, cortisol levels decrease and the HPA axis slowly returns to a typical pre-pregnant state (Duthie & Reynolds, 2013; O'Keane et al., 2011), however, dysfunction in HPA axis regulation in some does not allow for this change and instead remains hyperactive. This resulting hyperactivity has been established as playing a significant role in anxiety symptomatology.

Dysregulation in the HPA axis and inflammatory markers has been more recently recognized in the literature to play a role in the pathogenesis of various psychiatric disorders, including anxiety disorders. A recent large population cohort study (Naudé et al., 2018) of 54,326 individuals examined the associations between various anxiety disorders and serum CRP. Significant associations were observed between serum CRP levels and GAD, SAD, Panic Disorder, and Agoraphobia. Additional research conducted within the last decade or so have

reported similar associations between heightened levels of CRP, TNF-α, and IL-6 with non-puerperal anxiety disorders (Copeland et al., 2012; Khandaker et al., 2016; Vieira et al., 2010; Vogelzangs et al., 2013).

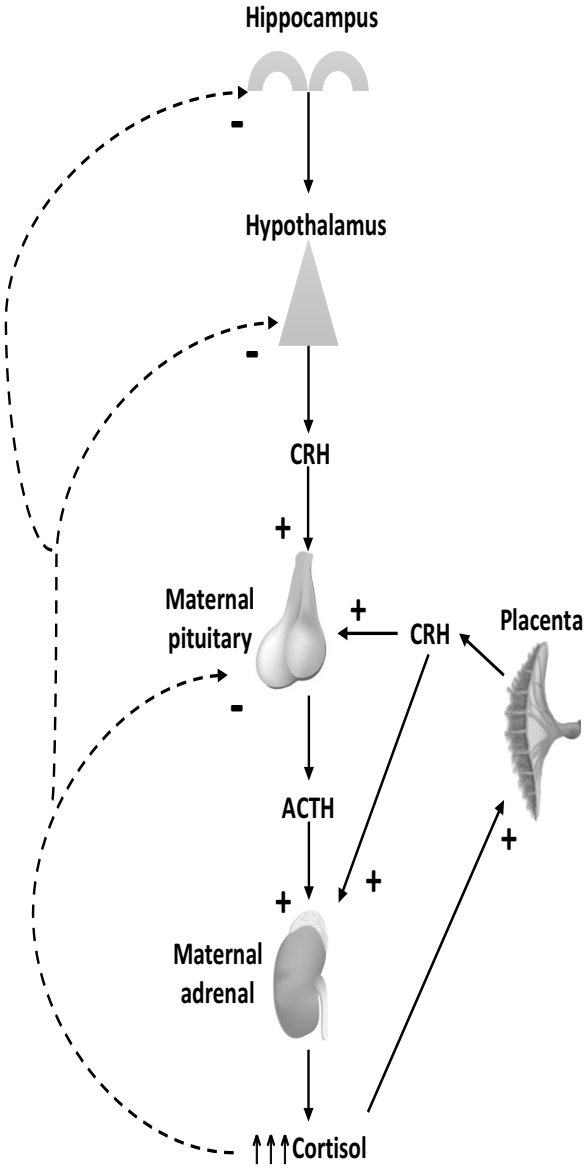

Figure 1.1. Hypothalamic-pituitary-adrenal axis regulation during pregnancy. Adapted from "Figure 1. HPA axis in pregnancy" in Duthie & Reynolds, 2013.

To our knowledge, no study to date has examined the associations between inflammatory biomarkers and anxiety worsening in the perinatal period. Given the already heightened levels of inflammatory markers, specifically CRP, IL-6, and TNF-α, during pregnancy and early postpartum, as well as in relation to non-puerperal anxiety disorders, investigating any associations that exist in pregnant women with pre-existing anxiety disorders can potentially aid in detection measures. Specifically, assessing whether there is any further dysregulation in these women, and whether or not this dysregulation has the ability to predict worsening of anxiety symptoms in the postpartum period.

Risk Factors for Perinatal Anxiety

The understanding and awareness of risk factors associated with psychiatric disorders is crucial for accurate and early detection, as well as to aid in informing prevention and treatment. Despite the high prevalence and negative effects of perinatal anxiety, little is known with regard to risk factors, and what is known is often inconsistent likely due to the limited number of studies.

It has been well-established in the literature that a history of mood and/or anxiety disorders is among the most significant predictors of perinatal anxiety development (Faisal-Cury et al., 2009; Giardinelli et al., 2011; Marchesi et al., 2014; Martini et al., 2015; Rubertsson et al., 2014). Despite this, there have only been 4 studies, to our knowledge, reporting information on risk factors for perinatal anxiety in women with pre-existing anxiety disorders (House et al., 2016; Kroll-Desrosiers et al., 2017; Muzik et al., 2016; Uguz et al., 2011). Of note however, is that 3 of these studies only examined women with previously categorized anxiety disorders (i.e., posttraumatic stress disorder and obsessive compulsive disorder), further highlighting the lack of

research in examining risk factors of perinatal anxiety. Most of the studies reporting on information regarding predictors of perinatal anxiety, discussed below, examine all women, such that they do not specify any differences between those with and without pre-existing anxiety disorders.

In terms of sociodemographic factors, low income (Faisal-Cury et al., 2009; Faisal-Cury & Rossi Menezes, 2007), low education level (Faisal-Cury & Rossi Menezes, 2007; Martini et al., 2015; Qiao et al., 2009), and decreased perceived support (Dunkel Schetter et al., 2016; Faisal-Cury & Rossi Menezes, 2007) are all well-established risk factors for anxiety occurring in the perinatal period. Other sociodemographic factors, specifically, maternal age and parity however, have displayed conflicting results. Although a number of studies have reported an association between a younger maternal age with perinatal anxiety (Bodecs et al., 2013; Martini et al., 2015; Qiao et al., 2009; Rubertsson et al., 2014), other studies have noted an association between older maternal age and perinatal anxiety (Bayrampour et al., 2012; Tearne et al., 2016). Similar inconsistencies are also observed with regard to parity, in which some studies have reported nulliparous or primiparous women as being at increased risk (Biaggi et al., 2016), while others suggest that multiparous women may be more likely to experience anxiety (Lederman & Weis, 2009). Further, a number of studies have not found any associations between maternal age and parity with perinatal anxiety (Faisal-Cury & Rossi Menezes, 2007; Karmaliani et al., 2009; Rubertsson et al., 2003).

Obstetrical risk factors for perinatal anxiety have also been reported in the literature, again with conflicting findings. This appears to be largely due to a lack of studies and inconsistent methodology. A current or previous history of pregnancy and delivery complications, such as stillbirths and miscarriages, have been shown to predict postpartum

anxiety (Ali et al., 2012; Bergner et al., 2008; Faisal-Cury et al., 2009; Faisal-Cury & Rossi Menezes, 2007; Gong et al., 2013), while others suggest no such relationship (Qiao et al., 2009; Rubertsson et al., 2003). The mode of delivery is an area that has received much less attention. In a study by Rowlands and Redshaw (2012), women who had a forceps-assisted vaginal delivery were at greater risk of reporting anxiety symptoms up to 3 months postpartum, compared to those who had unassisted vaginal births. With regard to caesarean deliveries, a recent systematic review (Olieman et al., 2017) sought to investigate the effect of elective caesarean section on postpartum anxiety. Women who had preferred and planned for an elective caesarean section but ended up having a vaginal delivery had significantly higher anxiety symptoms, specifically those related to trauma, compared to those who had a planned vaginal delivery.

In terms of psychological risk factors, women who have experienced childhood abuse are also at an increased risk of experiencing anxiety during pregnancy (Leeners et al., 2006; Martini et al., 2015; Mezey et al., 2005; Seng et al., 2014). These women can become much more vigilant and sensitive during this time, worrying that new or unusual physical sensations could be an indicator of problems (Leeners et al., 2006), while others sometimes dissociate or disconnect from their feelings. A recent longitudinal study (Martini et al., 2015) of 306 pregnant women found that a history of sexual trauma was associated with anxiety occurring during pregnancy, but not depression. These novel sensations and feelings of uncertainty may place these women at higher risk for perinatal anxiety.

Other psychological factors, such as maternal sleep, have also been linked to perinatal anxiety. Specifically, women reporting poor subjective prenatal sleep have been shown to exhibit greater levels of anxiety during the postpartum period (Skouteris et al., 2009; Swanson et al.,

2011), however, some studies have not found this association (Lawson et al., 2015; Tham et al., 2016), necessitating the need for clarification in this area.

Existing studies have also suggested that personality traits such as perfectionism and feelings of uncertainty predict anxiety symptoms (Boswell et al., 2013; Gentes & Ruscio, 2011; Gnilka et al., 2012; McEvoy & Mahoney, 2012; O'Connor et al., 2010). Dysfunctional perfectionism, specifically thoughts on being concerned over potential mistakes, doubts, and parental expectations, have been identified as a risk factor for postpartum anxiety (Oddo-Sommerfeld et al., 2016). Moreover, intolerance of uncertainty results from negative beliefs regarding uncertainty and its potential negative implications (Buhr & Dugas, 2009), and this constant worry about potential events is a cardinal symptom of anxiety disorders (Boswell et al., 2013). Although the association between intolerance of uncertainty and perinatal anxiety has yet to be examined in the literature, a recent study by Sweeny and colleagues (2015) reported that heightened levels of intolerance of uncertainty was significantly associated with greater levels of anxiety and worry during attempts to conceive. Examining whether this intolerance of uncertainty extends into the perinatal period, as well as whether it has the ability to predict anxiety worsening postpartum may impact screening and detection methods. This may therefore be an area of interest to investigate its associations with postpartum anxiety worsening.

In addition to the various psychosocial factors that have not yet been investigated in the perinatal population, the biological predictors of perinatal anxiety have also yet to be elucidated. Among the first and few studies to assess inflammatory biomarkers in relation to perinatal anxiety was conducted by Maes and colleagues (2000). In this study, blood samples were collected from 91 healthy pregnant women and 22 non-pregnant women, without any existing Axis I psychiatric disorders (with the exception of Major Depressive Disorder), 3-5 days before

expected delivery and 1 and 3 days post-delivery. In addition to blood samples assessing inflammatory markers (including IL-6), women completed the Spielberger State-Trait Anxiety Inventory (STAI) at each study visit. Given the dramatic alterations to the HPA axis and inflammatory response in pregnancy, serum levels of IL-6 were significantly elevated in pregnant women compared to non-pregnant women at each time point. However, pregnant women whose scores on the STAI increased postpartum had significantly higher IL-6 levels, compared to those who did not increase, demonstrating an association between IL-6 and postpartum anxiety. More recently, higher levels of IL-6 were also demonstrated throughout pregnancy and the postpartum period in women with heightened anxiety (Osborne et al., 2017), however it is not known if these women were free from pre-existing anxiety disorders. Despite the potential utility of biomarkers in predicting anxiety exacerbation, and treatment response, the biological predictors of perinatal anxiety and its worsening have yet to be elucidated. Unlike the increasing attention to biomarkers that has been seen in postpartum depression (Bränn et al., 2017; Liu et al., 2016; Mehta et al., 2014; Okun et al., 2013; Osborne et al., 2015; Simpson et al., 2016), relatively little attention has been paid to biomarkers in the perinatal anxiety field.

Aims and Hypotheses

A diagnosis of mood and/or anxiety disorders are among the most significant predictors of perinatal anxiety. Despite this, very little research has investigated the potential predictors of anxiety exacerbation in women with pre-existing anxiety disorders. Given that perinatal anxiety is a relatively new field of study and since to our knowledge, no research has looked specifically at the predictors of anxiety worsening in the postpartum period, this work seeks to identify the psychosocial and biological predictors of this phenomenon.

First, a meta-analysis and systematic review of the predictors of perinatal anxiety will be provided in Chapter 2, highlighting the lack of research in examining predictors of anxiety worsening in women with pre-existing anxiety disorders. In Chapter 3, the methodology of our study of risk factors of postpartum anxiety worsening will be described, with results detailed in Chapter 4.

The primary objective of the study outlined in Chapter 3 is to evaluate the predictors of postpartum anxiety exacerbation, defined by scores on the Hamilton Anxiety Rating Scale, prospectively from the third trimester of pregnancy to 24 weeks postpartum. As postpartum anxiety is estimated to be the most prevalent between 6 and 8 weeks postpartum (Dennis et al., 2013; Field et al., 2017; Matthey et al., 2003; Misri et al., 2015; Wenzel et al., 2005), our primary outcome of evaluating anxiety worsening was assessed at the 6 week postpartum visit.

We hypothesize that psychosocial factors, including perfectionism, intolerance of uncertainty, depression, childhood trauma, maternal sleep, and social and partner support will be significant predictors of anxiety worsening in women with pre-existing anxiety disorders. The secondary objective of this study is to evaluate the biological markers, specifically, CRP, IL-6, and TNF-α, of postpartum anxiety worsening from the third trimester of pregnancy to 6 weeks postpartum. We hypothesize that elevated baseline levels of CRP, IL-6, and TNF-α will predict postpartum anxiety exacerbation. Finally, in Chapter 5 a discussion of the study results reported in Chapter 4 and their implications will be discussed, with a focus on future directions, as well as highlighting both the study strengths and limitations.

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CHAPTER 2

Risk Factors of New Onset Anxiety and Anxiety Exacerbation in the Perinatal Period: A Systematic Review and Meta-Analysis

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Abstract

Background: Even though more than 20% of women meet diagnostic criteria for an anxiety disorder during the perinatal period, very little is known about the predictors of these problems. As a result, we systematically reviewed the literature on risk factors for new onset anxiety and maternal anxiety exacerbation in the perinatal period.
Methods: PubMed, MEDLINE, PsycINFO, CINAHL, Ovid, ProQuest Portal, and Web of Science were searched for studies assessing risk factors for the development of new onset anxiety or anxiety worsening in women during pregnancy and the postpartum period.
Results: 11,759 citations were identified, with 11 studies meeting eligibility criteria. New onset anxiety was assessed in 7 studies, anxiety worsening in 3, and 1 assessed both. Lower educational attainment, living with extended family members, multiparity, a family history of psychiatric disorders, hyperemesis gravidarum, comorbid sleep disorders, and prenatal oxytocin exposure were risk factors for new onset perinatal anxiety, while presence of comorbid psychiatric disorders and prenatal oxytocin were risk factors for anxiety worsening.
Limitations: Studies not explicitly stating whether participants had pre-existing anxiety disorders were excluded. As a result, meta-analysis was not possible for several risk factors.
Conclusions: Risk factors for new onset anxiety and anxiety worsening during the perinatal period include psychological, social, and biological exposures. Given the lack of studies differentiating women with and without pre-existing anxiety disorders, additional research is required in order to determine whether these factors differ from the non-puerperal population, as well as from each other.

Keywords: *anxiety; pregnancy; postpartum; risk factor*

Introduction

Anxiety disorders are among the most common mental disorders, with global prevalence rates as high as 25% (Remes et al., 2016). Women are twice as likely as men to develop an anxiety disorder in their lifetime, and as many as 20% of women are estimated to experience an anxiety disorder during the first 12 postpartum months (Goodman et al., 2016). For some women, this will be occurring for the first time in their life (i.e., new onset), while others will experience a worsening of existing symptoms or disorders (Ross & McLean, 2006). Unfortunately, fewer than 15% of women with perinatal mental disorders receive treatment for these problems (Smith et al., 2009). This may be due in part to the limited attention that has been paid to perinatal anxiety problems, a relative lack of validated screening measures, and a less than ideal awareness among clinicians of the risk factors for these disorders.

Anxiety disorders are often comorbid with depression, and so the distinction between disorders and their symptoms can sometimes be subtle. Unfortunately, this can lead to missed or inaccurate diagnoses, as well as sub-optimal treatment. As perinatal anxiety is still considered a relatively new area of scientific study research, its financial costs have yet to be estimated. However, postpartum depression is estimated to cost the United States $5.7 billion annually if left untreated (Diaz & Chase, 2010). As perinatal anxiety prevalence rates are equivalent, if not greater than postpartum depression (Dennis et al., 2016, 2017; Remes et al., 2016), the human and financial burden is potentially comparable.

Women with perinatal anxiety can experience significant suffering, with adverse effects for their infant, partner, and other children. These women are at increased risk of obstetric complications, including a difficult labour, pre-eclampsia, and preterm delivery (Dole et al., 2003; Kramer et al., 2009; Kurki et al., 2000; Littleton et al., 2007). Physical symptoms such as

nausea and vomiting, heartburn, and muscle aches during pregnancy, as well as increased rates of sick leave from work are also more common in women with perinatal anxiety (Anniverno et al., 2013). Perinatal anxiety may also put the mother-infant bond at risk, as these women are more likely to report decreased perceived bonding with their child (Tietz et al., 2014). These infants are also at increased risk of experiencing cognitive and motor performance deficits (Davis & Sandman, 2010), more difficult temperament, and elevated levels of negative affect (Blair et al., 2011; Brand & Brennan, 2009; Britton, 2011). These adverse effects can extend into childhood, leading to deficits in executive functioning, as well as heightened levels of anxiety in offspring (Bernstein et al., 2005; Buss et al., 2011; Davis & Sandman, 2012).

Despite its high prevalence, perinatal anxiety has received relatively little attention (Farr et al., 2014). Although a number of sociodemographic and psychological risk factors have been identified in the literature, these studies are small in number and their findings are inconsistent. For example, while some studies suggest that younger maternal age and nulliparity are predictors of increased risk, others suggest that older women and those who are multiparous are more likely to experience anxiety in the perinatal period (Bayrampour et al., 2012; Biaggi et al., 2016; Lederman & Weis, 2009; Tearne et al., 2016). Other studies suggest that women with less educational attainment, those who have lower income levels (Biaggi et al., 2016; Yelland et al., 2010), and mothers who received less social support (Dunkel Schetter, 2011; Peter et al., 2017) are at increased risk.

In terms of psychological risk factors, a past history of mood and/or anxiety disorders are among the most potent predictors of perinatal anxiety development (Faisal-Cury et al., 2009; Martini et al., 2015; Rubertsson et al., 2014). Similarly, women who have experienced abuse in their childhood are at increased risk of experiencing antenatal anxiety (Leeners et al., 2006).

Others have highlighted associations between dysfunctional perfectionism (e.g., doubts, parental expectations, concern over mistakes) and postpartum anxiety (Oddo-Sommerfeld et al., 2016). Finally, poor subjective maternal sleep during pregnancy has been linked to heightened levels of postpartum anxiety (Skouteris et al., 2009; Swanson et al., 2010), though some studies have not found an association (Lawson et al., 2015; Tham et al., 2016).

The biological risk factors of perinatal anxiety have yet to be elucidated, despite increasing interest in these as predictors and prognostic factors for anxiety in general population samples. These may be of particular relevance to the perinatal period since during the early stages of pregnancy, from implantation to the second trimester, levels of proinflammatory T-helper cells and their interleukins increase (e.g., interleukin-6, tumor necrosis factor-alpha) (Mor et al., 2011). These have the ability to stimulate the hypothalamic pituitary adrenal (HPA) axis and increased circulating cortisol (Mastorakos & Ilias, 2000; Silverman et al., 2005) which is associated with increased anxiety in both non-puerperal and puerperal populations (Kane et al., 2014; Lenze et al., 2011; Tafet et al., 2005). Following the delivery of a child, the HPA axis remains hyperactive (Duthie & Reynolds, 2013), and HPA hyperactivity has been widely associated with the neurobiology of non-puerperal anxiety and depression (Copeland et al., 2012; Khandaker et al., 2016; Lenze et al., 2011; Tafet et al., 2005; Vogelzangs et al., 2013). Given the intense hormonal changes that occur to women during pregnancy, particularly to the HPA axis (Duthie & Reynolds, 2013), this is an area worthy of further investigation.

Previous systematic reviews of perinatal anxiety (Biaggi et al., 2016; Goodman et al., 2014a, 2016; Ross & McLean, 2006) have focused mainly on estimating the prevalence of anxiety disorders occurring during the perinatal period. Unfortunately, they have not differentiated women who developed new onset anxiety problems and those who experienced an

exacerbation of a pre-existing anxiety disorder, including the social, psychological, and biological predictors of these problems. The literature has shown some differences between risk factors in women with and without pre-existing anxiety disorders, suggesting potential differences in etiology. For example, having a difficult delivery places women without a history of anxiety disorders at risk for postpartum anxiety, whereas no effect has been found in women with pre-existing anxiety (House et al., 2016; Srkalović et al., 2017). Similarly, education status (specifically lower education level) has been shown to be a predictor of new onset perinatal anxiety, whereas this association has not been found in women with pre-existing anxiety (Qiao et al., 2009; Uguz et al., 2007). To our knowledge, no systematic review has attempted to identify and delineate the predictors of new onset anxiety and anxiety worsening as separate clinical presentations. Understanding the predictors of perinatal anxiety in these two groups could assist in the timely and accurate detection of symptoms in women before they develop clinical anxiety or a worsening of their pre-existing symptoms. Perhaps most importantly, such knowledge can inform predictive and preventative strategies for this population at risk. For the purposes of this review, the perinatal period is defined as any time from pregnancy to 12 months postpartum. This is the traditional use of the term and the literature has shown that the prevalence of anxiety disorders is highest during this time (Goodman et al., 2016).

As the risk factors associated with the development and exacerbation of perinatal anxiety are not yet well understood, the aim of this systematic review was to identify predictors of both new onset anxiety and anxiety worsening occurring from pregnancy to twelve months postpartum, and to determine if they differ between these two groups. As the predictors of new onset perinatal anxiety and perinatal anxiety worsening in this systematic review will not limited to a single domain (i.e., sociodemographic characteristics only), the primary outcome of this

review was therefore any factor in any domain shown to be predictive of new onset anxiety or anxiety worsening.

Methods:

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines and Checklist and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Guidelines were followed for the current systematic review, which was registered on PROSPERO on March 15, 2017, under the registration number CRD42017057425 (Furtado et al., 2017).

Data Sources and Study Selection:

A literature search of PubMed, MEDLINE, PsycINFO, CINAHL, Ovid Portal, ProQuest Portal, and the Web of Science Portal was conducted from their respective inceptions through September 18, 2017. A health sciences research librarian was consulted during the creation of the search strategy, which included the use of subject headings as well as keywords, where appropriate. The following combinations of subject headings and keywords found in either the titles or abstracts of articles were used: anxi* OR pregnan* OR perinatal OR postpartum OR postnatal OR generalized anxiety OR obsessive compulsive OR panic OR agoraphobia OR post-traumatic stress OR stress disorders OR social anxiety disorder OR social phobia OR phobia OR anxiety disorder*. Search strategies were adjusted accordingly, based on the database being used. The specific search strategies used in this review are available from the first author upon request. Additionally, an ancestry search, in which reference lists of eligible papers are hand searched,

was conducted in order to ensure that all relevant articles had been identified. The search limits for the current review were the English language and human studies.

In this review, only those studies that clearly indicated (in the methodology or sample demographics sections) that the sample of included women did not have any pre-existing anxiety disorders, were included in the new onset anxiety group. Alternatively, studies in which it was identified that the women included in the study had pre-existing anxiety disorders and their anxiety was being assessed in the study, were included in the anxiety worsening group. As all of the included studies in this review were conducted pre- DSM-5, in which Posttraumatic Stress Disorder and Obsessive Compulsive Disorder were still considered to be part of the anxiety disorders, we therefore classified anxiety disorders in the same way as the included studies.

Studies were included if they: 1) assessed perinatal anxiety through the use of a validated diagnostic interview (e.g., Mini International Neuropsychiatric Interview, Structured Clinical Interview, etc.), clinician- (e.g., Yale-Brown Obsessive Compulsive Scale), or self-report questionnaires (e.g., State-Trait Anxiety Inventory) and 2) anxiety symptoms were assessed at any time point from pregnancy to 12 months postpartum. Following the removal of duplicate articles, titles and abstracts were independently screened by two reviewers (MF and SO) to identify those meeting the inclusion criteria. Any disagreements were resolved through discussion between reviewers, and taken to a third reviewer (CC) if necessary. Next, full text of the articles identified in the initial phase of screening were reviewed to ensure that all articles meeting complete inclusion criteria were included in the data extraction phase.

Data Extraction and Analysis:

A customized data extraction form was developed that contained information relevant to our research questions including: (a) study methods (e.g., study design, setting), (b) sample demographics (e.g., age, marital status), (c) outcome assessment (e.g., questionnaires used, type of anxiety), (d) effect estimates (e.g., means and standard deviations, odds ratios), and (e) risk of bias. RevMan 5.3 software was used to calculate adjusted odds ratios (OR) and 95% confidence intervals (CI), as well as to generate associated forest plots. The Newcastle-Ottawa Scale, which assesses risk of bias in observational studies, (NOS) (Wells et al., 2000), was used to assess the risk of bias of the included studies. Both the case-control and cohort study versions were used, dependent on the study design. The NOS is an 8-item scale assessing risk of bias across three domains: how study groups are selected (selection), the comparability of these groups (comparability), and the ascertainment of the exposure (exposure; in case-control studies) or outcome of interest (outcome; in cohort studies). The NOS utilizes a star rating system to assess study quality. A maximum of one star may be given for each item in the selection (4 items) and exposure/outcome domains (3 items), while 2 stars may be given in the comparability domain (1 item with 2 components). Articles may therefore achieve a maximum total score of 9.

Results:

Study Selection and Characteristics:

The database search yielded a total of 11,759 citations. Initial screening of these citations yielded 6296 potentially eligible studies following the removal of 5463 duplicates. Upon review of titles and abstracts, 128 articles were identified for full-text review, with 11 meeting full eligibility criteria. Figure 2.1 outlines the screening and selection process. See Figure 2.1.

Figure 2.1. Study Article Screening and Selection Flowchart**.**

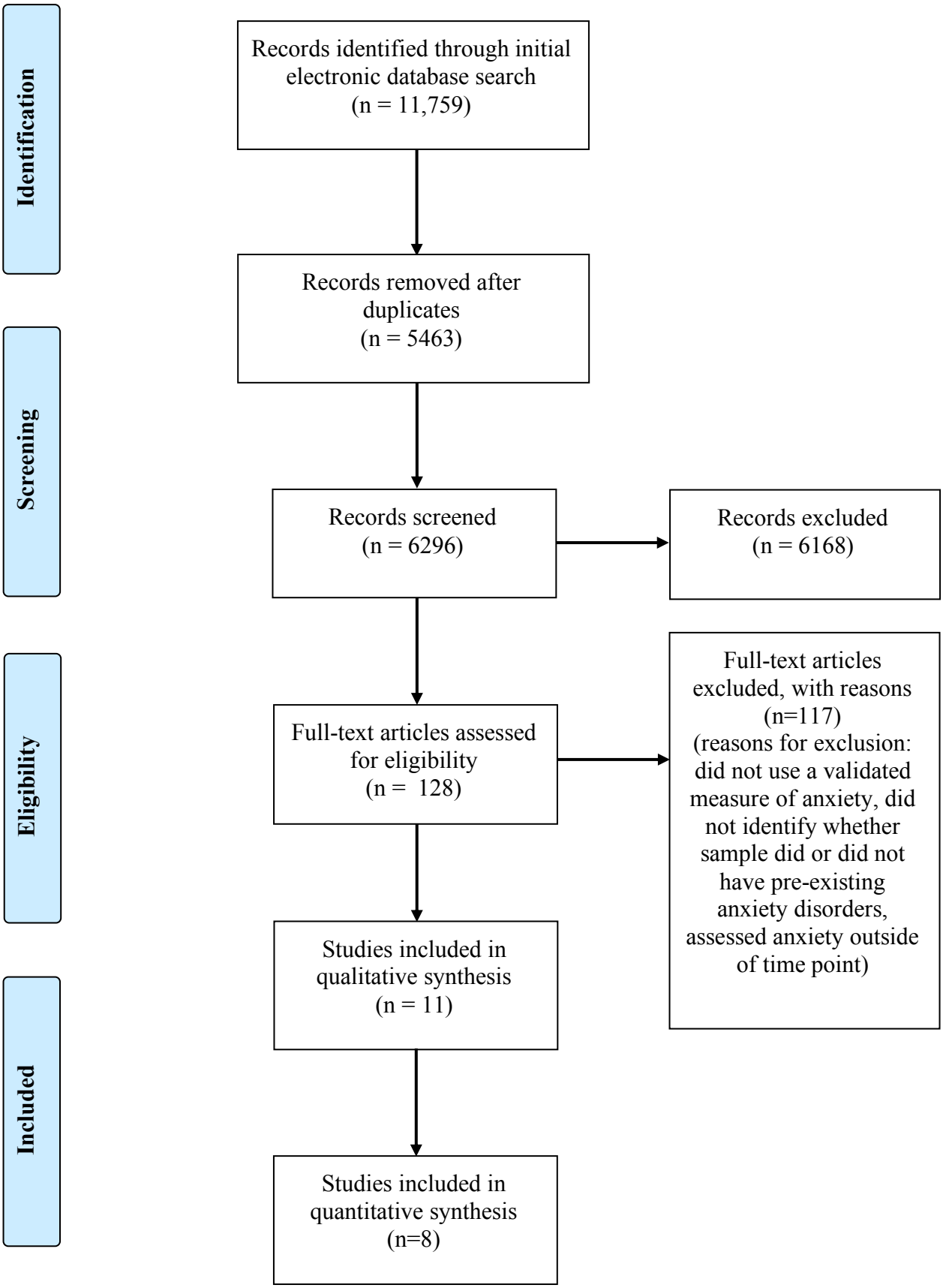


Table 2.1 outlines the characteristics of the included studies. Of the 11 included studies, 7 assessed new-onset perinatal anxiety (Couto et al., 2009; Ezberci et al., 2014; Fatoye et al., 2006; Forray et al., 2010; Qiao et al., 2009; Srkalović et al., 2017; Uguz et al., 2007), 3 assessed anxiety worsening (House et al., 2016; Muzik et al., 2016; Uguz et al., 2011), and 1 assessed both (Kroll-Desrosiers et al., 2017). Studies were conducted in 6 different countries; 4 were completed in the United States (Forray et al., 2010; House et al., 2016; Kroll-Desrosiers et al., 2017; Muzik et al., 2016), 3 in Turkey (Ezberci et al., 2014; Uguz et al., 2007, 2011), 1 in Nigeria (Fatoye et al., 2006), 1 in Brazil (Couto et al., 2009), 1 in Croatia (Srkalović et al., 2017), and 1 in China (Qiao et al., 2009). Studies were primarily conducted in out-of-hospital settings (n=6), obstetrical clinics (n=4), and mental health centres (n=1).

A total of 45,007 women were included in studies of new-onset perinatal anxiety, while 5450 women were evaluated for anxiety worsening. Women in new onset anxiety studies ranged in age from 15-69 years, while women were 15 years or older in anxiety worsening studies. Four studies however, did not identify their sample age range. Five studies assessed new onset anxiety during pregnancy and three during the postpartum period. Anxiety worsening was assessed during gestation in two studies, during the postpartum period in one study, and across both time periods in another study.

The majority of included studies (n=5) used standardized self-report measures to assess perinatal anxiety, 4 studies used both structured interviews and clinician-rated measures, 1 study used a structured clinical interview only, and 1 study used a structured clinical interview along with clinician-rated and self-report questionnaires. Studies provided information on risk factors for symptoms of anxiety (n=5), obsessive compulsive disorder (n=4), and post-traumatic stress disorder (n=2).

Risk of bias scores on the Newcastle-Ottawa Scale, ranged from 4 to 7, with two studies scoring 4, three studies scoring 5, five scoring 6, and one study scoring a 7 (See Table 2.1).

Table 2.1. Sample characteristics of included studies.

Study	Country	Study setting	Study Design	Outcome Assessment	Time of Assessment	Sample Size	Age Range	Mean Age (SD)
New Onset Anxiety								
Couto et al. (2009) *NOS Score= 5*	Brazil	University clinic, tertiary hospital, and municipal healthcare clinics	Cross-sectional	Short Form-36 and Hospital Anxiety and Depression Scale	18-24 weeks gestation	258 (18 excluded)	15-40	28.95 (6.04)
Ezberci et al. (2014) *NOS Score= 4*	Turkey	Obstetric Inpatient Clinic	Case-control	Hospital Anxiety and Depression Scale	Gestation	200	UNK	27.38 (5.6)
Fatoye et al. (2006) *NOS Score= 6*	Nigeria	Hospital	Case-control	State Trait Anxiety Inventory—State Subscale	Post-delivery to 6 weeks postpartum	166	UNK	30.05 (6.06)
Forray et al. (2010) *NOS Score= 5*	USA	Mental Health Center	Case-control	SCID for DSM-IV and Y-BOCS	Up to 12 months postpartum	126 (48 excluded)	18-69	40.8 (10.8)
Qiao et al. (2009) *NOS Score= 4*	China	Hospital	Cohort	Hospital Anxiety and Depression Scale	20-41 weeks gestation	593 (66 excluded)	18-42	29.1 (4.13)
Srkalović et al. (2017) *NOS Score= 5*	Croatia	Hospital	Cohort	Impact of Events Scale Revised	Post-delivery to 6 weeks postpartum	395 (23 excluded in phase 1 and 133 in phase 2)	15-45	UNK

Uguz et al. (2007) *NOS Score= 6*	Turkey	Obstetric Clinics	Case-control	SCID for DSM-IV, Y-BOCS	27-40 weeks gestation	566 (132 excluded)	17-44	28.57 (5.86)
Anxiety Worsening								
House et al. (2016) *NOS Score= 6*	USA	University Based Hospital	Cohort	SCID for DSM-IV-TR, Y-BOCS, STAI	1-3 month intervals during 12 months postpartum	208	UNK	33.2 (4.22)
Muzik et al. (2016) *NOS Score= 6*	USA	Obstetric Clinics	Cohort	CIDI short form for DSM-IV, National Women's Study PTSD Module	28-35 weeks gestation and 6 weeks postpartum	2689 (1108 excluded)	18 or older	26.06 (6.04)
Uguz et al. (2011) *NOS Score= 6*	Turkey	Hospital	Case-control	SCID for DSM-IV and Y-BOCS	Gestation	52	UNK	27.1 (5.3)
New Onset and Anxiety Worsening								
Kroll-Desrosiers et al. (2017) *NOS Score= 7*	USA	Hospital	Cohort	Diagnosis through ICD-9 and/or receipt of antidepressant or anxiolytic prescription	Up to 12 months postpartum	46,732	15-50	29.9 (6.2)

Risk Factors Associated with New Onset Perinatal Anxiety:

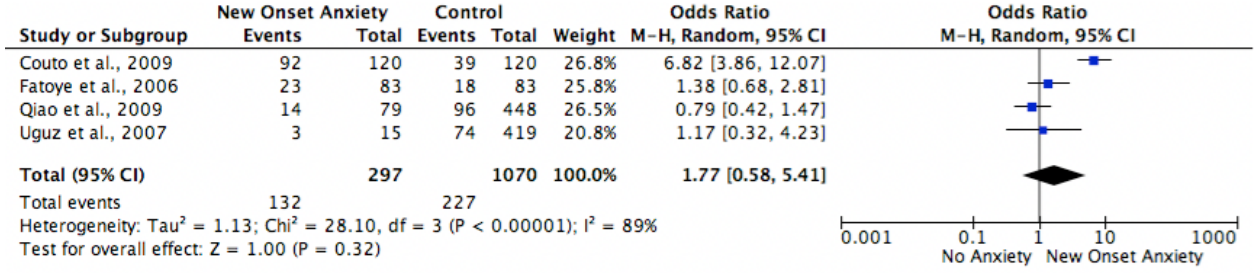
Obstetric and Pregnancy-Related Factors:

Five studies (Couto et al., 2009; Fatoye et al., 2006; Qiao et al., 2009; Srkalović et al., 2017; Uguz et al., 2007), examined obstetric and pregnancy-related factors predicting new onset perinatal anxiety, which included previous negative obstetric outcomes, difficult delivery, current hyperemesis gravidarum, and breastfeeding. Only one factor (previous negative obstetric outcomes) was assessed in more than 1 study and so this was the only risk factor that was

eligible for meta-analysis. All other risk factors assessed will be described in a narrative fashion based upon the findings of the associated individual study.

Mothers who had experienced a previous negative obstetric outcome (Couto et al., 2009; Fatoye et al., 2006; Qiao et al., 2009; Uguz et al., 2007; see Figure 2.2), defined as previous abortions, fetal death, preterm birth, or early neonatal death, were not at increased risk for experiencing elevated levels of perinatal anxiety symptoms [OR=1.77, 95% CI= 0.58-5.41, p=0.32; n=1367]. When abortion history was examined specifically (Fatoye et al., 2006; Qiao et al., 2009; Uguz et al., 2007), no statistically significant associations were found [OR=1.02, 95% CI=0.66-1.59, p=0.92; n=1127]. See Figure 2.2.

Figure 2.2. Association of Previous Negative Obstetric Outcomes with New Onset Perinatal Anxiety



However, a difficult delivery (defined as an emergency caesarean section) was a significant risk factor of elevated levels of symptoms of post-traumatic stress disorder, defined as a score of 24 or higher on the Impact of Events Scale—Revised (IES-R) [OR=2.05, 95% CI= 1.21-3.48, p=0.008; n=367] in one study (Srkalović et al., 2017), and women with current hyperemesis gravidarum [SMD=0.29, 95% CI=0.01-0.56, p=0.04; n=200] were at significant risk of increased new onset anxiety as well (Ezberci et al., 2014). In a single study (Srkalović et al., 2017), mothers who were successfully breastfeeding, with or without added formula

[OR=0.66, 95% CI= 0.30-1.46, p=0.30; n=259] did not appear to be protected from new onset perinatal anxiety. However, mothers who were exclusively breastfeeding, without added formula [OR=0.46, 95% CI=0.22-0.93, p=0.03; n=259], were protected against the development of new onset anxiety.

Sociodemographic Factors:

Four studies (Forray et al., 2010; Qiao et al., 2009; Srkalović et al., 2017; Uguz et al., 2007) examined sociodemographic factors including age, marital status, education level, employment, number of gestations, and number of household members, and their association with new onset perinatal anxiety. Only age and education level (primary school, college or higher) were examined in more than one study, with all other sociodemographic factors being assessed in a single study.

Our meta-analytic syntheses suggested that primary level education (i.e., poorer educational attainment) was a significant risk factor of new onset perinatal anxiety [OR=1.88, 95% CI= 1.17-3.03, p=0.009; n=961; Qiao et al., 2009; Uguz et al., 2007], however high school education [OR=0.38, 95% CI=0.05-2.95, p=0.36; n=434; Uguz et al., 2007], or a college/university level education or higher [OR=0.69, 95% CI=0.43-1.11, p=0.12; n=961;Qiao et al., 2009; Uguz et al., 2007] were not significant risk factors.

Maternal age between women with and without new onset anxiety was also not found to significantly predict new onset perinatal anxiety [SMD=0.15, 95% CI=-0.33-0.63, p=0.55; n=961; Qiao et al., 2009; Uguz et al., 2007], and neither did marital status. More specifically, being single [OR=2.28, 95% CI= 0.43-11.94, p=0.33; n=522; Forray et al., 2010; Qiao et al., 2009], married/common law [OR=0.43, 95% CI= 0.08-2.28, p=0.32; n=527; Forray et al., 2010;

Qiao et al., 2009], or divorced [OR= 0.78, 95% CI= 0.22-2.76, p=0.70; n=78; Forray et al., 2010] were not deemed risk factors.

Additionally, employment status (employed vs. unemployed) [OR=0.96, 95% CI= 0.21-4.35, p=0.96; n=434; Uguz et al., 2007], and the number of total pregnancies between women with and without new onset anxiety [SMD=0.21, 95% CI= -0.30-0.73, p=0.42; n=434; Uguz et al., 2007], were not significant risk factors.

Elevated levels of PTSD symptoms (defined as a score of 24 or higher on the IES-R) was predicted by mothers living with extended family members [OR=3.52, 95% CI= 1.66-7.43, p=0.001; n=261; Srkalović et al., 2017].

Psychological Factors:

Three studies (Forray et al., 2010; Qiao et al., 2009; Uguz et al., 2007) assessed links between a variety of psychological factors (e.g., family history of OCD, family history of alcohol abuse, and comorbid sleep disorders) and new onset perinatal anxiety, however, the aforementioned factors were only assessed in single studies. Having a family history of OCD was associated with an increased risk of a diagnosis of maternal OCD (as assessed through the Structured Clinical Interview for the DSM-IV) [OR= 20.45, 95% CI=5.90-70.91, p<0.00001; n=434; Uguz et al., 2007]. Maternal sleep disorders during pregnancy also predicted new onset perinatal anxiety [OR=1.98, 95% CI=1.10-3.59, p=0.02; n=527; Qiao et al., 2009]. A family history of alcohol abuse was not associated with an increased risk of OCD however [OR=0.15, 95% CI= 0.02-1.25, p=0.08; n=78; Forray et al., 2010].

Biological Factors:

Only a single study (Kroll-Desrosiers et al., 2017) assessed a biological risk factor (prenatal oxytocin exposure, defined as any prenatal clinical indication of exposure to synthetic oxytocin within 2 weeks of the expected delivery date) of new onset perinatal anxiety. In this study, women who were exposed to prenatal oxytocin [OR=1.44, 95% CI= 1.31-1.58, $p<0.00001$; n=43,123] were at significant risk of developing a postpartum anxiety disorder compared to those who were not exposed. Table 2.2 summarizes all of the risk factors examined for their links to new onset anxiety disorders.

Table 2.2. Risk factors assessed in new onset perinatal anxiety disorder studies

Risk Factor	Significant Findings	Non-Significant Findings
Obstetric and Pregnancy Related Factors		
Previous negative obstetric outcomes		OR=1.77, 95% CI= 0.58-5.41 (Couto et al., 2009) (Fatoye et al., 2006) (Qiao et al., 2009) (Uguz et al., 2007)
Difficult Delivery	OR=2.05, 95% CI= 1.21-3.48 (Srkalović et al., 2017)	
Breastfeeding		OR=0.66, 95% CI= 0.30-1.46 (Srkalović et al., 2017)
Hyperemesis Gravidarum	SMD=0.29, 95% CI=0.01-0.56 (Ezberci et al., 2014)	
Sociodemographic Factors		
Maternal Age		SMD=0.15, 95% CI=-0.33-0.63 (Qiao et al., 2009) (Uguz et al., 2007)
Marital Status (Single)		OR=2.28, 95% CI= 0.43-11.94 (Qiao et al., 2009)
Marital Status (Married/Common Law)		OR=0.43, 95% CI= 0.08-2.28 (Qiao et al., 2009)

Marital Status (Divorced)		OR= 0.78, 95% CI= 0.22-2.76 (Forray et al., 2010)
Education (Primary School)	OR=1.88, 95% CI= 1.17-3.03 (Qiao et al., 2009) (Uguz et al., 2007)	
Education (Secondary school/high school)		OR=0.38, 95% CI=0.05-2.95 (Uguz et al., 2007)
Education (College or higher)		OR=0.69, 95% CI=0.43-1.11 (Qiao et al., 2009) (Uguz et al., 2007)
Number of gestations (with or without new onset anxiety)		SMD=0.21, 95% CI= -0.30-0.73 (Uguz et al., 2007)
Living with extended family members	OR=3.52, 95% CI= 1.66-7.43 (Srkalović et al., 2017)	
Employed or not		OR=0.96, 95% CI= 0.21-4.35 (Uguz et al., 2007)
Parity (with or without new onset anxiety)		SMD=0.36, 95% CI=-0.16-0.87 (Uguz et al., 2007)
Psychological Factors		
Family history of OCD	OR=20.45, 95% CI=5.90-70.91 (Uguz et al., 2007)	
Family history of alcohol abuse		OR=0.15, 95% CI=0.02-1.25 (Forray et al., 2010)
Comorbid sleep disorder	OR=1.98, 95% CI=1.10-3.59 (Qiao et al., 2009)	
Biological Factors		
Prenatal Oxytocin Exposure	OR=1.44, 95% CI=1.31-1.58 (Kroll-Desrosiers et al., 2017)	

Risk Factors Associated with Perinatal Anxiety Worsening:

Obstetrical and Pregnancy-Related Factors:

Associations between obstetrical and pregnancy-related factors (i.e., previous negative obstetric outcomes and difficult delivery) with perinatal anxiety worsening was only assessed in a single study (House et al., 2016). Previous negative obstetric outcomes were not linked with

anxiety worsening [OR=0.48, 95% CI= 0.23-0.99, p=0.05; n=208], nor was having a difficult labour and delivery [OR=1.03, 95% CI=0.54-1.97, p=0.93; n=208].

Sociodemographic Factors:

Two studies (House et al., 2016; Muzik et al., 2016) assessed sociodemographic factors (e.g., age, marital status, education, and parity) for associations with perinatal anxiety worsening. Only age was assessed in more than one study, and was not found to be a significant risk factor of anxiety worsening compared to those who did not worsen [SMD=-0.60, 95% CI= -1.79-0.59, p=0.32; n=344; House et al., 2016; Muzik et al., 2016]. With respect to sociodemographic factors assessed in single studies, single marital status [OR=1.46, 95% CI= 0.90-2.36, p=0.12; n=319; Muzik et al., 2016], in women with and without an exacerbation of anxiety symptoms, having a college/university level education or higher [OR=1.09, 95% CI= 0.57-2.07, p=0.80; n=208; House et al., 2016], and being multiparous [OR=1.00, 95% CI= 0.53-1.87, p=1.00; n=208; House et al., 2016], were also not associated with perinatal anxiety worsening.

Psychological Factors:

Comorbid psychiatric diagnoses, specifically major depressive disorder or other existing anxiety disorders, were assessed in more than one included study (Muzik et al., 2016; Uguz et al., 2011), and were associated with anxiety worsening during the perinatal period [OR=2.83, 95% CI= 1.39-5.76, p=0.004; n=208]. A single study (Uguz et al., 2011) assessed the association between a family psychiatric history of OCD with perinatal OCD, which was not significantly associated [OR= 3.54, 95% CI= 0.53-23.53, p=0.19; n=52].

Biological Factors:

Prenatal oxytocin exposure was found to be associated with perinatal anxiety worsening was examined in a single study (Kroll-Desrosiers et al., 2017) [OR=1.50, 95% CI=1.26-1.79, p<0.00001; n=3609]. Table 2.3 outlines all anxiety worsening risk factors assessed.

Table 2.3. Risk factors assessed in perinatal anxiety worsening studies

Risk Factor	Significant Findings	Non-Significant Findings
Obstetric and Pregnancy Related Factors		
Previous negative obstetric outcomes	OR=0.48, 95% CI=0.23-0.99 (House et al., 2016)	
Difficult delivery		OR=1.03, 95% CI=0.54-1.97 (House et al., 2016)
Sociodemographic Factors		
Maternal Age		SMD=-0.60, 95% CI=-1.79-0.59 (House et al., 2016) (Muzik et al., 2016)
Marital Status (single)		OR=1.46, 95% CI=0.90-2.36 (Muzik et al., 2016)
Education (College or higher)		OR=1.09, 95% CI=0.57-2.07 (House et al., 2016)
Parity (more than 1)		OR=1.00, 95% CI=0.53-1.87 (House et al., 2016)
Psychological Factors		
Comorbid psychiatric diagnosis	OR=2.83, 95% CI=1.39-5.76 (Muzik et al., 2016) (Uguz et al., 2011)	
Family history of OCD		OR=3.54, 95% CI=0.53-23.53 (Uguz et al., 2011)
Biological Factors		
Prenatal Oxytocin Exposure	OR=1.50, 95% CI=1.26-1.79 (Kroll-Desrosiers et al., 2017)	

Discussion:

The present review systematically synthesized the literature identifying obstetrical and pregnancy-related, sociodemographic, psychological, and biological risk factors for new onset anxiety and anxiety worsening during the perinatal period. Even though only limited data were able to be meta-analyzed, we did identify a number of results that are of relevance to clinicians.

In terms of new onset perinatal anxiety, having a primary school education, living with extended family members, having a family history of psychiatric disorders, current hyperemesis gravidarum, multiparity, and a personal history of sleep disorders were found as significant risk factors. Exclusive breastfeeding was shown to be a protective factor against the development of new onset anxiety disorders. Maternal age and marital status, on the other hand, were not risk factors for the development of new onset anxiety disorders.

As for perinatal anxiety *worsening*, having a comorbid psychiatric disorder was the only significant risk factor identified in more than one study, while maternal age, again, demonstrated conflicting findings. Similar to that of new onset anxiety, marital status, a college level education (or higher), and parity were not identified as risk factors for anxiety worsening.

Interestingly, the only biological risk factor that was examined in this review, prenatal oxytocin exposure, demonstrated a significant association with both new onset anxiety and anxiety worsening during the perinatal period. This is a potential area of concern, as the administration of synthetic oxytocin is among one of the most used methods to induce delivery (Bell et al., 2014).

While this review identifies a number of risk factors for perinatal anxiety, many factors that have been linked to anxiety disorders in general population samples have not been examined in this special population. This is an important area of future research, as understanding which of

these are relevant to the perinatal period is essential in order to aid in prevention of perinatal anxiety. Importantly, factors that are unique to the perinatal period (e.g., obstetric and delivery complications, infections/illnesses originating during pregnancy) should also be examined as they may help to make more complete predictive models.

Even though appreciation of the prevalence and impact of perinatal anxiety has increased, the number of studies that examine risk factors for perinatal anxiety is still quite small. This prevents the development of screening tools and preventative strategies for women struggling with anxiety during pregnancy and/or the postpartum period. Moreover, many studies still do not differentiate women with pre-existing psychiatric conditions from those without. The presence of perinatal anxiety comorbid with other psychiatric disorders, such as depression, is highly prevalent, with some rates nearing 20% (Dikmen-Yildiz et al., 2017). Thus, studies aimed at delineating risk factors of perinatal anxiety with or without the presence of comorbid psychiatric conditions, for example, depression, are necessary. Additionally, determining whether risk factors of perinatal anxiety differ between women with varying levels of anxiety severity (i.e., symptomatic, sub-threshold, or threshold), often defined through cut-off scores on validated questionnaires, can further aid in screening and prevention. If the risk factors of perinatal anxiety differ between these women, screening measures that are tailored specifically to women with and without pre-existing anxiety disorders, specific anxiety disorders and severity level, or those with comorbid disorders could be developed. Through these screening measures, potential preventive strategies could be developed and aid in the prevention of either the onset of perinatal anxiety or the exacerbation of symptoms. Moreover, identifying risk factors of perinatal anxiety can further enhance our understanding of the underlying mechanisms and etiologies of these disorders. This

would allow us to better understand how these conditions manifest, which would aid in the development of appropriate and targeted preventative measures.

It has been well established that preventive measures are effective in preventing symptom onset and relapse, as well as the disability associated with postpartum disorders, such as postpartum depression (Sockol et al., 2013; Werner et al., 2015). Women who are identified to be at risk for either the development of an anxiety disorder or exacerbation of existing anxiety, could be closely monitored throughout their pregnancy for signs of anxiety symptoms. If these women are at increased risk, preventive strategies can be implemented dependent on the degree of severity, such as through cognitive behavioural therapy, prenatal support groups, or in some cases pharmacological treatments. Further, women at risk can be followed up on at a closer degree following the delivery of their child, in order to determine whether treatment is necessary. Without conducting further research in differentiating these women in studies however, it cannot be known whether they do in fact differ in terms of what predicts the development of anxiety or exacerbation of symptoms, and in turn what screening measures can be used.

Strengths and Limitations

The present review has several strengths. First, this was the first review to distinguish risk factors for both new onset and worsening of perinatal anxiety disorders. Eleven studies met our inclusion criteria, with seven assessing new onset, three worsening, and one assessing both. Second, only studies utilizing validated anxiety measures, specifically structured diagnostic interviews, clinician-administered, and self-report questionnaires, were included. Third, this systematic review was written following PRISMA and MOOSE guidelines.

With these strengths, come limitations. First, many of the included studies utilized self-report questionnaires to assess anxiety onset and/or severity. Although these studies included validated questionnaires, it is important to note that not all studies utilized structured diagnostic interviews in determining new onset anxiety and/or worsening. Future studies in this area may benefit from comparing the use of structured diagnostic interviews and clinician-administered questionnaires with self-report questionnaires, in order to determine whether there are any differences between methods. Second, many risk factors were only examined by a single study, therefore limiting our ability to meta-analyze these potential risk factors. This small number of studies however, highlights the urgent need for more research in this area. Interestingly, all included studies were published within the past decade which does show that research in distinguishing anxiety disorders between those women with and without pre-existing conditions is increasing. The primary reason for exclusion of studies was the lack of differentiation of study populations with and without pre-existing anxiety disorders. In the absence of this information, numerous studies that did discuss risk factors for new onset perinatal anxiety were excluded as it could not be assumed whether the study population being examined was in fact free of pre-existing anxiety problems. In order to determine whether women with and without pre-existing anxiety disorders should be in fact assessed and screened differently from one another, studies examining various obstetric, sociodemographic, psychological, and biological risk factors must be replicated. This could then potentially lead to the creation of appropriate screening tools, such as brief clinician- or self-report questionnaires assessing risk factors in pregnant women.

Conclusion and Future Directions:

Although the present review differentiated women with and without pre-existing anxiety disorders, only 4 risk factors (previous negative obstetric outcomes, age, education level, and psychiatric comorbidities) were examined in more than one study, highlighting the paucity of empirical data in this area. Despite various risk factors being identified and analyzed in this review, numerous factors that have been identified in general population samples have not been examined in these perinatal populations. Moreover, additional risk factors specific to the perinatal period (e.g., obstetric and pregnancy related factors) and those known to function differently during this time (e.g., inflammatory biomarkers) need to be studied to determine if they can help to identify women at risk.

Literature has shown that early detection and screening of psychiatric disorders, including perinatal anxiety, improves symptom management, leading to improved overall physical and mental health of both the women and her children (O'Hara & Wisner, 2014). Being aware of the potential risk factors for the development and/or exacerbation of perinatal anxiety can lead to accurate detection and in turn, interventions that can decrease symptomatology and associated distress, or even prevent onset or worsening. Various treatment options, including cognitive behavioural and interpersonal psychotherapies, mindfulness-based techniques, and/or pharmacological treatments, have all been shown to be effective in the treatment of perinatal disorders (Goodman et al., 2014; Green et al., 2015; Sockol et al., 2011; Stuart & Koleva, 2014). These are important areas of research and would aid in screening and detection in these women.

One well-established risk factor of non-puerperal anxiety disorders is a history of childhood trauma (Heim & Nemeroff, 2001; Khoury et al., 2010; Lochner et al., 2010), yet no included study examined childhood trauma in new onset or anxiety worsening during the

perinatal period. Women who experienced childhood abuse have been shown to be at increased risk of anxiety during pregnancy (Leeners et al., 2006), however this study did not distinguish any differences between women with and without pre-existing anxiety disorders.

Although there is some overlap between risk factors of non-puerperal anxiety disorders with those of perinatal anxiety, there remains a large gap in this area. For example, various studies suggest that personality traits, such as perfectionism and feelings of uncertainty predict anxiety symptoms (Boswell et al., 2013; Gnilka et al., 2012; McEvoy et al., 2012; O'Connor et al., 2010), however the association with perinatal anxiety disorders has yet to be examined in the literature.

Another area of research yet to be elucidated in these populations are those of biological markers. The only biological risk factor examined in the review was prenatal oxytocin exposure, which was significantly associated with perinatal anxiety. Further research into the area of biological factors has potential value in aiding in the screening and detection of anxiety onset and worsening of pre-existing symptoms. More recently, research has examined the role of inflammation in the pathogenesis of non-puerperal anxiety disorders (Copeland et al., 2012; Lenze et al., 2011; Tafet et al., 2005), revealing significant associations, with for example, increased levels of inflammatory cytokines (Copeland et al., 2012; Khandaker et al., 2016; Vogelzangs et al., 2013). The use of biomarkers in psychiatry could provide an objective screening measure (Bahn et al., 2013; Venkatasubramanian & Keshavan, 2016), which could be added to the multimodal approach for predicting and diagnosing these disorders. Given these findings in non-puerperal populations, it would be of value to extend this research into the perinatal period with the potential of aiding in detection and appropriate treatment.

Childbirth is typically a happy occasion for the mother and her family, however anxiety disorders occurring during the perinatal period can hinder this joy as a result of the various associated adverse effects. Approximately 1 in 5 women will experience an anxiety disorder within the first 12 months of their child's birth, a rate that is comparable to prevalence rates for postpartum depression. These women, their infants, and families are at increased risk of negative effects, which often result in both substantial personal and economic burden. Therefore, further research in this area is necessary as it has the potential to provide further information on what factors increase one's risk of developing an anxiety disorder or exacerbating already existing symptoms during the perinatal period.

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Citations marked with a (*) indicate inclusion in the systematic review.

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CHAPTER 3

Methodology and Materials

Participants

Thirty-five (35) pregnant women aged 18 years or older with a current or lifetime diagnosis of an anxiety disorder with or without comorbid depression were recruited during their third trimester of pregnancy (≥27 weeks gestation) from the greater Hamilton area. Women were recruited primarily (74%) from the Women's Health Concerns Clinic at St. Joseph's Healthcare Hamilton, as well as through advertising in midwifery, physician clinics, and online (e.g., Kijiji, Instagram, Facebook) between April 2017 and June 2018. Diagnoses of anxiety disorders (generalized anxiety disorder, panic disorder, social anxiety disorder, agoraphobia) were confirmed with the Mini International Neuropsychiatric Interview (MINI) English Version 7.0.2 for DSM-5 (Sheehan et al., 2016). Participants with comorbid depression and/or non-primary obsessive compulsive disorder and posttraumatic stress disorder were included. Participants were excluded if they (1) had current or a past history of any psychotic and/or bipolar disorder, (2) had an eating, alcohol, and/or substance use disorder in the previous six months, and/or (3) had a baseline score of 24 or greater on the Hamilton Anxiety Rating Scale. To reduce additional potential confounders, women with diagnosed autoimmune disorders (e.g., Rheumatoid Arthritis, Lupus, Crohn's Disease), in which inflammatory biomarkers are elevated (Bennike et al., 2014; Chang et al., 2015; Enocsson et al., 2014; Gensous et al., 2017; Srirangan & Choy, 2010; Vasanthi et al., 2007), were also excluded. All participants provided written informed consent to participate in the study, as approved by the Hamilton Integrated Research Ethics Board (HiREB).

Study Design

This study utilized a longitudinal observational design with five visits, one during the third trimester of pregnancy (baseline), followed by visits at two, six, twelve, and twenty-four weeks postpartum. Refer to Figure 3.1 for the study visit schedule.

Figure 3.1. Study visit schedule

Assessments	Third trimester (≥27 weeks gestation)	2 weeks postpartum	6 weeks postpartum	12 weeks postpartum	24 weeks postpartum
MINI for DSM-5	X				
Informed Consent Form	X				
Sociodemographic Characteristics	X				
Medical History (including medications)	X				
Obstetrical and Delivery Factors		X			
HAM-A	X		X	X	X
GAD-7	X	X	X	X	X
IUS	X	X	X	X	X
CPQ	X		X	X	X
EPDS	X	X	X	X	X
ISI	X	X	X	X	X
OCI-R	X	X	X	X	X
CTQ	X				
MSPSS	X		X	X	X

VPSQ	X				
PBI	X				
FHS	X				
CRP, IL-6, TNF-α	X	X	X		

MINI: Mini International Neuropsychiatric Interview; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; HAM-A: Hamilton Anxiety Rating Scale; GAD-7: Generalized Anxiety Disorder Scale—7 Items; IUS: Intolerance of Uncertainty Scale; CPQ: Clinical Perfectionism Questionnaire; EPDS: Edinburgh Postnatal Depression Scale; ISI: Insomnia Severity Index; OCI-R: Obsessive Compulsive Inventory—Revised; CTQ: Childhood Trauma Questionnaire; MSPSS: Multidimensional Scale of Perceived Social Support; VPSQ: Vulnerable Personality Style Questionnaire; PBI: Parental Bonding Instrument; FHS: Family History Screen; CRP: C-reactive protein; IL-6: Interleukin 6; TNF-α: Tumor necrosis factor-alpha

At the first study visit, informed consent was obtained and participants were interviewed with the MINI for DSM-5 to confirm diagnoses. During the first study visit, demographic information, medical history (i.e., current and past medication and psychotherapy use, diagnosed disorders, etc.), family psychiatric history, and anxiety symptom severity were also assessed through a series of interviews, followed by a battery of self-report questionnaires assessing various psychological domains (see clinical assessments below). At the remaining postpartum study visits, participants completed a battery of self-report questionnaires, and anxiety symptom severity (as assessed through the Hamilton Anxiety Rating Scale) was assessed at the six, twelve, and twenty-four postpartum week visits. Venous blood samples were collected from participants at the first study visit during the third trimester of pregnancy, as well as at the second (two weeks postpartum) and third (6 weeks postpartum) study visits, in order to assess serum cytokine levels of CRP, IL-6, and TNF-α. Participants who were uncomfortable with participating in the blood draw were not excluded from the study.

Study Objectives

The primary objective of this study is to evaluate the predictors of postpartum anxiety exacerbation, defined by scores on the Hamilton Anxiety Rating Scale, prospectively from the third trimester of pregnancy to 24 weeks postpartum. The primary outcome of the study, postpartum anxiety worsening, will be defined as an increase of 50% or greater in Hamilton Anxiety Rating Scale scores from baseline (third trimester) scores to 6 weeks postpartum.

The secondary objective of this study is to evaluate the biological markers, specifically, CRP, IL-6, and TNF-α, of postpartum, anxiety worsening from the third trimester of pregnancy to 6 weeks postpartum.

Study Outcomes

Psychiatric diagnoses, based upon the DSM-5, were assessed using the Mini International Neuropsychiatric Interview (MINI) version 7.0.2 (Sheehan et al., 2016).

Primary Outcome Measure

Anxiety symptoms and severity was assessed with our primary outcome measure, the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959). The HAM-A is a 14-item interviewer administered scale assessing overall anxiety severity across two subscales: psychic anxiety (i.e., mental agitation, psychological distress, fears) and somatic anxiety (i.e., physical complaints related to anxiety). Items are assessed on a scale ranging from 0 (not present) to 4 (severe), with higher scores indicating greater anxiety severity. Anxiety severity can be categorized into the following scoring cutoffs: no to very mild anxiety (0-7), mild anxiety (8-14), moderate anxiety (15-23), and severe anxiety (>24). The HAM-A has demonstrated good

validity and reliability in anxiety and depression populations (Maier et al., 1988). In order to ensure consistency of questioning across participants and visits, the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A) (Shear et al., 2001) was used. The SIGH-A utilizes clear anchor points, with the interviewer asking multiple questions for each of the items on the HAM-A, in order to aid in the rater's ability to assess symptom severity. The SIGH-A has demonstrated high test-retest reliability and inter-rater reliability (Shear et al., 2001). As has been conducted in previous studies examining anxiety worsening/relapse, this study defined postpartum anxiety worsening as a 50% or greater increase from baseline scores (O'Sullivan et al., 1996; Pecknold et al., 1993; Roy-Byrne et al., 1989).

Primary Predictive Measures

Participants' self-reported family psychiatric history was assessed with the Family History Screen (FHS) (Weissman et al., 2000). The FHS is utilized to assess psychiatric health history of immediate biological family members, specifically parents, siblings, and children. Participants are asked a series of questions pertaining to key symptoms for various psychiatric disorders. The FHS takes approximately 5 to 20 minutes to administer, as timing is dependent upon the number of relatives in the family, as well as the presence of psychiatric illness. The FHS is a useful brief tool to assess family history of psychiatric illness and has demonstrated good validity and reliability (Weissman et al., 2000).

Self-reported anxiety severity was assessed with the Generalized Anxiety Disorder 7-Item Scale (GAD-7) (Spitzer et al., 2006). The GAD-7 is a 7-item self-report measure assessing the severity of symptoms of generalized anxiety disorder over the past 2-weeks (Spitzer et al., 2006). Scores on each item are measured using a 4-point Likert scale, ranging from 0 (not at all)

to 3 (nearly every day), with higher scores indicating increased severity of anxiety. The sensitivity of the GAD-7 with a cut-off score of 10 for a diagnosis of GAD is 89% and specificity is 82%. Use of the GAD-7 has also been validated in the perinatal population, yielding sensitivity and specificity at 61.3% and 72.7%, respectively, with an optimal cut-off score of 13 (Simpson et al., 2014). The GAD-7 was utilized in this study over other validated anxiety questionnaires, such as the State-Trait Anxiety Inventory (STAI), as the STAI includes numerous questions that can be confounded by symptoms that occur in a normal pregnancy (e.g., "I tire quickly"), which may increase the rates of false positives (Simpson et al., 2014).

Intolerance of uncertainty was assessed with the Intolerance of Uncertainty Scale (IUS). The IUS is a 27-item self-report questionnaire that assesses intolerance of uncertainty, a predominant characteristic of anxiety disorders, including Generalized Anxiety Disorder, Social Anxiety Disorder, and Panic Disorder (Buhr & Dugas, 2002). The IUS includes questions that assess one's belief that uncertainty is stressful, unfair, and upsetting, leads to one's inability to act (i.e., is paralyzing), and uncertain situations are negative and should be avoided. The IUS is scored across two factors: 1) uncertainty has negative behavioural and self-referent implications (e.g., uncertainty stops me from having a firm opinion, being uncertain means that a person is disorganized, uncertainty keeps me from living a full life, I must get away from all uncertain situations), and 2) uncertainty is unfair and spoils things (e.g., it's unfair not having any guarantees in life, uncertainty makes me uneasy, anxious, or stressed, I can't stand being taken by surprise, the ambiguities in life stress me). Items are rated on a 5-point Likert scale and the IUS has demonstrated excellent internal consistency (α=0.91-0.95) and good test-retest reliability (r=0.78).

Self-reported perfectionistic traits were assessed with the Clinical Perfectionism Questionnaire (CPQ). The CPQ is a 12-item questionnaire assessing one's strive to meet standards and the effects on self-evaluation when those standards are not met (Stoeber & Damian, 2014). Items are rated on a 4-point Likert scale, ranging from 1 (not at all) to 4 (all day), with higher scores indicating greater clinical perfectionism. Higher scores on the CPQ have been found to be significantly associated with depression occurring during pregnancy (van Broekhoven et al., 2016). The CPQ has demonstrated good internal consistency and reliability (α=0.82) in a sample of pregnant women (van Broekhoven et al., 2016).

Self-reported depression symptoms and severity were assessed with the Edinburgh Postnatal Depression Scale (EPDS). The EPDS is a 10-item self-report questionnaire used to identify women with perinatal depression, with items corresponding to clinically relevant depressive symptoms (Cox et al., 1987). Items are scored on a 4-point scale (0-3) assessing one's symptoms over the past week, with higher scores indicating more depressive symptoms. Sensitivity and specificity in initial studies were 86% and 78%, respectively, with a diagnostic predictive value (cut-off score of 9/10) of 73% for Major Depressive Disorder. More recent studies (Matthey, 2006) have suggested an optimal cut-off score of 13 for postpartum depression. The EPDS has also been utilized to assess postpartum anxiety, with 3 of the 10 included questions specifically probing into anxiety symptoms (Matthey et al., 2013).

Subjective maternal sleep was assessed with the Insomnia Severity Index (ISI). The ISI is a 7-item self-administered questionnaire assessing the severity of sleep onset and maintenance, early morning awakening, as well as satisfaction with sleep and functional impairments due to sleep disturbances (Morin, 1993). Responses are rated on a 5-point Likert scale, ranging from 0 (not at all) to 4 (extremely), with higher scores indicating greater sleep disturbances. Unlike the

Pittsburgh Sleep Quality Index (PSQI) which assesses sleep over the previous month, the ISI assesses sleep over the past week. Additionally, the ISI contains fewer questions than the PSQI, and has demonstrated excellent internal consistency (α=0.84-0.91) and test-retest reliability when compared to the PSQI (Chen et al., 2017; Morin et al., 2011; Vegar & Hussain, 2017).

Traits of Obsessive Compulsive Disorder was measured with the Obsessive Compulsive Inventory—Revised (OCI-R). The OCI-R is an 18-item self-report scale adapted from the original 42 item OCI, that assesses frequency of symptoms and level of distress (Foa et al., 2002). The OCI-R items are scored on a 5-point Likert scale, with total scores of 21 or higher indicating a probable OCD diagnosis. The OCI-R demonstrates good internal consistency (α=0.81-0.93) and excellent test-retest reliability (r=0.74-0.91).

Self-reported childhood trauma history was assessed with the Childhood Trauma Questionnaire (CTQ). The CTQ is a 28-item questionnaire measuring 5 types of childhood abuse and neglect: emotional, physical, and sexual abuse, and emotional and physical neglect (Bernstein & Fink, 1997). Responses range on a 5-point Likert scale, ranging from ‘never true’ to ‘very often true’. The CTQ has demonstrated high internal consistency (α=0.81-0.95) and good test-retest reliability (r=0.80).

Perceived social support of participants was evaluated with the Multidimensional Scale of Perceived Social Support (MSPSS). The MSPSS is a 12-item questionnaire assessing the level of perceived support received by parents, friends, and significant others (Zimet et al., 1988). Responses are measured on a 7-point Likert scale, ranging from 1 (very strongly disagree) to 7 (very strongly agree) and has good reliability (α=0.81). In samples of postpartum women, the MSPSS has good internal consistency (α=0.83; Nakigudde et al., 2009) and is correlated with postpartum depression (Ege et al., 2008).

The Vulnerable Personality Style Questionnaire (VPSQ) was used to assess personality traits of participants. The VPSQ is a 9-item self-report questionnaire (Boyce et al., 2001) assessing personality traits (coping, nervy, timidity, sensitivity, worrier, organized, obsessive, expressive, and volatility), which increase one's risk of postpartum depression. Items are rated on a 5-point Likert scale, ranging from 1 (not at all) to 5 (very much so), with higher scores indicating increased vulnerability to developing postpartum depression. In a study of postpartum females by Gelabert et al. (2011), internal consistency was 0.63 (would increase if organized and expressive items were deleted) and test-retest reliability of items ranged from 0.69-0.91.

The Parental Bonding Instrument (PBI), a 25-item self-report questionnaire, was used to assess one's perception of the parenting they received up until the age of 16 years, with 2 subscales assessing care and overprotection (Parker et al., 1979). Items are scored on a 4-point Likert scale, ranging from "very like" to "very unlike", with higher scores on the care and overprotection subscales indicating affection and warmth, and overprotection and control, respectively. The PBI has demonstrated good internal consistency and test-retest reliability and has been utilized in perinatal samples.

Obstetrical and delivery factors were measured through self-report questions, assessing delivery method (e.g., vaginal or cesarean section), oxytocin exposure (e.g., administration of synthetic oxytocin pre- and/or post-delivery), and breastfeeding status (e.g., exclusively breastfeeding, breastfeeding with formula supplementation, not breastfeeding).

Blood Sampling Procedures

Blood samples were collected at varying times throughout the day (9am to 5pm) due to differences in participant availability. Venous blood was drawn from participants into a 10ml

serum separator tube and was left to clot for 30 minutes. Following the 30 minute clotting period, samples were centrifuged at 21°C for 15 minutes at 3000 rpm. Serum was then removed from the tube, aliquoted and immediately frozen at -80°C until analysis. Commercial ELISA kits for CRP, IL-6, and TNF-α were purchased from R&D Systems (Minneapolis, MN). On the day samples were assayed, single aliquots of serum were thawed for 60 minutes and all samples for each biomarker were assayed in duplicate. Laboratory analyses were performed according to the ELISA kit manufacturer protocol by an experienced technician (J.G.) at St. Joseph's Healthcare Hamilton.

Statistical Analysis

Independent samples t-tests were performed to compare means of baseline predictive outcomes (e.g., sociodemographic, obstetrical and delivery, psychological, and biological measures) between those who met criteria for anxiety worsening (increase of 50% or greater in HAM-A scores from baseline to 6 weeks postpartum) and those who did not. If variables did not meet assumptions of normality, as assessed by the Shapiro-Wilk test, the non-parametric Mann-Whitney U test was employed to compare group means. Cross-tabulations with Fisher's Exact Test were used to compare categorical predictive measures between those who worsened and those who did not. Binary logistic regression models were utilized to estimate the probability of the various predictors assessed. Pearson's correlations were performed to examine the association between anxiety severity and inflammatory biomarkers. All analyses were performed with IBM SPSS Statistics 23 (IBM Corp., 2015).

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CHAPTER 4

Results

Participant Characteristics

A total of 35 pregnant women were enrolled in the study. Scores on the primary outcome HAM-A at baseline ranged between 5 to 23, with a mean of 12.97 (SD=4.77). Participants ranged in age from 18-41 years, with a mean age of 31.11 years (SD=5.312). The majority of participants were Caucasian (85.7%), followed by First Nations (5.7%), Black (2.9%), East Asian (2.9%), and Middle Eastern (2.9%). Participants had predominantly higher levels of education (80%) (i.e., college diploma or higher) and in married (65.7%) or common-law (22.9%) relationships. The majority of participants were multigravida (62.9%). Refer to Table 4.1.

Generalized Anxiety Disorder was the most commonly diagnosed anxiety disorder (65.7%), followed by Panic Disorder (51.4%), Agoraphobia (14.3%), and Social Anxiety Disorder (2.9%). 77.1% of participants had a comorbid Major Depressive Disorder, with 11.4% of women meeting criteria for a current Major Depressive Episode. Additionally, 8.6% had Obsessive Compulsive Disorder and 11.4% had Posttraumatic Stress Disorder. Refer to Table 4.2.

At 6 weeks postpartum, a total of 17 women met criteria for anxiety worsening (defined as an increase of 50% or greater in HAM-A scores from baseline). HAM-A scores between those who worsened (17.29±5.25) and those who did not (13.61±4.26) were significantly different at 6 weeks postpartum ($p<0.05$). None of the women at 12 or 24 weeks postpartum met criteria for worsening. As the 6 week postpartum time point was considered the time in which anxiety worsening occurred, potential risk factors for worsening are detailed below.

Sociodemographic Factors

Table 4.1 outlines the participant demographics between groups at baseline. There were no statistically significant differences between those women who worsened at 6 weeks postpartum and those who did not in maternal age, ethnicity, marital status, parity, and educational background ($p>0.05$).

Table 4.1. Participant demographics between the worsening and non-worsening groups.

	Worsening (n=17)	**Non-Worsening (n=18)**	**Sig.**
Mean Age (SD)	29.76 (5.82)	32.39 (4.59)	0.147
Ethnicity			0.125
Caucasian	17 (100%)	13 (72.2%)	
Black	0 (0%)	1 (5.6%)	
First Nations	0 (0%)	2 (11.1%)	
Middle Eastern	0 (0%)	1 (5.6%)	
East Asian	0 (0%)	1 (5.6%)	
Marital Status			0.690
Single	1 (5.9%)	3 (16.7%)	
Married	12 (70.6%)	11 (61.1%)	
Common-law	4 (23.6%)	4 (22.2%)	
Parity			1.000
Primigravida	6 (35.3%)	7 (38.9%)	
Multigravida	11 (64.7%)	11 (61.1%)	
Education			0.835
Elementary	1 (5.9%)	0 (0%)	
High school	3 (17.6%)	3 (16.7%)	
College/diploma	4 (23.6%)	7 (38.9%)	
University/degree	4 (23.6%)	4 (22.2%)	
Postgraduate	5 (29.4%)	4 (22.2%)	
Current Psychiatric Medication			1.000
Escitalopram (10-15mg)	1 (5.9%)	2 (11.1%)	
Citalopram (30mg)	0 (0%)	1 (5.6%)	
Quetiapine (150mg)	1 (5.9%)	0 (0%)	
Sertraline (100-150mg)	2 (11.8%)	1 (5.6%)	
None	13 (76.5%)	14 (77.8%)	

Table 4.2. Psychiatric history of participants, as assessed by the MINI for DSM-5.

Psychiatric Diagnosis	Worsening (n=17)	Non-Worsening (n=18)	Sig.
Generalized Anxiety Disorder			
Current	6 (35.3%)	4 (22.2%)	0.471
Lifetime	13 (76.5%)	10 (55.6%)	0.289
Panic Disorder			
Current	1 (5.9%)	1 (5.6%)	1.000
Lifetime	7 (41.2%)	11 (61.1%)	0.318
Agoraphobia			
Current	1 (5.9%)	4 (22.2%)	0.338
Lifetime	1 (5.9%)	4 (22.2%)	0.338
Social Anxiety Disorder			
Current	0 (0%)	1 (5.6%)	1.000
Lifetime	0 (0%)	1 (5.6%)	1.000
Major Depressive Disorder			
Current	0 (0%)	4 (22.2%)	0.104
Lifetime	12 (70.6%)	9 (50%)	0.443
Obsessive Compulsive Disorder			
Current	0 (0%)	1 (5.6%)	1.000
Lifetime	1 (5.9%)	2 (11.1%)	1.000
Posttraumatic Stress Disorder			
Current	1 (5.9%)	1 (5.6%)	1.000
Lifetime	1 (5.90%)	3 (16.7%)	0.603

Obstetrical and Delivery Factors

At the 2 week postpartum visit, various obstetrical and delivery factors were assessed. Method of delivery (vaginal or caesarean section), breastfeeding status (exclusively breastfeeding or not), and gestational age were not related to postpartum anxiety worsening at 6 weeks postpartum ($p>0.05$). Obstetrical and delivery data are contained in Table 4.3.

Table 4.3. Obstetrical and delivery-related factors assessed at 2 weeks postpartum between the worsening and non-worsening groups.

	Worsening (n=17)	Non-Worsening (n=18)	Sig.
Mean Gestational Weeks at Delivery (SD)	39.47 (1.07)	39.78 (0.94)	0.373
Breastfeeding Status			0.688
Yes, exclusively	13 (76.5%)	13 (72.2%)	
Yes, with formula	3 (17.6%)	5 (27.8%)	
No	1 (5.9%)	0 (0%)	
Delivery Method			0.690
Vaginal	15 (88.2%)	14 (77.8%)	
Cesarean Section	2 (11.8%)	4 (22.2%)	

Psychological Factors

Various baseline psychological factors differentially predicted women who experienced anxiety worsening (n=17) and those that did not (n=18). No specific diagnosed psychiatric disorder, as assessed by the MINI for DSM-5, increased one's risk of anxiety worsening at 6 weeks postpartum, nor did a comorbid diagnosis of current major depressive disorder ($p>0.05$), obsessive compulsive disorder ($p>0.05$), or posttraumatic stress disorder ($p>0.05$). Further, there were no significant differences between groups with regard to the number of diagnosed disorders ($p>0.05$). When assessing participants' biological family members' psychiatric history, as assessed by the Family History Screen, no significant associations were found ($p>0.05$). Current and/or past use of psychiatric medication, past or current receipt of psychotherapy, or combined treatment with medication and psychotherapy were not associated ($p>0.05$) with postpartum anxiety worsening at 6 weeks postpartum.

Women who met criteria for anxiety worsening had significantly higher baseline scores on the IUS, compared to those who did not [$t(33)=-2.33$, MD=-14.80, 95%CI [-27.74, -1.87],

p=0.026] (Figure 4.1). When examining the two factor structure of the IUS (Factor 1: uncertainty has negative behavioural and self-referent implications; Factor 2: uncertainty is unfair and spoils everything), it was revealed that women who worsened also had significantly higher scores during their third trimester of pregnancy on factor 1 [t(33)=-2.44, MD=-8.74, 95%CI [-16.02, -1.46], p=0.020] (Refer to Figure 4.2), but not on factor 2 (p>0.05).

Figure 4.1. Intolerance of Uncertainty as a predictor of postpartum anxiety worsening at 6 weeks postpartum. IUS: Intolerance of Uncertainty Scale.

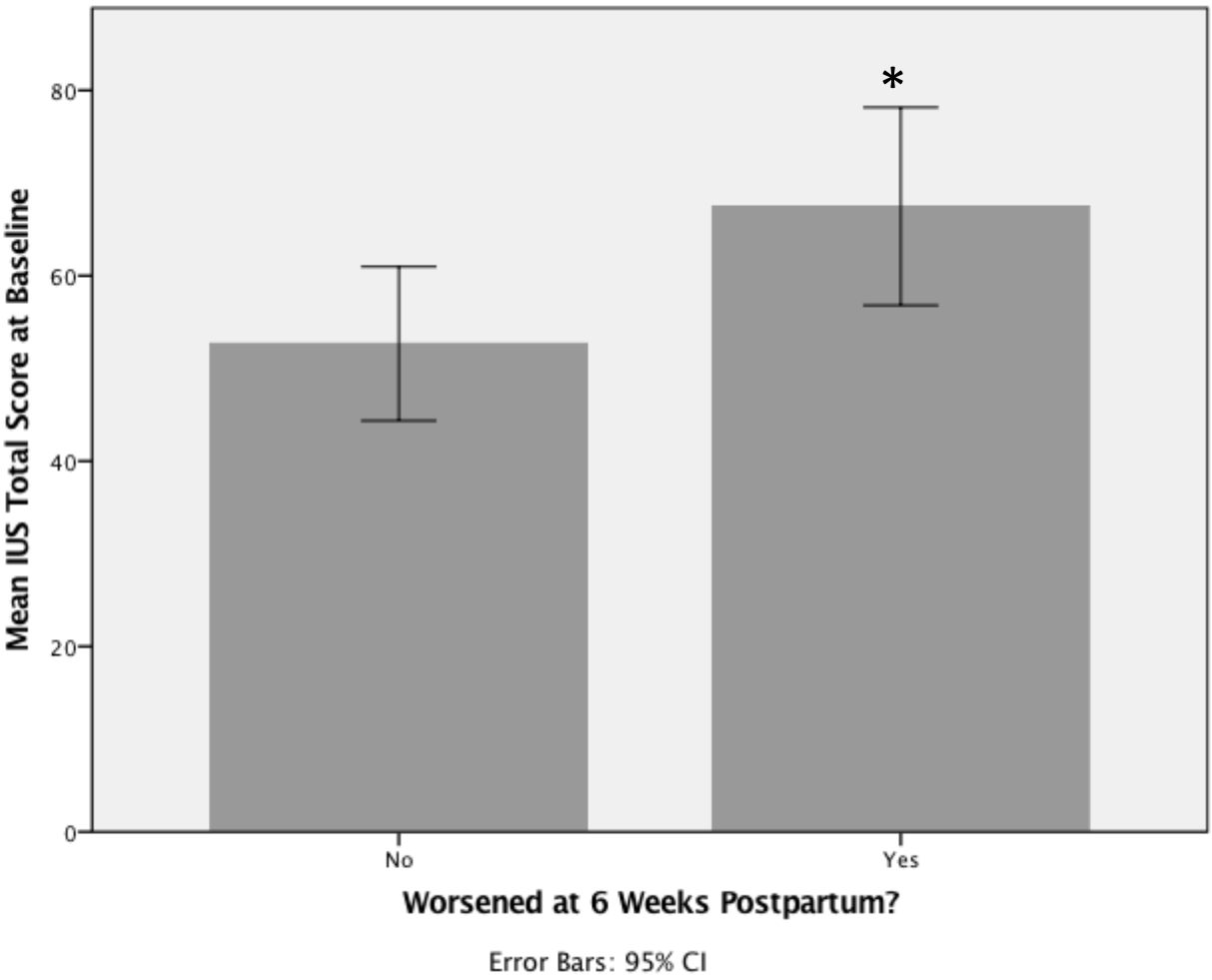
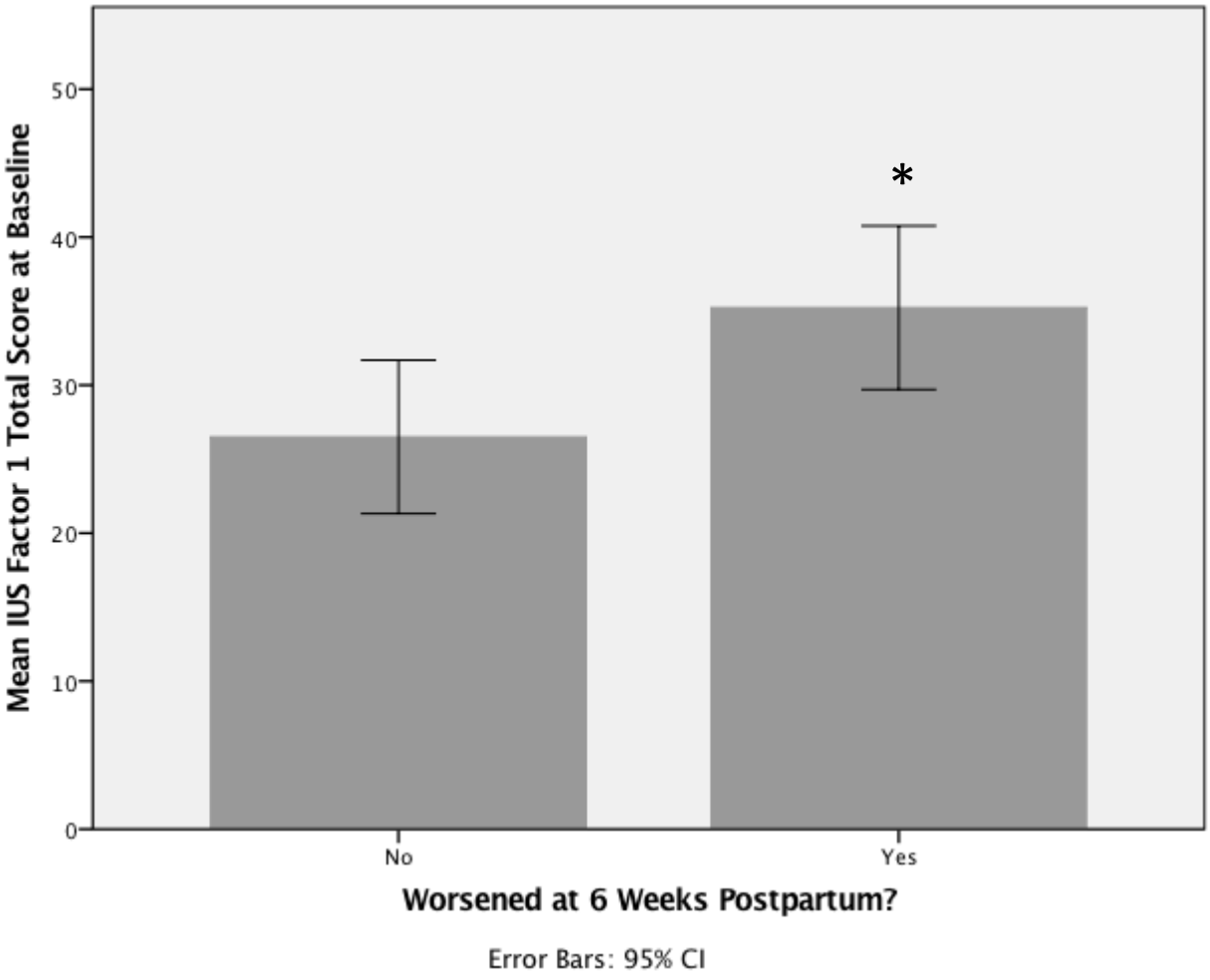
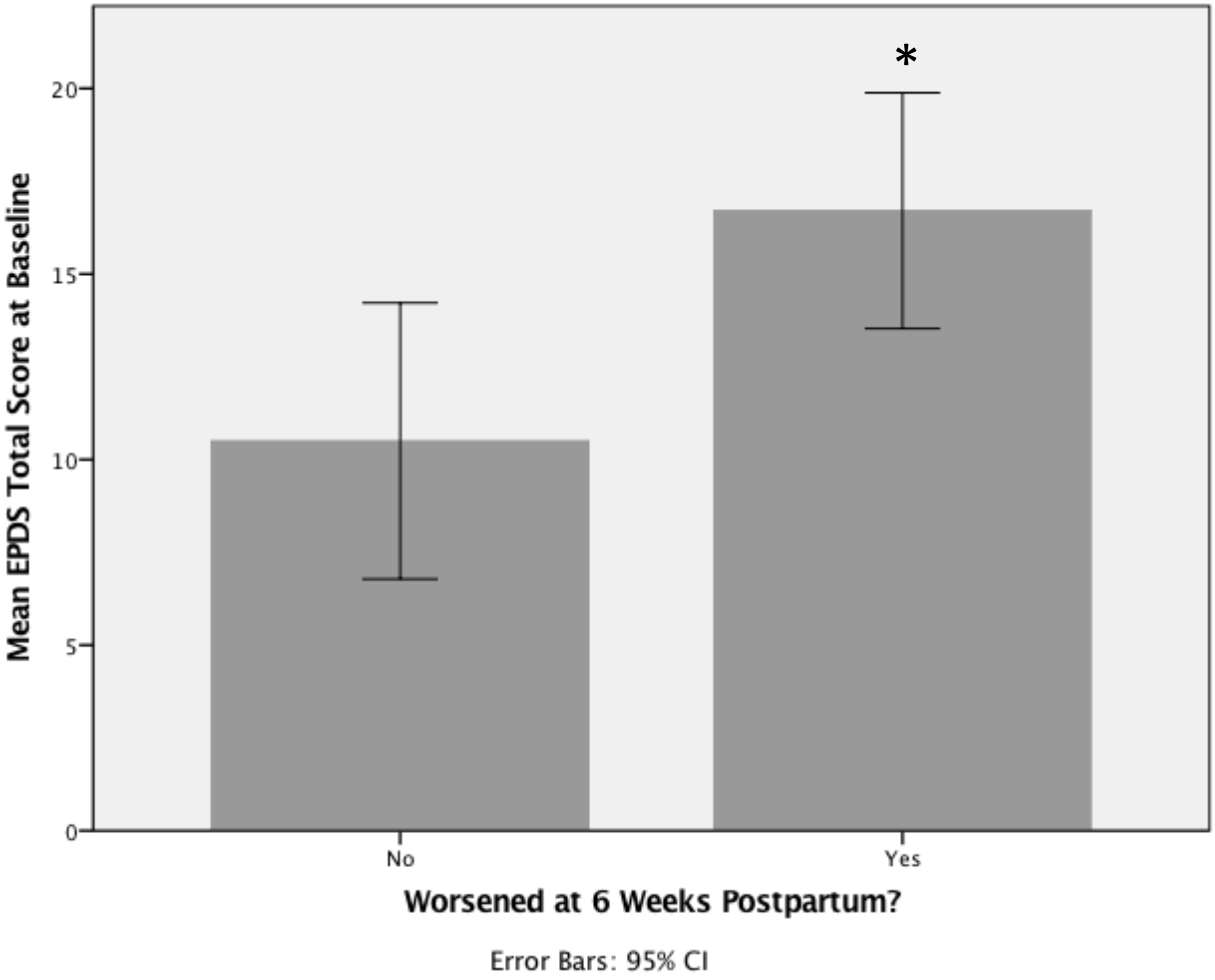


Figure 4.2. Intolerance of Uncertainty—Factor 1 as a predictor of postpartum anxiety worsening at 6 weeks postpartum. IUS: Intolerance of Uncertainty Scale.



Severity of depressive symptoms during the third trimester of pregnancy was significantly associated with anxiety worsening, with those having worsened having significantly higher EPDS scores [t(33)=-2.67, MD=-6.21, 95%CI [-10.94, -1.47], p=0.012] (Refer to Figure 4.3). Further, this significant association was also found in both the anxiety [t(33)=-2.49, MD=-2.02, 95%CI [-3.66, -0.38], p=0.018] and depression [t(33)=-2.40, MD=-4.19, 95%CI [-7.73, -0.64], p=0.022] subscales of the EPDS.

Figure 4.3. Depressive symptom severity as a predictor of postpartum anxiety worsening at 6 weeks postpartum. EPDS: Edinburgh Postnatal Depression Scale.



Obsessive compulsive symptoms, as assessed by the OCI-R during the third trimester of pregnancy, were significantly greater in women who worsened at 6 weeks postpartum [U=68.00, p=0.004] (Refer to Figure 4.4) compared to those who did not. Differences in scores on the IUS, EPDS, and OCI-R between the worsening and non-worsening groups are presented in Table 4.4 and Table 4.5.

Table 4.4. Baseline group differences between the worsening and non-worsening groups for psychological risk factors.

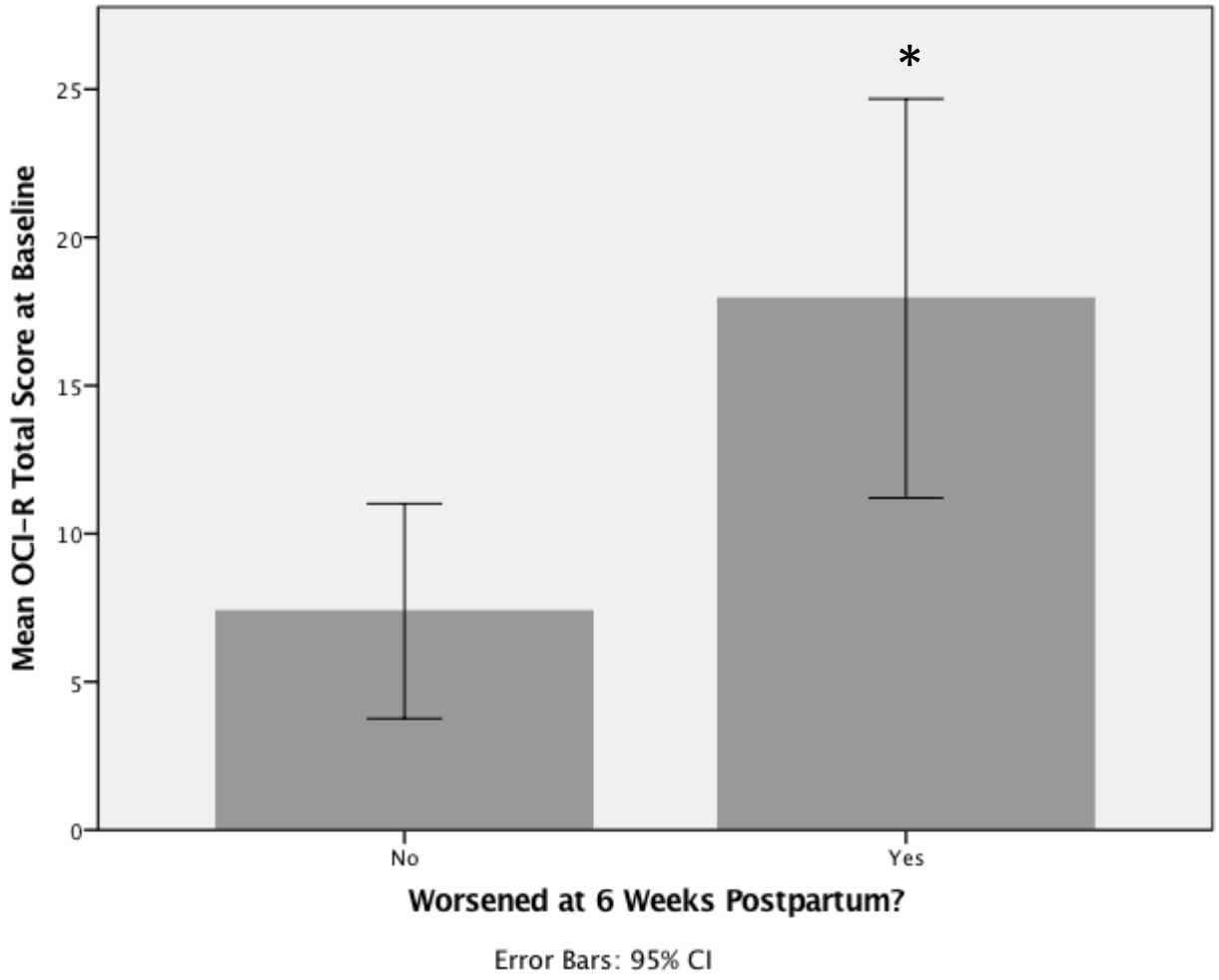
	Mean (SD)		Mean Difference	95% CI	Sig.
Baseline Measures	**Worsening (n=17)**	**Non-worsening (n=18)**			
IUS Total	67.47 (20.77)	52.67 (16.73)	-14.81	-27.74, -1.87	0.026
IUS Factor 1	35.24 (10.74)	26.50 (10.42)	-8.74	-16.02, -1.46	0.020
EPDS Total	16.71 (6.18)	10.50 (7.48)	-6.21	-10.94, -1.47	0.012
EPDS- Depression	10.35 (5.35)	6.17 (4.96)	-4.19	-7.72, -0.64	0.022
EPDS- Anxiety	6.35 (1.32)	4.33 (3.09)	-2.02	-3.67, -0.369	0.018

IUS: Intolerance of Uncertainty Scale; EPDS: Edinburgh Postnatal Depression Scale.

Table 4.5. Baseline group differences between the worsening and non-worsening groups for obsessive-compulsive disorder symptoms, as assessed by the Obsessive Compulsive Inventory—Revised (OCI-R).

	Mean Rank	Sum of Ranks	U	Z	p
Worsening (n=17)	23.00	391.00	68.000	-2.810	0.004
Non-Worsening (n=18)	13.28	239.00			

Figure 4.4. Obsessive compulsive disorder symptoms as a predictor of postpartum anxiety worsening at 6 weeks postpartum. OCI-R: Obsessive Compulsive Inventory—Revised.



Baseline self-reported anxiety severity (GAD-7), subjective maternal sleep (ISI), perceived social support (MSPSS), personality (VPSQ), parental bonding (PBI), and childhood trauma (CTQ) were all not significantly associated with postpartum anxiety worsening ($p>0.05$).

As noted above, none of the participants met criteria for anxiety worsening at either 12 or 24 weeks postpartum. However, 7 of the women who worsened at 6 weeks postpartum had begun psychopharmacological and/or psychotherapeutic treatment between 6 to 12 weeks

postpartum, with their HAM-A scores decreasing below worsening criteria by 12 weeks postpartum.

Biological Factors

Pre- and/or post-delivery oxytocin exposure were not significantly associated with anxiety worsening at 6 weeks postpartum ($p>0.05$). A total of 24 participants, 12 of which met criteria for anxiety worsening, agreed to participate in the blood draw at baseline. With regard to CRP, IL-6, and TNF-α, assay concentration values that fell below the appropriate limit of detection (R&D Systems) were classified as missing data. In total, 1 CRP value (4.2%) and 17 IL-6 values (70.8%), fell below the limit of detection, resulting in a sample size of 23 and 7, respectively, for these biomarkers. Baseline concentrations of CRP ($p=0.381$), IL-6 ($p=0.696$), and TNF-α ($p=0.219$), were not significantly associated with anxiety worsening at 6 weeks postpartum. When assessing correlations between these inflammatory biomarkers and anxiety severity at 6 weeks postpartum, no significant correlations were identified ($p>0.05$).

CHAPTER 5

Discussion

This is the first study to our knowledge that has specifically sought to investigate the antenatal predictors of postpartum anxiety worsening in women with pre-existing anxiety disorders. A few psychological factors were revealed as potential predictors of postpartum anxiety worsening, specifically intolerance of uncertainty, depressive symptom severity, and obsessive compulsive disorder symptoms.

Intolerance of uncertainty has been established in the literature as a predominant characteristic of anxiety disorders (Boswell et al., 2013; Buhr & Dugas, 2002; McEvoy & Mahoney, 2012; Wright et al., 2016), yet this phenomenon has previously never been examined within the perinatal population. In this study, it was found that women whose anxiety worsened at 6 weeks postpartum had significantly higher levels of intolerance of uncertainty as assessed by the IUS, compared to those who did not worsen. Intolerance of uncertainty is any emotional, cognitive, and behavioural reaction to uncertainty that triggers feelings of unfairness and biases information processing, resulting in perceived negative implications (Freeston et al., 1994). Previously, intolerance of uncertainty was thought to only be related to Generalized Anxiety Disorder, as it is significantly correlated with excessive worry. Yet, recent research has implicated a relationship between intolerance of uncertainty and the other anxiety disorders, as well as with symptoms of depression (Boelen & Reijntjes, 2009; McEvoy & Mahoney, 2011).

It has been well established that heightened levels of intolerance of uncertainty are positively correlated with worry (Counsell et al., 2017; Dugas et al., 1995, 2001; Freeston et al., 1994; Yook et al., 2010). Further, individuals with exaggerated intolerance of uncertainty are more likely to engage in negative thinking patterns (e.g., rumination) (de Jong-Meyer et al.,

2009; Yook et al., 2010). Over one third of the women who worsened at 6 weeks postpartum in our study sample initiated a psychotherapeutic and/or psychopharmacological intervention by 12 weeks postpartum. It can be hypothesized that those women who worsened, potentially as a result of their heightened intolerance of uncertainty which exacerbates their worry and anxiety, would want to engage in certainty seeking behaviours, such as through treatment. More specifically, individuals who have higher scores on factor 1 (uncertainty has negative behavioural and self-referent implications), are more likely to seek reassurance and actively engage in activities to seek predictability and certainty (Berenbaum et al., 2008). Hence, these women would be more likely to seek reassurance from those around them, as well as from authority figures such as clinicians (Berenbaum et al., 2008; Lauriola et al., 2018).

Transitioning from pregnancy into parenthood is often considered a time in which women are more vulnerable to adverse effects on their mental health (Parfitt & Ayers, 2014). During this transition, women are having to adapt to the various changes occurring to their body during pregnancy and postpartum, as well as having to respond to the numerous physical and emotional demands of an infant. Moreover, the stress and uncertainties associated with being responsible for an infant, such as having to know when they are hungry or sick, adapting to changes to romantic relationships, and financial strain, may only further exacerbate any underlying intolerance to uncertainty women with pre-existing anxiety disorders already have. As a result, women with heightened levels of intolerance of uncertainty may be even more at risk of postpartum anxiety exacerbation in response to the stressors and uncertainties of parenthood.

If the IUS were to be used as a predictor of postpartum anxiety, clinicians may be able to determine which women should be followed up on at a greater rate, as they may be more likely to worsen and in turn, require treatment. Nevertheless, as this is the first study to identify

intolerance of uncertainty as a predictor of postpartum anxiety worsening, future studies should aim to replicate these findings in larger study samples, in addition to assessing the psychometric properties of the IUS in the perinatal population.

Efficacious cognitive behavioural therapies aimed at mitigating intolerance of uncertainty have been developed for use in non-puerperal populations (Dugas & Ladoucer, 2000), demonstrating impressive results. This is a potential area of interest to investigate further in the perinatal population, with the potential to introduce these types of therapies to those at risk (i.e., heightened intolerance of uncertainty). Nevertheless, this is an interesting finding and is the first reported finding in the literature to not only investigate intolerance of uncertainty in the perinatal population, but to also demonstrate a significant association.

Another significant risk factor identified was depressive symptom severity, as assessed by the EPDS. The EPDS has been a well validated screening tool used to aid in the diagnosis of perinatal depression (Matthey et al., 2006). More recently, research investigating the use of the EPDS to aid in the detection of perinatal anxiety symptoms has been conducted (Bowen et al., 2008; Matthey, 2008; Ross et al., 2003; Swalm et al., 2010). This led to the development of the EPDS-3A, which consists of 3 questions included in the original EPDS that are associated specifically to anxiety symptoms (Matthey, 2008). Further, the EPDS has been significantly correlated to self-report anxiety questionnaires, such as the State Trait Anxiety Inventory (Brouwers et al., 2001; Giakoumaki et al., 2009; Spielberger et al., 1970), the Beck Anxiety Inventory (Beck & Steer, 1991; Phillips et al., 2009), and the anxiety subscale of the Hospital Anxiety and Depression Scale (Jomeen & Martin, 2004; Zigmond & Snaith, 1983). Although the EPDS has been utilized to detect anxiety symptomatology, our study is the first to use it as a predictor of anxiety worsening.

Women who experienced anxiety worsening postpartum had significantly higher baseline scores on the EPDS, as well as on both the anxiety and depression subscales, compared to those who did not worsen. It has been well established that anxiety disorders are highly comorbid with depression, and additionally, depression considerably worsens the outcome of individuals with anxiety disorders leading to a decreased quality of life (Field et al., 2010; Hirschfeld, 2001; Zhou et al., 2017). A study by Field et al., (2010) investigated the effects of comorbid anxiety and depression compared to each disorder alone on mood during pregnancy and neonatal outcome and found that those with the comorbidity experienced increased anxiety and irritability, decreased sleep quality, and worsened relationships. Additionally, women with comorbid anxiety and depression had an increased incidence of a premature birth and lower gestational birth weight. In our study sample, 27 of the 35 enrolled women met criteria for a lifetime and/or current major depressive disorder, however those who worsened had significantly higher self-reported scores on the EPDS. This is an important finding that can aid in early detection of anxiety worsening, and in turn treatment outcome. This study revealed that a diagnosis of a comorbid depressive disorder alone does not predict whether or not women's anxiety symptoms will worsen in the postpartum period, but rather, self-reported severity of depressive symptoms during the late stages of pregnancy is predictive.

As noted above, it has been well established that comorbidity between depression and anxiety worsens outcome (Field et al., 2010; Hirschfeld, 2001; Novick et al., 2016; Penninx et al., 2011; Thaipisuttikul et al., 2014; Zhou et al., 2017). Specifically, individuals who experience both symptoms of depression and anxiety together will experience greater severity of these symptoms, as compared to someone who only experiences one or the other, that is, depression or anxiety alone. The women who did not worsen may have only experienced heightened anxiety

during the third trimester of pregnancy, without any significant depressive symptoms, compared to women who did worsen who would have had both heightened baseline anxiety and depressive symptoms. Perhaps, it is this interaction between both the comorbid anxiety and depression during the third trimester of pregnancy that contributed to the exacerbation of postpartum anxiety severity.

In addition to intolerance of uncertainty and depression severity as significant risk factors for anxiety worsening, symptoms of obsessive compulsive disorder during pregnancy was also predictive. In our study, 3 women met diagnostic criteria for comorbid OCD (non-primary), with only 1 of these women meeting criteria for anxiety worsening at 6 weeks postpartum. Interestingly, women who worsened at 6 weeks postpartum had significantly higher self-reported symptoms of OCD, as assessed by the OCI-R, during their third trimester of pregnancy. Miller and colleagues (2013) reported that as many as 11% of women screen positively for OCD symptoms by 2 weeks postpartum, with anxiety and depression severity as positive predictors, yet no known studies have assessed OCD traits as a predictor of postpartum anxiety worsening.

Perhaps those women with increased baseline OCD symptoms who experienced anxiety worsening postpartum suffered from more OCD-related symptoms, such as those related to worries and obsessions related to their infant, which in turn increased their anxiety. These women may also engage in avoidance behaviours to ensure that they are in the continuous presence of their infant, such as avoiding baths (Wenzel et al., 2001). Intolerance of uncertainty has also been shown to be associated to OCD, specifically to compulsions and checking behaviours (Tolin et al., 2003). Women who experience postpartum OCD often report increased obsessions about their infant's health and safety, resulting in compulsions such as checking the infant's breathing, recurrent visits to the pediatrician, and compulsive washing to prevent

contamination (Uguz et al., 2011). Perhaps the interaction between intolerance of uncertainty and the associated OCD symptoms further contributed to the exacerbation of anxiety symptoms postpartum.

Although women may not necessarily meet criteria for OCD in the prenatal period, screening for OCD-related symptoms during pregnancy may provide valuable information as to who may be at risk for experiencing distressing OCD symptoms postpartum, in turn worsening anxiety symptoms.

A number of psychological factors that have previously been identified in the literature as predictors of perinatal anxiety were not found to be predictors in this study. Importantly, one must note that the studies in which those factors were significantly associated with perinatal anxiety, combined women with and without pre-existing anxiety disorders, whereas the current study only examined women with pre-existing anxiety disorders. This is an important distinction as a history of mood and/or anxiety disorders is among the most significant predictors of worsening in the postpartum period, however, little to no knowledge is known as to what places these women at risk of worsening during the postpartum period.

Previous studies have reported that women who experience childhood trauma are at increased risk of suffering from perinatal anxiety (Leeners et al., 2006; Martini et al., 2015; Mezey et al., 2005; Seng et al., 2014), however, we did not find any associations between these variables in our study. As noted earlier, distinguishing between women with and without pre-existing anxiety disorders is important, in order to fully understand the risk factors of perinatal anxiety. In our sample, a history of childhood trauma, as assessed by the CTQ, were nearly equivalent between groups, that is, women in both groups had relatively high levels of childhood trauma, and therefore an association with worsening could not be established. Similarly,

maternal sleep has been another area in which worsened sleep has been associated to perinatal anxiety, however other studies have not reported this association. In our study, we utilized the ISI which is a self-report measure of sleep. As sleep disturbances are extremely common in the postpartum period, for example, several waking's throughout the night for feedings and attending to the infant, inconsistencies in self-reported sleep could have occurred, which is a limitation with subjective sleep measures. Future studies may also include an objective sleep measure, such as through actigraphy, in order to account for any inconsistencies in self-reported sleep quality.

With regard to sociodemographic factors, no significant associations were found between women who worsened and those who did not. Previous studies have reported that women with lower educational backgrounds (Faisal-Cury & Rossi Menezes, 2007; Martini et al., 2015; Qiao et al., 2009) and being single (Biaggi et al., 2016) are at increased risk of experiencing perinatal anxiety, however we did not find this association. It is important to note the homogeneity of our study sample, which likely contributed to this result. Some inconsistencies have been reported in the literature with regard to maternal age, and our study did not find any associations. Again, the ages of included women were fairly consistent between groups, and perhaps with a greater sample size including women of varying ages, differences may have been seen. The assessed obstetrical and delivery factors in our study did not identify any significant risk factors as well. Of the 35 women enrolled in this study, only 1 was not breastfeeding in the postpartum period and only 6 had a caesarean delivery. Having a greater sample size with a more heterogeneous sample may have revealed other predictors of postpartum anxiety worsening, highlighting the need for continued research in this field to determine risk factors and resolve any inconsistencies reported in the literature.

In this study, pre- and post-natal oxytocin exposure was evaluated to determine whether or not it was a significant risk factor of postpartum anxiety worsening, however, no associations were identified. A previous study conducted by Kroll-Desrosiers and colleagues (2017) examined the risk of peripartum oxytocin exposure in women with pre-existing anxiety disorders, noting a significant association. Yet, this study was a large database study that included nearly 10,000 women with pre-existing anxiety and/or depressive disorders greatly increasing study power. Nevertheless, this is an area of interest as oxytocin is among the most commonly used methods to induce delivery and to aid in treatment of postpartum hemorrhaging (Bell et al., 2014).

Our study did not identify any significant associations between CRP, IL-6, or TNF-α with postpartum anxiety worsening. Further, no significant correlations were observed between these inflammatory biomarkers with anxiety severity, as assessed by the HAM-A at 6 weeks postpartum. As this is the first known study to assess these inflammatory biomarkers specifically in predicting anxiety exacerbation in women with pre-existing anxiety disorders, it is not known whether our results are comparable to other studies, however the insignificant correlation between anxiety severity and biomarker concentrations are in contrast to previous studies which have demonstrated significant associations (Maes et al., 2000; Osborne et al., 2017; Roomruangwong et al., 2017). This may be due to differences in study design and measures used to assess psychiatric diagnoses and anxiety severity, in addition to our small sample size. The studies conducted by Maes et al., (2000), Osborne et al., (2017), and Roomruangwong et al., (2017), all utilized the self-report STAI to assess anxiety severity, whereas our study utilized the interviewer-administered Hamilton Anxiety Rating Scale. Similarly, only Maes et al., (2000) assessed psychiatric diagnoses with a structured clinical interview, as our study did with the

MINI for DSM-5. Unlike our study, these studies did not compare women with and without pre-existing anxiety disorders.

Levels of CRP, IL-6, TNF-α are expected to increase throughout pregnancy, specifically by the third trimester of pregnancy. As our baseline biomarker samples were conducted during the third trimester, when the concentrations are expected to be at their highest, this may have decreased the probability of observing any associations between heightened inflammatory concentrations with anxiety worsening. Another potential limitation that may have played a role in the lack of association between inflammation and anxiety worsening was the small sample size. Only 24 women agreed to undergo blood draw in this study. This small sample size had even greater implications with our IL-6 concentrations, as only 7 were within the detectable limit. Despite the lack of significant associations with regard to our inflammatory biomarkers, this is a new and interesting area of research that requires further investigation. Continuing research in this area with larger sample sizes, as well as assessing biomarker concentrations at various time points throughout pregnancy, may provide further information as to whether any associations do in fact exist.

Strengths and Limitations

The present study has a range of strengths. This is the first known study to specifically investigate risk factors of postpartum anxiety worsening in women with pre-existing anxiety disorders. Focusing on a high-risk group of women with pre-existing anxiety disorders allowed us to accurately identify risk factors of symptom worsening. The longitudinal design of this study is another strength which allowed us to determine the time point in which women worsen. Many of the previous studies that have examined risk factors of perinatal anxiety had a small

number of study visits, for example, only having a single pre- and post-natal visit to assess anxiety. Utilizing a structured clinical interview to confirm psychiatric diagnoses, as well as an interviewer-reported measure, the Hamilton Anxiety Rating Scale, as our primary outcome were additional strengths of this study. Further, the inclusion of a multitude of sociodemographic, obstetrical and delivery, psychological, and biological factors allowed for a comprehensive investigation of potential risk factors of perinatal anxiety. Finally, various included factors such as intolerance of uncertainty and inflammatory biomarkers, were investigated for the first time as potential risk factors of postpartum anxiety worsening. Although this study had several strengths, it also had limitations.

The small sample size of women included in this study hinders the generalizability of our results, highlighting the need for continued research with larger samples sizes in this area. Similarly, the homogeneity of the study sample's demographic characteristics also impairs our ability to generalize the results, as well as to detect any potential associations to anxiety worsening. The majority of the sample were from the Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, and therefore most of the study sample were undergoing or had just discontinued some form of psychopharmacological and/or psychotherapeutic treatment. Future studies should include a more diverse sample of women both receiving and not receiving various forms of treatment.

Although we utilized an interviewer-administered measure for the primary outcome, all other psychological factors were assessed through self-report questionnaires. While self-report questionnaires are more user-friendly and easily administered, they are subjective measures which have the potential to decrease the reliability of respondent's answers. Additionally, for the primary outcome measure (HAM-A), worsening criteria was defined as an increase of 50% or

greater from baseline scores. Although this is the most commonly used criterion for anxiety exacerbation/relapse, many women were excluded from meeting this criterion due to higher baseline scores on the HAM-A. For example, women with mild baseline anxiety (defined as a score of 8-14 on the HAM-A) would have had to have a less severe increase in score than those women with moderate baseline anxiety (defined as a score of 15-23 on the HAM-A).

The time points in which our study assessments were conducted were also a limitation of this study. Women were enrolled during their third trimester of pregnancy, in which many of the assessed domains are at their highest. Perhaps, including a visit during the second trimester of pregnancy would have allowed for a better understanding of the baseline predictive measures. This may be particularly valid with the inflammatory biomarkers, as they are highest during the third trimester of pregnancy. Additionally, the primary outcome of our study was assessed at 6 weeks postpartum. As the prevalence of postpartum anxiety is highest between 6 to 8 weeks postpartum, future studies could also include a visit at the 8 week postpartum time point in which the HAM-A is again conducted.

With regard to the inflammatory biomarkers, due to the somewhat invasiveness of the blood draw, a number of women declined to participate in this part of the study, further decreasing the sample size for analysis. Additionally, some inflammatory biomarkers (e.g., CRP) are known to follow a diurnal pattern (Lange et al., 2010), however, due to differences in participant availability, blood samples were taken at various time points throughout the day.

Conclusions and Future Directions

Despite the increasing prevalence of perinatal anxiety and appreciation of its impact on women, their infant, and families, relatively little attention has been paid to understanding risk

factors. In particular, an examination of the risk factors of postpartum anxiety worsening in women with pre-existing anxiety disorders is nearly non-existent. This lack of awareness prevents the development of screening tools aimed at improving early and accurate detection of symptoms and severity. Through the identification of risk factors of postpartum anxiety worsening, we would be able to enhance our understanding of its etiology, allowing us to further comprehend how postpartum anxiety disorders and symptoms manifest and worsen. Further, investigating risk factors of postpartum anxiety worsening can allow us to determine whether or not these factors differ from non-puerperal populations. Conducting research that is aimed at delineating the risk factors of anxiety worsening would in turn aid in the development and use of appropriate and targeted measures, with the potential to even prevent the worsening from occurring.

Preventive measures, particularly in the psychiatric population, have been well established in the literature as being effective in preventing both symptom onset and exacerbation (O'Hara & Wiser, 2014; Sockol et al., 2013; Werner et al., 2015). Additionally, early and accurate detection of perinatal anxiety can improve management of symptoms, resulting in improved overall health and outcome for both the mother and her infant. The study results discussed in Chapter 4 revealed intolerance of uncertainty, depressive symptom severity, and obsessive compulsive symptoms all as significant predictors of postpartum anxiety worsening.

Identified women at risk for anxiety symptom relapse and exacerbation could then be more closely monitored throughout their pregnancy and early postpartum period for signs of worsening. Introducing preventative strategies, such as cognitive behavioural and interpersonal therapies, psychopharmacological treatments, mindfulness-based strategies, prenatal support

groups, or a combination of any of these strategies can be implemented dependent on the severity and stage of symptoms. In addition to the psychotherapeutic treatment inventions that have been established as effective strategies for perinatal mental health disorders (Green et al., 2015; Goodman et al., 2014; Sockol et al., 2011; Stuart & Koleva, 2014), psychopharmacological medications may also be implemented dependent on the severity of symptoms, as well as the presence of any comorbidities. More specifically, medications that have been effective in treating postpartum depression, such as selective serotonin reuptake inhibitors, have also been shown to improve anxiety symptoms during the perinatal period (MacQueen et al., 2016; Marchesi et al., 2016; Misri et al., 2007, 2015). Further, short-acting benzodiazepines may be implemented for women who are experiencing greater severity of their anxiety symptoms, or for those who may not benefit from psychotherapeutic interventions (Anniverno et al., 2013). Nevertheless, the associated and unknown adverse effects of these medications during the perinatal period must be considered, as randomized controlled trials investigating the efficacy of psychopharmacological medications in this population are scarcely conducted. If research is not conducted specifically aimed at investigating potential risk factors of postpartum anxiety worsening however, early detection and treatment efforts are hindered for these women.

Although the perinatal period and childbirth are often joyful occasions for the mother and her family, experiencing the debilitating symptoms of anxiety can impede this joy and instead result in negative effects. Within the first postpartum year as many as 1 in 5 women experience an anxiety disorder, yet only 15% of these women will receive treatment. Although these rates and associated negative effects are comparable to those of postpartum depression, little attention has been focused on perinatal anxiety. Unlike postpartum depression, perinatal anxiety disorders have yet to be recognized in the Diagnostic and Statistical Manual of Mental Disorders.

Although awareness of perinatal anxiety and appreciation of its debilitating course and outcome has increased in recent years, greater attention and research needs to be placed on delineating its risk factors. While we are aware of the negative impact anxiety disorders has on women during the perinatal period, the risk factors of symptom worsening in these women are still unknown. Therefore, further research and investigation into the sociodemographic, obstetrical and delivery, psychological, and biological risk factors of postpartum anxiety worsening is crucial in order to improve symptom detection and overall outcome.

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