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Preterm Birth: Understanding Temporal Changes in Anxiety and Depression Measures

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Preterm Birth: Understanding Temporal Changes in Anxiety and Depression Measures

by

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Abstract

Background: This study aimed to understand whether there is a pattern of change in levels of anxiety and depression between the second and third trimesters of pregnancy that are associated with a risk of PTB. Chronic stress was assessed as a potential modifier of the relationship.

Methods: This study conducted a secondary data analysis on the All Our Babies prospective cohort. Logistic regression modeling was used to analyze the data.

Results: A worsening of anxiety during pregnancy increased the odds of preterm delivery (OR 2.70, 95% CI 1.28, 5.69; p=0.009). An improvement in anxiety reduced the odds of PTB (OR 0.96, 95% CI 0.94, 0.98; p=<0.001). Consistently low depression decreased the odds of PTB (OR 0.65, 95% CI 0.45, 0.96; p=0.029). Chronic stress did not modify any of these relationships.

Conclusions: Efforts should be made to replicate these results in a cohort with a larger sample size.

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List of Abbreviations

PTB	Preterm Birth
PSS	Perceived Stress Scale
PPROM	Preterm Premature Rupture of Membranes
RR	Risk Ratio
OR	Odds Ratio
SES	Socioeconomic Status
AOB	All Our Babies
MES	Maternity Experiences Survey
EPDS	Edinburgh Postnatal Depression Scale
aOR	Adjusted Odds Ratio
HPA	Hypothalamic-Pituitary-Adrenocortical
CRH	Corticotropin-Releasing Hormone

Contribution of Authors

Dr. Shahirose Premji acted in the position as primary supervisor to the trainee. Dr. Premji guided the trainee on formulating the research question, design of the study including securing AOB data, interpretation of the analysis, writing of the thesis, and was the content expert on preterm birth from a clinical perspective.

Dr. Scott Patten acted in the position as the co-supervisor to the trainee. Dr. Patten mentored the trainee on content knowledge of mental health disorders, designing the analysis, interpreting data, and writing of the thesis.

Dr. Donna Slater acted in the position of a committee member to the trainee. Dr. Slater provided guidance on content of preterm birth from a basic science perspective, assisted with the formulation of the research question, and offered technical advice and support on analysis and writing of the thesis.

Dr. Tyler Williamson acted in the position of a committee member to the trainee. Dr. Williamson guided the trainee with analysis of the dataset, interpretation of the results, and support with writing of the thesis.

Dr. Suzanne Tough is the Principal Investigator of the All Our Babies study cohort, and provided the dataset for this study. She offered guidance in the ethics process as well as the formation of the research questions.

CHAPTER 1: INTRODUCTION

1.1 Background

Preterm birth (PTB) is the birth of an infant prior to 37 weeks' gestation, whereas a typical pregnancy is approximately 40 weeks of gestation (World Health Organizationo, 2015). Data from across 184 countries reported that the prevalence of PTB ranged from 5% to 18% (World Health Organization, 2015). In Canada, approximately 8% of all deliveries are preterm, resulting in an economic burden estimated to be $587 million per year (Johnston et al., 2014). Anxiety and depression can jeopardize a pregnancy and lead to PTB (Dunkel Schetter & Tanner, 2012). This can impact survival and growth and development of the preterm infant and lead to serious health issues, both short-term (e.g., lung and respiratory development) and long-term (e.g., intellectual development and long-term academic ability) (Institute of Medicine Committee, 2007; McGowan, Alderdice, Holmes, & Johnston, 2011).

Evidence collected from three systematic reviews and meta-analyses, and a narrative review of the literature has shown that anxiety is a potential risk factor for PTB (Ding et al., 2014; Dunkel Schetter & Tanner, 2012; Rose, Pana, & Premji, 2016; Staneva, Bogossian, Pritchard, & Wittkowski, 2015). Depression has also been identified as a potential risk factor for PTB (Dayan et al., 2006; Dunkel Schetter & Tanner, 2012; Grote et al., 2010). However, the literature remains inconsistent, and some studies have found no significant relationship between anxiety and PTB, or depression and PTB (Accortt, Cheadle, & Dunkel Schetter, 2015; Andersson et al., 2003; Dayan et al., 2006; Dole et al., 2003). These inconsistencies may be a result of measuring anxiety and depression only once during pregnancy, and not considering important covariates

such as chronic stress. Further, this literature may be inconsistent due to varied use of anxiety constructs, including state, trait, and pregnancy-specific anxiety (Rose et al., 2016).

During pregnancy, anxiety and stress have been shown to change between early and late pregnancy (Glynn, Schetter, Hobel, & Sandman, 2008). This dynamic behavior of anxiety and stress during pregnancy is reflected physiologically as well. Biological indicators of stress, including cortisol and C-reactive protein, have been shown to change during pregnancy in response to anxiety and stress (Kane, Dunkel Schetter, Glynn, Hobel, & Sandman, 2014; Mancuso, Dunkel Schetter, Rini, Roesch, & Hobel, 2004). For example, cortisol has a more dramatic increase during pregnancy in women with anxiety compared to women without anxiety (Kane et al., 2014). This literature emphasizes the importance of considering temporality of anxiety and depression during pregnancy, and how these changes might influence the course and outcomes of pregnancy. By understanding the temporal changes of anxiety and depression during pregnancy, it may be possible to identify a clear association between anxiety and depression with PTB, and therefore explain the inconsistency of the literature (Shapiro, Fraser, Frasch, & Seguin, 2013). Furthermore, it has been shown that depression and anxiety as comorbidities can have detrimental and additive effects on birth outcomes (Field et al., 2010). Consequently, it is important to clarify how changes in depression and anxiety during pregnancy can interact with one another and influence the risk of delivering preterm (Dunkel Schetter & Tanner, 2012).

Chronic stress has been defined as consistent exposure to a stressor over a long period of time that does not desist (Latendresse, 2009). Stress, as a comparison, is the term referring to the

general biological and psychological response to these stressors (Latendresse, 2009). Chronic stress may heighten perceived levels of anxiety and depression, resulting in additive psychological and physiological effects (Chrousos, 1998; Latendresse, 2009). These interactions may influence and accelerate the physiological processes of parturition, and possibly result in preterm delivery (Latendresse, 2009). Therefore, it is important that chronic stress is taken into account when trying to understand the risk that anxiety and depression may have on PTB. This may explain why not all women who experience chronic stress during pregnancy go on to deliver a preterm infant (Latendresse, 2009). Allostatic load is defined as a physiological "wear and tear" on the body caused by chronic stress (McEwen & Seeman, 1999). This "wear and tear" leads to dysregulation of physiological systems in the body, increasing the risk for disease and therefore susceptibility to PTB (Olson et al., 2015). Allostatic load provides a framework that conceptualizes how chronic stress may increase the risk of PTB, and will be used to help understand the research presented in this thesis (Premji and MiGHT Group, 2014). Understanding the interaction between chronic stress, anxiety and depression may help to explain the inconsistencies found in the literature.

1.2 Study Rationale

Compared to other Canadian provinces, Alberta has the second highest rate of PTB at 8.7% (Canadian Institute for Health Information, 2016). This results in approximately 4700 premature infants born per year in Alberta (Canadian Institute for Health Information, 2012; Canadian Premature Babies Foundation, 2015). More importantly, 33% of infant mortality has been attributed to PTB (Callaghan, MacDorman, Rasmussen, Qin, & Lackritz, 2006). For those babies that survive, they face challenges beyond infancy – neurodevelopmental damage (such as

cerebral palsy and mental retardation), respiratory dysfunction, and sepsis (Institute of Medicine Committee, 2007). Furthermore, there are serious repercussions for maternal mental health as mothers of preterm infants are at higher risk of postpartum depression than mothers of full-term infants (Brandon et al., 2011; Vigod, Villegas, Dennis, & Ross, 2010). Thus, there is a need to reduce the number of PTBs and alleviate these negative consequences.

It has been suggested that anxiety and depression during pregnancy can increase a woman's risk of having a preterm delivery (Dayan et al., 2006; Ding et al., 2014). However, the evidence is inconsistent (Accortt et al., 2015; Andersson, Sundström-Poromaa, Wulff, Åström, & Bixo, 2004; Dayan et al., 2006; Dole et al., 2003). Measuring anxiety and depression at two time points during pregnancy (at the second and third trimesters) may help clarify how these psychosocial risk factors influence PTB. The literature also indicates that chronic stress may interact with anxiety and depression, and this interplay can lead to PTB (Latendresse, 2009; McEwen & Seeman, 1999; Premji and MiGHT Group, 2014). ***By incorporating measures from two points in time, this study provides novel insight into the psychological responses to distress, the patterns of change leading up to a PTB event, and how these changes in anxiety and depression interact with chronic stress to increase the risk of PTB. This research uses data from the AOB study, a prospective cohort situated in Calgary, Alberta Canada.***

1.3 Research Purpose

The purpose of this study is to understand whether women who deliver preterm infants exhibit different changes in anxiety and depression during pregnancy compared to women who deliver full term, and whether chronic stress modifies this relationship.

1.4 Research Objectives

This study will test the following research objectives using the All Our Babies Study Cohort:

1a. Is there a change in measures of antenatal anxiety (i.e., an increase or decrease in anxiety, or consistently low or high anxiety, as compared to women who delivered full term infants) between <24weeks gestational age and 32-36 weeks gestational age of pregnancy?

1b. Is this change in antenatal anxiety associated with greater odds of delivering preterm infants?

2a. Is there a change in measures of antenatal depression (i.e., an increase or decrease in depression, or consistently low or high depression, as compared to women who delivered full term infants) between <24 weeks gestational and 32-36 weeks gestational age of pregnancy?

2b. Is this change in antenatal depression associated with greater odds of delivering preterm infants?

3. To determine whether co-occurring changes in anxiety and depression increase the odds of PTB.

4. To determine whether chronic stress is a modifier of the effects that changes in anxiety and depression have on PTB.

1.5 Manuscript-Based Thesis

This manuscript-based thesis provides a review of the literature on preterm birth, anxiety, depression, and chronic stress. This examination of the literature in Chapter 2 identified gaps in knowledge, which created the basis for the objectives and analysis of the manuscript. The manuscript in Chapter 3 provides a description of the methods, the results, and a focused discussion of the findings. Lastly, Chapter 4 provides an in-depth discussion of the results of the research in context with recent literature, the strengths and limitations of the study, and implications of the findings on future research.

In this manuscript-based thesis, the Perceived Stress Scale (PSS) scale was used to measure chronic stress. The PSS has been validated to measure perceived stress of an individual within the past month (Cohen, Kamarck, & Mermelstein, 1983). However, rather than using the term "perceived stress", the term "chronic stress" is appropriate in this situation because (1) the PSS scale has been suggested to be an appropriate measure of chronic stress, (2) chronic stress does not have a clear beginning and end point, and (3) there are no gold standard scales for measuring chronic stress (Cohen et al., 1983). Importantly, chronic stress fits within the allostatic load framework, which allows the conceptualization of this research.

CHAPTER 2: LITERATURE REVIEW

2.1 PTB

2.1.1 Epidemiology of PTB

PTB is defined as the delivery of an infant prior to 37 weeks gestation (World Health Organization, 2015). Infants born premature can be classified as being extremely preterm (<28 weeks gestation), very preterm (28 to <32 weeks gestation) or moderate to late preterm (32 to <37 weeks gestation) based on their age at delivery (World Health Organization, 2015). Worldwide, approximately 15 million infants are born prematurely per year, meaning that 10% of infants are born prematurely (Beck et al., 2010; World Health Organization, 2012). Canada is not far behind, with the PTB rate being 7.7% in 2010 (Public Health Agency of Canada, 2013). Out of the Canadian provinces, Newfoundland and Labrador had the highest rate of PTB in 2015 at 9%, and Alberta had the second highest at 8.7% out of the Canadian provinces (Canadian Institute for Health Information, 2016). The territories had an even higher rate of PTB, the highest being Nunavut (10.6%) (Canadian Institute for Health Information, 2016). This study hopes to better understand the predictors of PTB to reduce this burden.

2.1.2 PTB Classifications

PTB can be classified as medically indicated PTB and spontaneous PTB (Dekker et al., 2012). Medically indicated birth accounts for approximately 30-35% of all PTB (Goldenberg, Culhane, Iams, & Romero, 2008). This often occurs because the mother is suffering from one or more pregnancy-related complications, including hypertension or fetal distress. Spontaneous birth, with or without preterm premature rupture of membranes (PPROM), is the second medical classification, and accounts for approximately 65-70% of all preterm deliveries.

Other literature suggests that classifying PTB as more distinct phenotypes may provide a better understanding of PTB causes and mechanisms, which can improve PTB prevention and treatment (Villar et al., 2012). Various PTB phenotype have been proposed, including 1) maternal health conditions prior to delivery (e.g., preeclampsia); 2) fetal health conditions prior to delivery (e.g., intrauterine growth restriction); 3) placental pathological conditions (e.g., placenta previa); 4) possible signs of labor (e.g., PPROM); and 5) delivery pathways (e.g., medical indication or induction) (Villar et al., 2012 p. 119). Other phenotypes have been developed, including a classification system that has nine phenotypes of PTB (e.g., infection, stress, and PPROM) (Manuck et al., 2015). However, recent findings suggest that there is little difference between gene expression profiles between PPROM and spontaneous PTB, thus the current study operationalizes PTB as having two classifications (spontaneous and medically indicated) (Heng et al., 2016).

2.1.3 PTB Complications and Consequences

PTB can result in various morbidities, and the risks of morbidities and mortality increase with decreasing gestational age at birth (McIntire & Leveno, 2008). In 2010, 76% of all infant deaths in Canada were neonatal, and prematurity was among the leading causes of neonatal deaths (Public Health Agency of Canada, 2013). Furthermore, mortality among extremely preterm infants is 25%, and the mortality rate decreases as gestational age increases (Deb-Rinker et al., 2015; Stoll et al., 2010). The risk of short-term morbidities (including ventilator-treated respiratory distress, sepsis, and intubation in the delivery room, among others) decreases with increasing gestational age for the infant (McIntire & Leveno, 2008). For example, approximately

14% of infants born at 39 weeks suffered from morbidities, compared to 17%, 24% and 34% for those infants born at 36, 35 and 34 weeks' gestation (respectively) (McIntire & Leveno, 2008). Those infants who are born preterm and survive may suffer from disability, particularly those infants that are extremely preterm (Wood, Marlow, Costeloe, Gibson, & Wilkinson, 2000). Approximately 49% of extremely preterm infants suffer from at least one type of disability, including neuromotor disability, blindness and/or hearing loss (Wood et al., 2000). Furthermore, these disabilities can have long-term effects on the preterm infant (Moster, Lie, & Markestad, 2008). Preterm infants who were born prematurely were more likely to attain lower levels of education and have lower incomes in adulthood, compared to those infants that were born full term (Moster et al., 2008). One study that followed individuals from their birth between 1967 and 1983 until 2003 demonstrated that for those infants born between 23-27 weeks' gestation, 17.8% survived into adult life, 9.1% developed cerebral palsy, 4.4% developed intellectual disabilities, and 10.6% received disability pension later in life (Moster et al., 2008). This drastically contrasted to those infants born at 37 weeks' gestation or later, where 96.5% survived into adult life, 0.1% developed cerebral palsy, 0.4% developed intellectual disabilities, and 1.7% received disability pension (Moster et al., 2008). Finally, children born extremely preterm are at an increased risk of developing chronic diseases, as well as using medical services more often than children who were born full term (Farooqi, Hägglöf, Sedin, Gothefors, & Serenius, 2006).

Mothers and fathers of preterm infants are also susceptible to depression, in addition to emotional distress (Institute of Medicine Committee, 2007; Treyvaud, 2014). The family unit can be affected, resulting in issues such as marital stress (Institute of Medicine Committee, 2007). Severity of prematurity (gestational age at birth and birth weight), as well as severity of the

medical complications, may potentially be a risk factor for poor family outcomes (Treyvaud, 2014). This underscores the importance of preventing PTBs in order to reduce the short-term and long-term risk of mortality, morbidity, and disability on the infant as well as the family.

2.1.4 Causes and Risk Factors of PTB

The etiology of PTB appears to be multifactorial, with various mechanisms at play, with multiple contributing risk factors (Romero et al., 2006). Many of the risk factors for PTB are well established in the literature and described elsewhere (Berkowitz & Papiernik, 1993; Dekker et al., 2012). A narrative review from the United States identified some notable maternal characteristics that have been identified as risk factors including ethnicity (e.g., lower rates in Caucasian women), low SES, low and high maternal age, single marital status, and shorter inter-pregnancy intervals (less than six-months) (Goldenberg et al., 2008). Women who have had a previous PTB, a multiple pregnancy, medical complications (thyroid disease, asthma, diabetes, and hypertension), placental abruption or placenta previa, intrauterine infection, tobacco use, clinical depression, and psychological or social stress are also at risk for PTB (Goldenberg et al., 2008). Anxiety and chronic stress were not considered in this review, further emphasizing the need for research that assesses these as potential risk factors for PTB. A study conducted in Quebec also found that a BMI of less than 20, previous intrauterine growth restriction, standing up for more than two hours a day, and anxiety-stress are risk factors for PTB (Moutquin, 1999). One meta-analysis of 84 studies found that women who were overweight or obese were at an increased risk of PTB (McDonald, Han, Mulla, & Beyene, 2010). These articles, however, do not discuss the importance of anxiety, depression, chronic stress, nor their interactions with each

other. It is important to understand how each of these conditions might influence the risk of delivering preterm.

2.2 Anxiety, Depression, Chronic Stress, and PTB

2.2.1 Anxiety, Depression, and PTB

Anxiety can be described as state anxiety, which is a nervous system reaction to a perceived threat or danger (Spielberger, 2010). Trait anxiety describes a stable susceptibility to anxiety inherent in one's personality (Spielberger, 2010). Anxiety has been shown to be a significant risk factor for PTB in a meta-analysis of 31 studies (Rose et al., 2016). Importantly, this study found that heterogeneity in the meta-analysis was significantly reduced when limiting the sample of studies to only those that measured state anxiety. This meta-analysis was not able to assess publication bias due to a small number of included studies, and noted that many of the included studies did not account for important covariates (e.g., chronic stress and depression), emphasizing the need for future research to consider such covariates (Rose et al., 2016). These assertions were supported by another recent systematic review and meta-analysis of twelve studies (measuring state and trait anxiety, not pregnancy-specific anxiety), which found an increased risk of PTB when mothers experienced anxiety during pregnancy, reporting a pooled Risk Ratio (RR) of 1.50 (95% CI 1.33-1.70) (Ding et al., 2014). There was no significant heterogeneity among the studies included ($I^2 = 0.0\%$, $p = 0.514$), and the studies included in the meta-analysis were of high quality (as assessed by the Newcastle Ottawa Scale for Prospective Cohort Studies). A Begg's and Egger's test confirmed no publication bias was present. In summary, there is evidence from high quality studies that maternal anxiety during pregnancy

may increase the risk of PTB. Of note, this systematic review did not discuss subgroup analysis of various important modifiers such as chronic stress (Ding et al., 2014).

Despite the relationships reported in the above meta-analyses, individual studies in the literature report inconsistent findings. For example, one particular study concluded that depression was significantly associated with increased numbers of PTB, but anxiety was not significantly associated with PTB (Dayan et al., 2006). This study was prospective; with a sample size of 681 (with 31 women having a spontaneous preterm delivery) and used validated psychosocial scales. A second study that did not identify a significant relationship between anxiety and PTB had a study population of 1465, with only 26 of those women delivering preterm (Andersson, Sundström-Poromaa, Wulff, Åström, & Bixo, 2004). However, due to the small sample sizes of women who delivered preterm in these studies, the possibility of random error increases, which was evident in the imprecise odds ratio estimates. For example, Andersson et al. reported that anxiety was not associated with overall PTB (odds ratio (OR) 0.90, 95% CI 0.28, 2.96) nor was it associated with spontaneous PTB (OR 0.52, 95% CI 0.07, 3.89) (Andersson et al., 2004). These studies also only measured antenatal anxiety and depression at one time point.

Studies that did not find a significant relationship between anxiety, depression and PTB did not assess the interaction between depression and anxiety during pregnancy, nor how chronic stress might influence these relationships. Various other reasons may explain these results, including variability in study design, differences in study samples (e.g., inclusion/exclusion criteria), the classification of PTB measured in the study (spontaneous or medically-indicated), inconsistency in the instrument used to measure anxiety and depression, and a lack of control of confounders

(Wadhwa, Entringer, Buss, & Lu, 2011). The type of anxiety measured (state, trait, general, and pregnancy-specific) may also contribute to these inconsistent findings. One systematic review and meta-analysis found a significant association between anxiety and PTB, but noted that there was a reduction in heterogeneity when restricting the analysis to only state anxiety as the exposure variable (Rose et al., 2016).

Depression is characterized by feelings of sadness, fatigue and loss of interest (World Health Organization, 2016). Similar to anxiety, there are inconsistent findings in the literature that assesses depression and PTB. One meta-analysis found that antenatal depression (measured as a categorical variable) was significantly associated with PTB (RR 1.39, 95% CI 1.19, 1.61) (Grote et al., 2010). In the meta-analysis 15 of the 20 studies evaluated were of high quality (scoring above 6 out of a possible 12) as determined by the Downs and Black quality assessment tool for Randomized Controlled Trials and Observational Studies. The heterogeneity of the studies was relatively high (I^2 = 61%, p = <0.001), indicating that these studies had methodological or clinical differences, changing the interpretation of the final results (Grote et al., 2010). This high heterogeneity was possibly due to country location of the study, or level of measurement used to operationalize depression (e.g., categorical versus continuous). Sensitivity analysis revealed that no particular study influenced the pooled RR. Notably, there was significant publication bias in this meta-analysis as determined by a funnel plot, and studies with negative results may not have been included (Grote et al., 2010). Therefore, the measure of association presented in this meta-analysis may overestimate how much depression increases the risk of PTB. Further, the studies included in this meta-analysis only measured depression at one time point during pregnancy, and did not assess whether depression interacted with anxiety, or the influence of chronic stress on

these relationships. This may contribute to the high heterogeneity of the study. Finally, the investigators emphasized the need for a longitudinal study that could prospectively examine the relationship between depression, key covariates, and PTB as this would help to gain a more comprehensive understanding of the risk factors of PTB (Grote et al., 2010).

In contrast, another systematic review found depression to be significantly associated with low birth weight, however failed to find an association between depression and PTB (Accortt et al., 2015). In this systematic review, only one-quarter of the studies found depression to be significantly associated with an increased risk of PTB. This may be due to variability in the scales used to measure psychosocial variables as well as inclusion and exclusion criteria of the studies. One meta-analysis emphasized the lack of consistency in the literature with respect to when anxiety and depression are measuring during pregnancy (Staneva et al., 2015). This was supported by an observation in another review, which found that the majority of studies in the literature measured anxiety and/or depression only once during pregnancy (Alder, Fink, Bitzer, Hösli, & Holzgreve, 2007). The current research addresses these limitations by assessing the change in anxiety and depression between the second and third trimesters, rather than measuring these conditions only at one time point; further, it assesses whether a co-occurring increases in anxiety and depression is associated with PTB.

2.2.2 The Importance of Measuring Patterns of Anxiety and Depression

Women's perception of stress and negative life events are reduced as gestation progresses, and thus measuring a trajectory of anxiety and depression may be a better predictor of PTB (Glynn, Wadhwa, Dunkel Schetter, Chicz-DeMet, & Sandman, 2001; Glynn, Dunkel Schetter, Wadhwa,

& Sandman, 2004). This decline in perception of stress is hypothesized to be a natural biological response to pregnancy, where the mother responds differently to stress in order to protect her and the fetus from negative health consequences due to stress (Glynn et al., 2001). Biological indicators for stress (i.e., cortisol) have also been shown to decline as gestation progresses which supports this assertion (Entringer et al., 2010). Women who continue to have high levels of cortisol throughout pregnancy are more likely to have shorter pregnancy duration (Buss et al., 2009). Based on this literature, one hypothesis could be that women who do not show a decline in anxiety and depression during pregnancy, and therefore do not have a dampening of biological stress responses, would be at an increased risk of PTB (Premji et al., 2015). Despite this, very few studies measured anxiety at more than one time point during pregnancy (Glynn et al., 2008; Kane et al., 2014; Mancuso et al., 2004). Mancuso et al. (2004) noted that women who had high anxiety at two time points–18-20 weeks' gestation and 28-30 weeks' gestation–were more likely to deliver preterm compared to those that had high anxiety at only the second time point (Mancuso et al. 2004). Glynn et al. (2008) noted that women who showed increases in anxiety and stress between the second and third trimesters were more likely to deliver preterm compared to those women who had decreases in anxiety (Glynn et al 2008). These results were supported by Kane et al. (2014), who found that if pregnant women experienced high anxiety during pregnancy, their cortisol trajectories were significantly increased compared to those women who had low levels of anxiety (Kane et al., 2014). This study measured cortisol and anxiety at four time points throughout pregnancy. It is reasonable to hypothesize that many women show a decline in anxiety and depression during pregnancy; however, some women who have an increase in anxiety and depression may be more likely to deliver earlier (Shaikh et al., 2013).

However, this hypothesis has not yet been adequately evaluated. Overall, it is evident that anxiety and depression should be considered dynamic conditions during pregnancy.

2.2.3 Comorbid Anxiety and Depression

Many studies have found that there is a lack of research distinguishing the relationship between anxiety and depression, and how they contribute to PTB both as independent conditions and as comorbid conditions (Dunkel Schetter & Tanner, 2012; Shaikh et al., 2013; Staneva et al., 2015). One meta-analysis assessed whether studies measuring comorbid anxiety and depression increased the risk of PTB, however results were inconclusive (Staneva et al., 2015). The authors suggest that the results of these studies were difficult to interpret, as anxiety and depression were measured at varying times during pregnancy, and only at one time point. In another study, the primary objective was to understand how comorbid anxiety and depression influenced various adverse birth outcomes, including PTB (Field et al., 2010). In this study, the prevalence of PTB was 14.5% among women with comorbid anxiety and depression, compared to only 10.2% among women with anxiety alone, and 6.5% among women with depression alone (Field et al., 2010). ***In summary, recent literature suggests that measuring anxiety and depression at two time points during pregnancy, as well as measuring co-occurring anxiety and depression, may offer more meaningful insight into potential pathways to PTB. The research presented in this thesis addressed these gaps in knowledge, in order to explain the inconsistencies observed in the literature with respect to the relationship between depression, anxiety, and PTB.***

2.2.4 Chronic Stress and PTB

Latendresse (2009) defined chronic stress as a repetitive or constant exposure to a stressor without resolution of the issue. A review conducted by Dunkel Schetter (2011) emphasized the importance of social determinants of health, particularly housing, income, social support, and low socioeconomic status (SES) and how these can influence a variety of health outcomes (Dunkel Schetter & Dolbier, 2011). Chronic stress can result when women persistently lack positive social determinants of health (Dunkel Schetter & Dolbier, 2011; Kramer et al., 2001). Many of these social determinants can be enduring stressors (e.g., low income), which may lead to chronic stress and potentially increase the risk of PTB (Dunkel Schetter & Dolbier, 2011; Latendresse, 2009). For example, low SES, low income, and a lower level of education have been shown to contribute to PTB (Peacock, Bland, & Anderson, 1995). To further support this, women living in low SES environments and African American women both have increased susceptibility to PTB, suggesting that there is a link between social determinants of health and the risk of delivering preterm (Institute of Medicine Committee, 2007). Furthermore, depression has been shown to be more common in women experiencing chronic stressors including low socioeconomic status, low income, and low social support (Seguin, Potvin, Denis, & Loiselle, 1995). Reducing chronic stress and inequities in these social determinants of health early on in pregnancy may be an important step in decreasing the incidence and prevalence of PTB on a population level. Based on the population health approach, it may be possible to reduce inequities and improve the health of an entire population by looking at PTB from this social perspective (Public Health Agency of Canada, 2012).

There is considerable evidence suggesting an association between chronic stress and disease processes, yet we do not understand the full extent of how chronic stress influences pregnancy and adverse birth outcomes (Latendresse, 2009; McGonagle & Kessler, 1990; Premji and MiGHT Group, 2014). Chronic stress can interact with anxiety and depression, thereby resulting in biological responses that can lead to PTB (Latendresse, 2009; Premji and MiGHT Group, 2014). Chronic stress can heighten the person's perceived stress, and influence their resiliency and coping skills (Dunkel Schetter & Dolbier, 2011). Depression and anxiety may also occur more commonly in women suffering from high levels of chronic stress (Chrousos, 1998; Latendresse, 2009). ***Having high chronic stress in addition to anxiety and depression throughout pregnancy may put women at greater risk for delivering a preterm infant compared to those women with low chronic stress. Thus, in the current thesis, chronic stress was assessed as a modifier of the relationship between changes in anxiety and depression, and PTB.***

2.3 Allostatic Load as a Conceptual Framework for this Research

Allostatic load is a framework used to define the negative physiological impact and dysregulation that chronic stress can have on the body, as a result of the body constantly trying to return to homeostasis following exposure to a change in environment (McEwen & Seeman, 1999). Diseases and abnormalities can be a result of allostatic load, including intrauterine growth restriction, pre-eclampsia, and potentially PTB (Olson et al., 2015). Using this framework allows the conceptualization of how chronic stress interacts with the patterns of anxiety and depression over the course of pregnancy, and its potential impact on PTB outcomes (McEwen, Nasveld, Palmer, & Anderson, 2012). Within this framework, the brain is the primary response unit to

external stimuli and appraisal of stressful situations (McEwen, 2000). In response to chronic stress, the brain becomes taxed, resulting in changes in stress perception and chemical imbalances. Allostatic load not only consists of physiological changes, but behavioral ones as well; increases in risk-taking behavior (i.e., smoking and alcohol use) result from the body's attempt to cope with the exposure to chronic stress, contributing further to susceptibility to disease (McEwen & Seeman, 1999). In a typical pregnancy, perceptions and biological responses to stress are blunted in order to protect the fetus from the harmful consequences of stress in the mother (Glynn et al., 2001). As a result of allostatic load, these responses to stress may be dysregulated. If a woman has increased anxiety and depression in addition to chronic stress, her physiological stress responses may be dysregulated, thus initiating pathways to PTB. In conclusion, it is appropriate that allostatic load is used as a framework within this prospective observational study.

2.4 The All Our Babies (AOB) Dataset

The All Our Babies cohort study from Calgary, Alberta, Canada offered an opportunity to answer the research questions asked in this thesis. The AOB prospective cohort study ran for approximately 2.5 years (beginning in May of 2008, and ending in December of 2010), enrolling 3,388 pregnant women (McDonald et al., 2013). This study aimed to identify predictors of PTB, and understand barriers to healthcare in Calgary. The AOB cohort is a suitable source of data to complete the research objectives, as it uses various validated psychosocial instruments to assess mental health of the participants during pregnancy, including Speilberger State-Trait Anxiety Scale, Edinburgh Postnatal Depression Scale, and the Perceived Stress Scale (a scale used as a proxy to measure chronic stress) (McDonald et al., 2013). This cohort also collected information

on clinical and obstetric features of pregnancy and labor, patient demographics, and patient lifestyle, allowing this study to assess many of the appropriate covariates. This thesis is classified as an analytic prospective cohort design, as it is a secondary analysis of data collected from a prospective cohort study. Prospective cohort studies are better able than most other observational study designs to determine temporality between exposures and outcomes (Patten, 2015).

Prospective cohort studies are subject to attrition; however, in the AOB cohort there was a 95% retention rate between the first and second questionnaires (3363 participants responded to the first questionnaire; 3186 participants responded to the second questionnaire) (McDonald et al., 2013). The investigators examined the difference between the target population and the study population, the non-respondents and the respondents, using perinatal surveillance data (McDonald et al., 2013). Although information on non-respondents was limited, they were younger, had lower incomes, were less likely to be married, and had poorer psychosocial health compared to those women who continued in the cohort (McDonald et al., 2013). Using the Maternity Experiences Survey (MES) (a cross-sectional survey of women in Canada, developed by the Public Health Agency of Canada and Statistics Canada to be a nationally representative reference standard), the investigators were able to compare the target population to the AOB cohort (Public Health Agency of Canada, 2009). Of importance to this thesis study, women in the AOB cohort were more likely to be older (35 years of age and older) and have a higher household income, compared to those women in the national MES survey (McDonald et al., 2013). Additionally, the prevalence of PTB was higher in the AOB cohort. Other characteristics described in this study are comparable to the national population as assessed by the MES survey. Overall, the cohort was deemed a comparable cohort to the Calgarian, Albertan, and Canadian

populations (Appendices 1) (McDonald et al., 2013). The AOB data has been previously collected, and therefore using this cohort is a feasible way to answer these research questions in a timely and cost-effective manner. The comparability of the cohort to the target population, high response rate, low attrition, and high prevalence of PTB makes this cohort a comprehensive and effective dataset to use to answer these research questions. This thesis will use the AOB cohort to complete the stated objectives, by conducting a secondary analysis on the data.

2.5 Summary

In conclusion, this thesis addressed gaps in knowledge by measuring the pattern of change in anxiety and depression between the second and third trimesters of pregnancy, in a cohort of Calgarian women using the AOB dataset. This research aimed to understand whether changes in anxiety and depression influence the risk of PTB as individual stress responses, as well as co-occurring stress responses, within the framework of allostatic load. Finally, chronic stress was assessed as a potential modifier of the relationship between changes in anxiety and depression, and the risk of delivering preterm.

CHAPTER 3: MANUSCRIPT

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Patterns of Change in Anxiety and Depression During Pregnancy Predict Preterm Birth

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3.1 Abstract

Background: To determine whether changes in anxiety and depression during pregnancy influence the risk of having a preterm birth (PTB), and whether chronic stress modifies this relationship.

Methods: The data source for the current study is the All Our Babies prospective cohort (AOB). Anxiety and depression were measured at 17-24 weeks and again at 32-36 weeks gestation using the Spielberg State Anxiety Scale and the Edinburgh Postnatal Depression Scale, respectively. Chronic stress was assessed at 17-24 weeks gestation as a potential covariate, and was measured using the Perceived Stress Scale. Multivariable logistic regression modeling was used to assess each relationship.

Results: Women who experienced an increase in anxiety scores, (time point 32-36 weeks, compared to the earlier time point 17-24 weeks), had 2.70 times higher odds of preterm delivery, compared to those with a reduction in anxiety scores (95% CI 1.28, 5.69). Consistent low or high depression scores did not significantly influence the odds of PTB compared to a decrease in depression scores. A co-occurring increase in anxiety and depression scores was not found to increase the risk of PTB, and chronic stress did not modify any of these relationships.

Limitations: This study was limited by a relatively small sample of women who delivered preterm, and therefore it was not possible to conduct additional analyses. Further, the analyses were limited to mostly late preterm infants.

Conclusions: These findings should be validated with additional cohorts and a larger sample size. Ultimately, primary prevention should be considered, to reduce anxiety during pregnancy.

Key Words

Pregnancy, Preterm Birth, Anxiety, Depression, Chronic Stress, Women's Health

3.2 Introduction

In Canada, approximately 8% of all live births are preterm, with Newfoundland and Labrador having the highest rate at 9%, and Alberta the second highest at 8.7% out of the Canadian provinces (Canadian Institute for Health Information, 2016). More importantly, 38% of infant mortality is due to PTB (Public Health Agency of Canada, 2013), and the risk of having one or more morbidity increases as the gestational age at delivery decreases (Stoll et al., 2010). Worldwide, approximately 15 million infants are born prematurely per year (World Health Organization, 2012). Babies that do survive a premature birth can face challenges beyond infancy – neurodevelopmental damage such as cerebral palsy and delayed mental development, and various adult onset chronic diseases which resulted from neurodevelopmental impairment (Institute of Medicine Committee, 2007). In addition to the risks for the premature infant, there are serious health consequences for maternal mental wellbeing as mothers of preterm infants are at higher risk of postpartum depression than mothers of full-term infants (Brandon et al., 2011; Vigod et al., 2010). The financial burden of all preterm infants born in Canada for the first ten years of age equates to approximately $587 million due to healthcare utilization, medical costs, and mortality (Johnston et al., 2014). Consequently, there is a need to reduce the number of preterm deliveries and alleviate the negative consequences to the infant, their families, and society.

Anxiety and depression during pregnancy have been implicated as possible risk factors for PTB (Dayan et al., 2006; Ding et al., 2014; Dunkel Schetter & Tanner, 2012); however, findings are inconsistent. A meta-analysis conducted on depression and PTB discovered that only 25% of the studies analyzed found a significant association between depression during pregnancy and PTB

(Accortt et al., 2015). Similarly, a meta-analysis examining maternal anxiety during pregnancy and PTB has also reported conflicting findings with anxiety and PTB (Rose et al., 2016). However, after a thorough analysis of these studies, Rose et al. concluded that these conflicting findings may be due to heterogeneity of the studies, including differing operationalization of anxiety, and assessing PTB only once and at differing times during pregnancy (Staneva et al., 2015). Measuring stress, anxiety, and depression as a combined construct during pregnancy was a superior predictor of PTB compared to measuring each dimension independently (Staneva et al., 2015). It is therefore important to measure anxiety and depression as co-occurring conditions.

During pregnancy, perception of stress and negative life events decline and physiological responses to stress diminish (Glynn et al., 2004), probably as a way to protect the mother and fetus from adverse health outcomes (Glynn et al., 2001). Chronic stress can result from ongoing, repetitive exposure to stressors, is thought to alter the perception of anxiety and depression (Latendresse, 2009). Differing levels of chronic stress may heighten the perception of stressors, while reducing resiliency and the ability to cope (Chrousos, 1998; Dunkel Schetter & Dolbier, 2011; Latendresse, 2009). One can hypothesize that women who exhibit consistently high or increasing levels of anxiety or depression are at a greater risk of PTB. One study measured the change in anxiety and perceived stress between two time points during pregnancy, and found an association between worsening perceived stress and anxiety, and an increased risk of PTB (Glynn et al., 2008). The results from Glynn et al. suggest that identifying patterns of anxiety and perceived stress during pregnancy is a more accurate predictor of PTB than assessment at a single time point. It is therefore important to understand how a woman's psychosocial state can change and be modified throughout pregnancy, and how this may contribute to pregnancy

outcomes, in the context of PTB. However, the study conducted by Glynn and colleagues did not consider how chronic stress might influence the relationship between anxiety and PTB, nor did it measure changes in depression during pregnancy to examine inter-relationships between anxiety and depression and how this influences PTB.

Allostatic load is a conceptual framework that describes the harmful physiological effects of chronic stress over time, and may explain the biological mechanisms behind PTB (McEwen & Seeman, 1999). Chronic stress can initiate a cascade of behavioral (e.g., smoking) and neuroendocrine (e.g., cortisol) responses which may negatively affect regular physiological systems, thereby increasing the susceptibility to disease or PTB (McEwen & Seeman, 1999). It is therefore important to consider chronic stress as a potential modifier when understanding the relationship between anxiety, depression, and PTB. Studies have not evaluated whether chronic stress modifies this relationship, which may explain the lack of consistency reported in the literature.

The current study aimed to determine: 1) the relationship between changes in anxiety and depression at two time points in pregnancy and the incidence of PTB, 2) whether a co-occurring increase in anxiety and depression scores increased the risk of delivering preterm, 3) whether important covariates, particularly chronic stress, modify this relationship, and 4) if changes in anxiety and depression during pregnancy differentially influence the risk, comparing PTB due to a medical indication or spontaneous preterm birth.

3.3 Methods

3.3.1 Study Design

The data source for this study was the All our Babies (AOB) prospective cohort (McDonald et al., 2013). The AOB study, conducted in Calgary, Alberta, Canada, enrolled 3,388 pregnant women (those participants who completed at least one survey) recruited from primary health care offices, community advertising, and the Calgary Laboratory Services. Self-reported questionnaires were administered at 17-24 weeks gestation and 34 to 36 weeks gestation, with response rates ranging from 76% to 84% (McDonald et al., 2013).

3.3.2 Participants

Inclusion criteria for eligible participants were; a minimum of 18 years old, ability to communicate in English, and receiving prenatal care in Calgary from August 2008 until July 2011. In Canada, 94.9% of women receive prenatal care within the first trimester of pregnancy (Public Health Agency of Canada, 2009). Pregnancies with multiple-gestation were excluded.

3.3.3 Measures of Anxiety, Depression and Chronic Stress

State anxiety was measured on the Speilberger State Anxiety Scale (Spielberger, 2010) to detect symptoms of anxiety and their magnitude (Julian, 2011). The scale is a self-report questionnaire including 20 questions on a 4-point Likert scale, with higher numbers corresponding to increasing anxiety (Spielberger, 2010). Scores range from 20 to 80, with a cutoff score of 40 and over indicating an anxious state (Lushene, Gorsuch, & Spielberger, 1970). Finally, the Cronbach's alpha is reported to be 0.89, indicating that the scale has high internal consistency (Barnes, Harp, & Jung, 2002).

Depression was measured with the Edinburgh Postnatal Depression Scale (EPDS), which is a 10-item self-report screen that measures symptoms of depression during pregnancy (Cox, Holden, & Sagovsky, 1987). Each question can be assigned a score of 0, 1, 2, or 3; scores can range from 0-30, with higher numbers corresponding to worse depression (Cox et al., 1987). The EPDS has a Cronbach's alpha of 0.87, which is considered a reliable score (Knight, Williams, McGee, & Olaman, 1997). To classify whether someone had depressive symptoms, an established cutoff score of 10 or greater was used to indicate minor depression (Santos et al., 2007). An ROC curve analysis of various cut-off scores using the EPDS scale found that a cut-off score of 10 or greater had the best overall validity (Santos et al., 2007). Using this cut-off, the sensitivity was 82.7% (95% CI 74.0, 89.4) and the specificity was 65.3% (95% CI 59.4, 71.0).

Chronic stress was measured using the Perceived Stress Scale (PSS), which is often used as a proxy measure for chronic stress (Cohen et al., 1983). Chronic stress was assessed at one time point, at 17-24 weeks gestation. The PSS includes 10 items on a five-point Likert scale (range 0 to 40), where higher scores correspond to increased stress levels (Cohen et al., 1983). The questions prompt the participant to consider stressful events, coping resources, and control over situations and emotions that have occurred over the past month. The PSS has a Cronbach's alpha and test-retest reliability of over 0.70 (both meeting the requirements of a minimal reliability) (Lee, 2012). Similar to a previous study using the same AOB dataset, those women with PSS scores in the 80th percentile were classified as having chronic stress (Raguz, McDonald, Metcalfe, O'Quinn, & Tough, 2014).

3.3.4 Covariates

A list of covariates was generated from key articles in the literature, as well as background knowledge of the topic. Potential modifiers included chronic stress, social support (measured using the Medical Outcomes Study Social Support Survey, with a cutoff score of 70 (Sherbourne & Stewart, 1991)), maternal age at delivery, ethnicity, having one or more previous PTB, and income. Potential confounders included parity, an increased volume of amniotic fluid (either diagnosed as polyhydramnios or oligohydramnios), smoking, or pregnancy complications (at least one of the following vaginal bleeding, placenta previa, placental abruption, preeclampsia, or gestational diabetes).

3.3.5 Analysis

Descriptive statistics were used to illustrate the demographic characteristics of the sample (Tables 1, 2 & 3). Logistic regression was used to analyze the relationships between changes in anxiety, depression and PTB using hierarchically well-formulated models, which assessed modification by covariates, followed by an assessment of confounding by covariates. Separate regression models were used for anxiety and depression, in addition to a comprehensive model that assessed anxiety and depression together to understand how the variables interact with one another. PTB was classified as spontaneous PTB (with and without preterm premature rupture of membranes (PPROM)), and medically indicated PTB. Alternative definitions of PTB include spontaneous, medically indicated, and PPROM as a third classification (World Health Organization, 2015). However, spontaneous and PPROM PTB have similar gene expression profiles, and can be grouped together as a single classification (Heng et al., 2016). A

multivariable logistic regression model was used to assess PTB as defined by two classifications, and a multinomial regression model was used to assess PTB as defined by three classifications.

To examine the relationship between changes in anxiety and depression during pregnancy and the risk of PTB, anxiety and depression were treated as continuous variables, as well as categorical variables with either two or four categories. Changes in scores were calculated by subtracting the scores obtained from the questionnaire administered in the third trimester from the score obtained in the second trimester. Clinically meaningful changes were calculated as a 10-point change for anxiety and a 3-point change for depression (Corsaletti et al., 2014; Matthey, 2004). When used as a dichotomous variable, anxiety and depression were categorized as either a clinically meaningful increase (an improvement of the condition) or a clinically meaningful decrease (a worsening of the condition). When anxiety and depression were used as variables with four categories, the categories included an increase in score, a decrease in score, consistently low levels of anxiety and depression, and consistently high levels. In order to be classified as having "consistently low" or "consistently high" anxiety or depression, a change of score of <10 for anxiety and <3 for depression were required. For assessing co-occurring changes in depression and anxiety, there was not enough power to analyze as four categorical outcomes, so the analysis only compared two categories: a clinically meaningful increase in both anxiety and depression, to a clinically meaningful decrease in both anxiety and depression.

In order to assess important covariates in this analysis, a bivariate analysis was conducted on potential confounders to ensure that they were associated with both the exposures (anxiety or depression) and the outcome (PTB). Variables were excluded from the analysis if they were not

significantly associated with either the outcome or exposures (using a significance level of 0.1). To assess chronic stress as a potential modifier, women who were identified as having chronic stress at 17-24 weeks' gestation were compared to those who were not identified as having chronic stress. Chronic stress and other covariates were first assessed as potential modifiers in the analysis. This was accomplished by creating interaction terms between modifiers and each variable of interest. An omnibus likelihood ratio test was then used to identify whether any modification was present in the model, with the significance level of <0.05. If the covariates were not modifiers, they were assessed as potential confounding variables. A covariate was considered a confounder if the adjusted odds ratio (aOR) was different from the crude odds ratio (OR).

3.4 Results

3.4.1 Participant Characteristics

The overall rate of PTB was 6.9% in the AOB dataset. Participants' sociodemographic, psychosocial, and obstetric characteristics are described in Tables 1, 2 and 3 (respectively). Fewer women experienced a lack of social support (12.8%), and 20.3% of women experienced chronic stress. When examining changes in anxiety between the two time points, 14.1% of women experienced an increase in anxiety score, while 7.3% had consistently high anxiety scores. When examining changes in depression, 20.7% of women had an increase in depression score, while 3.7% had consistently high depression scores.

Table 1: Participant Sociodemographic Characteristics

Covariate	Total Sample* n (%)	Full Term* n (%)	Preterm* n (%)
Maternal Age			
<35 years	2184 (77.4)	2038 (77.3)	146 (79.8)
≥35 years	636 (22.6)	599 (22.7)	37 (20.2)
Ethnicity			
White/Caucasian	2220 (79.1)	2086 (79.4)	134 (74.9)
Other	585 (20.9)	540 (20.6)	45 (25.1)
Income			
High Income (≥$80 000)	1910 (70.2)	1799 (70.7)	111 (63.8)
Low Income (<$80 000)	810 (29.8)	747 (29.3)	63 (36.2)
School Education			
Completed High School or Less	294 (10.5)	275 (10.5)	19 (10.6)
Some or Completed Post-Secondary	2512 (89.5)	2351 (89.5)	161 (89.4)
Smoking			
No	2235 (88.4)	2108 (88.8)	127 (82.5)
Yes	293 (11.6)	266 (11.2)	27 (17.5)

*Due to missing data, sample numbers are not identical between groups.

Table 2: Participant Psychosocial Characteristics

Covariate	Total Sample* n (%)	Full Term* n (%)	Preterm* n (%)
Anxiety			
Decreased (>=10 point change)	185 (7.7)	176 (7.8)	9 (6.5)
Increased (>=10 point change)	338 (14.1)	297 (13.1)	41 (29.7)
Consistently Low (score <40)	1707 (71.0)	1636 (72.1)	71 (51.5)
Consistently High (score >=40)	176 (7.3)	159 (7.0)	17 (12.3)
Depression			
Decreased (>= 3 point change)	597 (22.5)	551 (22.1)	46 (28.6)
Increased (>=3 point change)	549 (20.7)	516 (20.7)	33 (20.5)
Consistently Low (score <10)	1413 (53.2)	1340 (53.7)	73 (45.3)
Consistently High (score >=10)	98 (3.7)	89 (3.6)	9 (5.6)
Anxiety and Depression			
Both Decreased	113 (36.2)	108 (37.8)	5 (19.2)
Both Increased	199 (63.8)	178 (62.2)	21 (80.8)
Social Support (SS)			
High SS (score <70)	2433 (87.2)	2284 (87.5)	149 (83.2)
Low SS (score ≥70)	357 (12.8)	327 (12.5)	30 (16.8)
Chronic Stress			
<80th percentile (score <19)	2215 (79.7)	2084 (80.1)	131 (74.0)
≥80th percentile (score ≥19)	564 (20.3)	518 (19.9)	46 (26.0)

*Due to missing data, sample numbers are not identical between groups.

Table 3: Participant Obstetric Characteristics

Covariate	Total Sample* n (%)	Full Term* n (%)	Preterm* n (%)
Parity			
0 Previous Pregnancies	1377 (49.4)	1276 (48.8)	101 (57.4)
≥1 Previous Pregnancies	1412 (50.6)	1337 (51.2)	75 (42.6)
History of PTB			
No	2687 (95.3)	2533 (96.1)	154 (84.2)
Yes	132 (4.7)	103 (3.9)	29 (15.9)
Pregnancy Complications			
No	2290 (81.2)	2168 (82.2)	122 (66.7)
Yes (at least 1)	530 (18.8)	469 (17.8)	61 (33.3)
Polyhydramnios and/or Oligohydramnios			
No	2743 (97.3)	2577 (97.7)	166 (90.7)
Yes	77 (2.7)	60 (2.3)	17 (9.3)

*Due to missing data, sample numbers are not identical between groups.

3.4.2 Modification by Chronic Stress and Other Covariates

Chronic stress, social support, maternal age at delivery, ethnicity, having a history of PTB, and income did not significantly modify any of the relationships between changes in anxiety and depression, and PTB. Chronic stress was not found to modify the relationship between A) changes in anxiety (Table 4); B) changes in depression (Table 5); C) co-occurring worsening of both anxiety and depression (Table 6); D) changes in anxiety and the two classifications of PTB (Table 7), and E) changes in depression and the three causes of PTB (Table 7).

All of the presented regression models (presented in Tables 4, 5, 6, and 7) accounted for covariates that were found to be potential confounding variables: parity, an increased volume of amniotic fluid, smoking, pregnancy complications, chronic stress, social support, maternal age at

delivery, ethnicity, having a history of PTB, and income. However, the odds ratios in each of the multivariable models were similar to the odds ratios in the crude models, indicating that there was negligible confounding present in the models. Therefore, as there was neither modification nor confounding in each of the models, the crude model is used to report the final measure of association, although both are presented.

3.4.3 The Change in Anxiety and PTB

Women who showed an increase in anxiety scores between the second and third trimesters were more likely to deliver preterm compared to those women who had a decline in anxiety scores (OR = 2.70, 95% CI 1.28, 5.69; p = 0.009) (Table 4.). Women who were consistently not anxious and consistently anxious were not at a lesser or greater odds of delivering preterm (OR = 0.85, 95% CI 0.42, 1.73; p = 0.651 and OR = 2.09, 95% CI 0.91, 4.82; p = 0.084, respectively). When measuring anxiety as a continuous variable, women who delivered full term infants were more likely to have a reduction in anxiety scores, compared to women who delivered preterm (OR = 0.96, 95% CI 0.94, 0.98; p = 0.001).

Table 4: Change in Anxiety and PTB

Model	Modification? (P-Value LR Test)	Crude OR (95% CI)	P-Value	Adjusted OR* (95% CI)	P-Value
Anxiety: Decrease (baseline) vs Increase	No (0.325)	**2.70 (1.28, 5.69)**	**0.009**	**2.35 (1.01, 5.45)**	**0.048**
Anxiety: Decrease (baseline) vs 1. Increase, 2. Consistently Low, 3. Consistently High	No (0.460)	**1: 2.70 (1.28, 5.69)** 2: 0.85 (0.42, 1.73) 3: 2.09 (0.91, 4.82)	**0.009** 0.651 0.084	**1: 2.82 (1.24, 6.44)** 2: 0.97 (0.44, 2.17) 3: 2.09 (0.84, 5.24)	**0.014** 0.949 0.114
Δ Anxiety Score	No (0.815)	**0.96 (0.94, 0.98)**	**<0.001**	**0.96 (0.94, 0.98)**	**0.001**

*Multivariable models accounted for the following confounding variables: parity, an increased volume of amniotic fluid, smoking, pregnancy complications, chronic stress, social support, maternal age at delivery, ethnicity, having a history of PTB, and income.

3.4.4 The Change in Depression and PTB

Unlike anxiety, women who experienced a worsening of depression between the second and third trimesters were not significantly more likely to have a PTB, compared to those women who had an improvement in depression (OR = 0.77, 95% CI 0.48, 1.22; p = 0.259). Those women that had consistently low depression were significantly less likely to deliver preterm, compared to those women that had a decreased depression score at two time points (OR 0.65, 95% CI 0.45, 0.96; p = 0.029). However, the effect was attenuated and no longer significant after including the covariates in the model (aOR= 0.72, 95% CI 0.45, 1.14; p = 0.159). These results are shown in Table 5.

3.4.5 Co-Occurring Changes in Anxiety and Depression, and PTB

Due to sample size limitations, the analysis of co-occurring changes in anxiety and depression did not include consistently low or consistently high anxiety and depression. In the first instance, the variables were treated as categorical variable, and women who had a worsening of both anxiety and depression between the second and third trimesters of pregnancy (21, 80.8%) were compared to women with an improvement in both anxiety and depression (5, 19.2%). When both anxiety and depression worsened, women did not show a statistically significant increased risk of having a PTB compared to those women who had an improvement of anxiety and depression scores (OR = 2.55, 95% CI 0.93, 6.96; p = 0.068). In the second instance, a simultaneous increase in anxiety and depression scores was assessed (i.e., as continuous variables). The crude model also did not show significant associations between improved anxiety and depression, and PTB (OR = 1.00, 95% CI 1.00, 1.01; p = 0.083).

Table 5: Change in Depression and PTB

Model	Modification? (P-Value LR Test)	Crude OR (95% CI)	P-Value	Adjusted OR* (95% CI)	P-Value
Depression: Decrease (baseline) vs Increase	No (0.604)	0.77 (0.48, 1.22)	0.259	0.92 (0.53, 1.59)	0.763
Depression: Decrease (baseline) vs: 1. Increase, 2. Consistently Low, 3. Consistently High	No (0.278)	1: 0.77 (0.48, 1.22) **2: 0.65 (0.45, 0.96)** 3: 1.21 (0.57, 2.56)	0.259 **0.029** 0.616	1: 0.86 (0.51, 1.46) 2: 0.72 (0.45, 1.14) 3: 1.59 (0.70, 3.63)	0.584 0.159 0.271
Δ Depression Score	No (0.534)	1.01 (0.97, 1.06)	0.542	1.00 (0.96, 1.05)	0.984

*Multivariable models accounted for the following confounding variables: parity, an increased volume of amniotic fluid, smoking, pregnancy complications, chronic stress, social support, maternal age at delivery, ethnicity, having a history of PTB, and income.

3.4.6 Analysis of PTB Classifications

As shown in Table 6, a classic logistic regression model was used to assess the relationship between changes in anxiety and depression, and PTB defined as two separate categories: medically indicated and spontaneous birth. Depression and anxiety were assessed as continuous variables, and not as categorical variables, due to sample size limitations. An improvement in depression during pregnancy did not appear to significantly influence the risk of delivering PTB from any particular classification. However, age modified this relationship. Those women 35 years of age and over were more likely to have a medically indicated preterm birth rather than a spontaneous preterm birth. Women under 35 were not at a significant risk of delivering preterm due to either of the classifications.

Table 6: Anxiety and Depression and Two Classifications of PTB

Model	Modification? (P-Value LR Test)	Crude OR (95% CI)	P-Value	Adjusted OR* (95% CI)	P-Value
Δ Anxiety Scores: Medically Indicated/ Spontaneous	Yes (p = 0.0229)	1.03 (0.99, 1.07)	0.154	Age <35: 1.04 (0.99, 1.09) **Age ≥35: 1.09 (1.02, 1.16)**	0.093 **0.009**
Δ Depression Scores: Medically Indicated/ Spontaneous	No (p = 0.7435)	1.06 (0.97, 1.16)	0.176	1.11 (0.98, 1.25)	0.089

*Multivariable models accounted for the following confounding variables: parity, an increased volume of amniotic fluid, smoking, pregnancy complications, chronic stress, social support, maternal age at delivery, ethnicity, having a history of PTB, and income.

3.5 Discussion

Women who experience a worsening of anxiety during pregnancy are at a greater risk of delivering preterm compared to those with an improvement in anxiety. Our finding is consistent with previous research, which demonstrated a significant association between increasing anxiety scores during pregnancy and PTB (Glynn et al., 2008). Anxiety is suggested to increase the risk of PTB by increasing hypothalamic-pituitary-adrenocortical (HPA) axis activity (Obel et al., 2005). Because typical pregnancies exhibit a decline in anxiety, this increase in anxiety is a marked departure from normal physiological responses (Glynn et al., 2004). One group of investigators demonstrated that corticotropin-releasing hormone (CRH), which is released when anxiety stimulates the HPA axis, was significantly higher in women who delivered preterm infants compared to those who delivered full term infants (Mancuso et al., 2004). These studies provide a possible physiological explanation of how increasing maternal anxiety during pregnancy can lead to PTB.

The AOB cohort study did not measure pregnancy-specific anxiety, which was found in one study to be a stronger predictor of PTB compared to other forms of anxiety (Staneva et al., 2015). Another contrasting systematic review and meta-analysis, after controlling for heterogeneity, revealed that the odds of delivering preterm when exposed to pregnancy-specific anxiety compared to state anxiety were not different (OR 1.67, 95% CI 1.35, 2.07 and OR 1.70, 95% CI 1.33, 2.18) (Rose et al., 2016). These authors suggested that these two unique constructs of anxiety have potentially similar implications for the HPA axis response and allostatic load, that may lead to PTB (Rose et al., 2016). Rose et al. did not discuss the interaction between pregnancy-specific anxiety and state anxiety. Not only is it important to clarify the relationship

between changes in state anxiety and PTB, but also future studies should examine how state anxiety can interact with pregnancy-specific anxiety, and possibly lead to PTB.

Unlike anxiety, an increase in depression scores during pregnancy did not significantly increase the risk of PTB. However, women who had consistently low depression were less likely to deliver preterm compared to women who had reduced depression scores during pregnancy. These results indicate that consistently low depression levels appear protective from PTB, however this effect became insignificant in the model that adjusted for potential covariates. There is a possibility that the significant results of the crude analysis are due to a type I error. Only 73 women had consistently low depression, and only 46 women had reduced depressive symptoms. In addition, depression may increase the risk of PTB through poor behavioral outcomes such as substance abuse, low social support, and smoking (Kelly et al., 2002; Zuckerman, Amaro, Bauchner, & Cabral, 1989). The sample in the current study was affluent with a low prevalence of smoking (11.6%) and a high prevalence of high social support (87.2%) (McDonald et al., 2013). These results should be interpreted with caution, as this sample is not generalizable to the Canadian population.

A simultaneous worsening of anxiety and depression during pregnancy was not found to have an effect on PTB. This is contradictory to the literature, as comorbid depression and anxiety during pregnancy increased the risk of PTB (Field et al., 2010). However, small sample numbers limited the analysis of the current study. Only 5 women who delivered preterm had a simultaneous worsening of both anxiety and depression, and only 21 women had a simultaneous improvement in anxiety and depression. Similarly, changes in depression did not impact the risk of delivering

a spontaneous or medically indicated PTB differently. However, women who were 35 years of age and over were more likely to have a medically indicated PTB, compared to a spontaneous PTB. Women who were under 35 years of age were not statistically more likely to have a medically indicated PTB; this finding is supported in the literature (Henderson, McWilliam, Newnham, & Pennell, 2012). The literature has shown that allostatic load accumulates with age, posing greater health risks to women as they age (Chyu & Upchurch, 2011). This may help explain why older women are more susceptible to medically indicated PTB. Future interventions should target this group of women, and intervene early on in pregnancy to reduce the risk of delivering preterm.

Chronic stress and other important potential modifiers (i.e., social support, maternal age, ethnicity, history of PTB, and income) were not found to significantly influence these relationships. One possible reason why chronic stress was not a modifier is that the number of pregnant women who experienced chronic stress was small (20.3%), thus limiting the ability to detect the effect of chronic stress on the relationship between changes in anxiety and depression, and PTB. Additionally, the analysis of chronic stress as a modifier may also be limited as a result of low power. Participants in the AOB cohort were more affluent than the target population, thus chronic stress was likely lower in this sample and may explain the negative results (McDonald et al., 2013). Although the PSS has been used as a measure for chronic stress, it is recommended that the instrument be administered multiple times to get a true sense of the ongoing "chronic" stress that pregnant women might be experiencing (Cohen et al., 1983). However, chronic stress does not have a defined beginning or end point (Dunkel Schetter & Dolbier, 2011). Future clarification around the definition of chronic stress, and appropriate application of the PSS scale

will help more critically examine whether chronic stress modifies the association between changes in anxiety and depression, and PTB.

This study is not without its limitations. The sample size did not allow the analysis of how changes in anxiety and depression during pregnancy influence the three severities of PTB (extremely preterm, early preterm, and late preterm), as extremely preterm and early preterm infants were not as prevalent in the sample. Further, the current study found that some estimates had wide confidence intervals, indicating imprecision of the estimates. Increasing the sample size may help alleviate this issue. Future studies will need to increase the sample size of the cohort in order to comprehensively assess these relationships. This study was also not able to examine changes in anxiety and depression earlier than in the 2nd trimester of pregnancy. The majority of infants in this study were born late preterm, and therefore a future study is needed to explore this relationship on this subset of infants. Finally, there remains a possibility that some important covariates were not considered in the analysis.

The current research provides necessary information to develop a future prospective longitudinal study, which can confirm the current findings and re-examine the relationships that this study was not able to explore (e.g., how increases in anxiety during pregnancy influences the risk of delivering extremely preterm, very preterm, or late preterm). This future study would ideally use gold standard measures of anxiety, depression and chronic stress. Additionally, it would explore the potential interactive effects of anxiety, depression and chronic stress. This future prospective longitudinal study could additionally assess biological plausibility by measuring the expression of markers of PTB, and measure anxiety and depression at multiple points in pregnancy. The

ultimate goal of this research will be to help decision-makers implement a primary prevention initiative, such as reducing levels of prenatal anxiety through implementation of stress reduction workshops. Such an initiative would ultimately reduce the risk of PTB in at-risk women.

3.6 Compliance with Ethical Standards

This research was conducted in accordance with prevailing ethical principles and was approved by the Conjoint Health Research Ethics Board. An amendment to the AOB cohort study ethics agreement was made to incorporate the first author as a researcher on the project (ethics ID: REB15-0248_MOD1). Because we are performing secondary data analysis on existing de-identified questionnaires, there were few foreseeable ethical considerations.

3.7 Acknowledgements

We would like to thank Ms. Nikki Stephenson and the AOB research team for their support and guidance with the dataset and analysis.

3.8 Declarations

3.8.1 List of Abbreviations

PTB – Preterm Birth

AOB – All Our Babies

EPDS – Edinburgh Postnatal Depression Scale

PSS – Perceived Stress Scale

PPROM – Preterm Premature Rupture of the Membranes

OR – Odds Ratio

aOR – Adjusted Odds Ratio

HPA – Hypothalamic-Pituitary-Adrenocortical

3.8.2 Competing Interests

The authors have no competing interests to declare.

3.8.3 Funding

No funding was required for the completion of this study, as the authors conducted a secondary analysis on data previously collected.

3.9 Supplementary File: Analysis of PTB Classifications Using Three Categories

In this study, PTB was operationalized as two distinct classifications: spontaneous PTB (with and without PPROM), or medically indicated PTB. However, this is not a universally accepted classification system for PTB, and can alternatively be classified as PPROM, medically indicated, and spontaneous preterm birth. Changes in anxiety and depression may influence the pathways that lead to these three classifications differently. A multinomial logistic regression model was used to assess this (Table 8). Depression and anxiety were assessed as continuous variables, and not as categorical variables, due to sample size limitations. An improvement in depression or anxiety during pregnancy did not appear to significantly influence the risk of delivering PTB from any particular classification.

Table 7: Anxiety and Depression and Three Classifications of PTB

Model	Modification? (P-Value LR Test)	Crude RR (95% CI)	P-Value	Adjusted RR* (95% CI)	P-Value
Δ Anxiety Scores	No (p = 0.093)	PPROM/Spontaneous: 0.97 (0.92, 1.03) Medically Indicated/Spontaneous: 1.02 (0.98, 1.06)	0.359 0.255	PPROM/Spontaneous: 0.94 (0.87, 1.01) Medically Indicated/Spontaneous: 1.04 (0.98, 1.09)	0.114 0.170
Δ Depression Scores	No (p = 0.732)	PPROM/Spontaneous: 0.91 (0.79, 1.05) Medically Indicated/Spontaneous: 1.04 (0.96, 1.14)	0.195 0.341	PPROM/Spontaneous: 0.86 (0.72, 1.03) Medically Indicated/Spontaneous: 1.09 (0.96, 1.22)	0.102 0.185

*Multivariable models accounted for the following confounding variables: parity, an increased volume of amniotic fluid, smoking, pregnancy complications, chronic stress, social support, maternal age at delivery, ethnicity, having a history of PTB, and income.

CHAPTER 4: OVERALL DISCUSSION AND CONCLUSIONS

4.1 Discussion

4.1.1 Discussion of Findings

Change in anxiety significantly altered the outcome of pregnancy in the context of PTB. Similar to Glynn et al.'s (2008) study, a clinically meaningful increase in anxiety scores (ten or more points on the state anxiety scale) during pregnancy significantly increased the risk of PTB, compared to those who had a decrease in anxiety. Studies assessing the physiological mechanisms behind this relationship found that increases in anxiety during pregnancy also elevated stress hormones such as corticotropin-releasing hormone (CRH) (Mancuso et al., 2004). CRH stimulates the adrenal cortex to release cortisol, and has been found to increase during pregnancy (Carr, Parker, Madden, MacDonald, & Porter, 1981). It has also been shown that CRH interacts with prostaglandins and oxytocin to stimulate uterine contractility, leading to labor (Challis, Matthews, Van Meir, & Ramirez, 1995; Petraglia, Florio, Nappi, & Genazzani, 1996). Studies have shown that women who delivered preterm had higher levels of CRH, compared to those who delivered full term (Mancuso et al., 2004). Few studies assess the simultaneous trajectories of anxiety throughout pregnancy, and physiological responses to anxiety (Mancuso et al., 2004). This relationship may clarify the pathways behind PTB.

Consistently low depression scores during pregnancy were protective from PTB, when compared to women who had a decrease in depression scores. Alternatively, women who had an increase in depression scores did not appear to be more at risk for PTB than women who had a decrease in depression scores. The number of women who experienced an increase and decrease in

depression scores was too low, 33 and 46 respectively, suggesting that the negative finding doesn't necessarily rule out the possibility of an association. The finding that consistently low depression scores during pregnancy were protective from PTB may have been a result of Type 1 error. Type 1 error occurs when there is a statistically significant finding but there is no true relationship. Further, depression has been associated with poor health behaviors (Kelly et al., 2002; Zuckerman et al., 1989). However, the AOB sample is highly affluent compared to the Canadian population, with few women having poor health behavior like smoking and social support (McDonald et al., 2013). This may also explain why we do not see a significant relationship between worsening of depression during pregnancy and PTB. Overall, depression can have negative physiological consequences on the autonomic, immune-inflammatory, and HPA-axis systems potentially resulting in the increased risk for various other comorbidities (e.g., cardiovascular diseases) (Penninx, Milaneschi, Lamers, & Vogelzangs, 2013). Future research may consider not only how depression-associated health behaviors influence PTB, but also how depression influences biological responses during pregnancy that increase the risk of PTB.

Co-occurring changes in anxiety and depression did not appear to significantly influence the odds of delivering preterm. Similarly, Perkin et al. found that comorbid anxiety and depression did not increase the risk of delivering preterm (Perkin, Bland, Peacock, & Anderson, 1993). Contradictory to these findings, two other studies found that comorbid anxiety and depression was a stronger predictor of PTB compared to anxiety and depression alone (Field et al., 2010; Ibanez et al., 2012). In the current study, co-occurring anxiety and depression was limited by sample size, as only 5 women who delivered preterm had co-occurring worsening of anxiety and depression, and 21 women who delivered preterm had an improvement in co-occurring anxiety

and depression. The inconsistencies across the literature can also be explained by inappropriate use of anxiety and depression scales, and not accounting for appropriate confounding variables (Staneva et al., 2015). To better understand how comorbid anxiety and depression may increase the risk of PTB, these inconsistencies should be addressed. Further, behaviors and biological responses should be studied as well, to provide a more comprehensive understanding of this interaction on PTB (Field et al., 2010).

This study addressed additional covariates that Glynn et al. (2008) did not address, including chronic stress and social support, as well as measured the association between the pattern of depression during pregnancy and PTB. Chronic stress and other covariates, however, did not modify nor confound any of these relationships. Only 20.3% of the AOB sample experienced chronic stress. This limits the ability to make inferences about whether chronic stress modified the relationship between changes in anxiety and depression, and PTB. The AOB cohort sample is an affluent sample (McDonald et al., 2013) thus chronic stress was lower and may explain why it did not significantly modify the associations between the relationships examined. Due to these circumstances, the negative finding may be due to a type II error. Further investigation with a larger sample size, and a sample representative of the affluence of the population, would be preferred.

PTB was operationalized as having two classifications: spontaneous, and medically indicated. Interestingly, age was found to be a modifier of the relationship between change in anxiety, and medically indicated PTB and PPROM/spontaneous PTB. The odds of delivering preterm was only elevated in women over 35 years of age and older, compared to women who were under 35

years of age. Henderson et al. (2012) similarly found that those women who had a medically indicated PTB were more likely to be 35 years of age and older (Henderson et al., 2012). Allostatic load has been shown to increase with age, resulting in an accumulation of physiological dysregulation over time (Chyu & Upchurch, 2011; Crimmins, Johnston, Hayward, & Seeman, 2003). Women over 35 years of age may therefore have a higher allostatic load. This would result in increased physiological dysregulation over time, and therefore increase the risk of adverse birth outcomes, such as PTB.

Currently, there is no universally accepted operational definition of PTB. Supplementary analysis was conducted, which classified PTB as spontaneous, PPROM, and medically indicated. The results of this analysis did not find any significant association between changes in anxiety or depression and any of the three classifications of PTB. This finding was similar to the analysis using two classifications of PTB, with the only difference being that when operationalized as two classifications, an increased odds of medically indicated PTB was found only in women 35 years of age and older. Similar etiologies between the two subtypes may explain why changes in anxiety and depression do not influence these categories differently. A worsening of anxiety during pregnancy initiates an increase in physiological stress responses (Arborelius, Owens, Plotsky, & Nemeroff, 1999). These physiological stress responses, within the framework of allostatic load, would have negative consequences on multiple organ systems throughout the body (McEwen & Seeman, 1999). For example, women with higher allostatic load during pregnancy were shown to be at risk for preeclampsia (Hux & Roberts, 2015). A review by Ananth et al. found that ischemic placental diseases, including preeclampsia, placental abruption, intrauterine growth restriction, and fetal distress, are found in approximately 87% of medically

indicated PTB, and in 20% of spontaneous PTB (Ananth, Ananth, & Vintzileos, 2006). Thus, these stress responses may impact the mechanism of each of the three classifications of PTB similarly.

Emerging evidence suggests that pregnancy-specific anxiety is a strong predictor of PTB (Staneva et al., 2015). Pregnancy-specific anxiety has also been shown to have long-term consequences to the infant, including cognitive development in children ages 6-9, highlighting the importance of reducing this condition during pregnancy (Buss, Davis, Hobel, & Sandman, 2011). However, the AOB dataset did not measure this unique construct. A recent meta-analysis has further suggested that pregnancy-specific anxiety and state anxiety similarly influence PTB (Rose et al., 2016). Thus, pregnancy-specific anxiety would be an important type of anxiety to consider in future research, however state anxiety appears to contribute comparably to PTB as pregnancy-specific anxiety (Rose et al., 2016).

The current study did not measure anxiety during the first trimester, which may provide more information regarding the association with PTB. Physiological stress and stress appraisal have been shown to dampen throughout pregnancy as a mechanism to protect the fetus from negative health outcomes (De Weerth & Buitelaar, 2005; Glynn et al., 2001; Glynn et al., 2004). If this negative appraisal of stress during pregnancy continues or worsens, this may pose a health threat to the fetus (Glynn et al., 2004). Further, anxiety has been shown to be at the lowest levels during the first trimester of pregnancy, and increase in the third trimester (Da Costa, Larouche, Dritsa, & Brender, 1999). Therefore, measuring patterns of change in anxiety and depression starting from the 1st trimester of pregnancy may be a more accurate predictor of PTB.

This research exhibits various strengths. By using logistic regression to analyze the data, we were able to control for multiple confounders at once, and assess continuous exposure variables (i.e., change in anxiety and change in depression). The AOB cohort data was available to us, which offered previously collected data, and met the needs of this research by offering validated scales capable of answering our research questions. The AOB cohort was a prospective cohort study design, as was our study design. This design allowed the establishment of temporality between causes and effects. The AOB cohort had a 79% response rate of those participants who completed both questionnaires (McDonald et al., 2013). This allowed efficient and cost-effective data-collection procedures to answer the research inquiries proposed in this thesis.

Despite the aim to be comprehensive with this research, there remain limitations. Primarily, the dataset lacked the sample size to conduct an ordinal regression model that would assess how changes in anxiety and depression during pregnancy influenced the three severities of PTB (extremely preterm, very preterm, and late preterm). Further, because the first questionnaire was implemented in the 2nd trimester, the changes in anxiety and depression during pregnancy would not apply to extremely preterm infants, as they would have been born prior to the second questionnaire. Therefore, the majority of the preterm infants in this study were late preterm infants. The pattern of anxiety and depression would also only be assessed between the second and third trimester. In order to address these issues, a future prospective cohort study would require a larger sample size, along with an additional questionnaire administered in the 1st trimester.

The PSS scale was used to measure chronic stress, which has been suggested to be an appropriate proxy measure for chronic stress (Cohen et al., 1983). The accuracy of this measure in identifying chronic stress may be limited, as it has not been validated as a measure for this construct. Moreover, chronic stress has been defined as an enduring stress, however the beginning and end point of when chronic stress occurs has not been clearly identified (Dunkel Schetter & Dolbier, 2011). Without a clear definition of chronic stress, it is difficult to develop a validated and reliable tool to measure it. To strengthen future research in this field, we recommend implementing the PSS scale multiple times prior to and during pregnancy, to better assess chronic stress. We also suggest that the definition of chronic stress be clarified, and a validated tool be created that measures the breadth and depth of chronic stress, particularly during pregnancy.

A future study could have one of two purposes: 1) to understand the independent contributions of changes in anxiety with PTB, or 2) to predict PTB by assessing changes in anxiety. If the main purpose of a future study would be to understand the independent contributions of changes in anxiety with PTB, other covariates should be considered that were not included in the analysis. This would strengthen the internal validity of the study, and reduce bias resulting from confounding (Patten, 2015). As a prerequisite to be a potential confounder, these variables would need to be associated with both PTB and changes in anxiety. Such covariates might include a validated measure of socioeconomic status (which includes consideration of occupation, education, and income together), substance abuse, hypertension and other chronic diseases, history of abuse, and time in Canada. Alternatively, if the purpose of a future study would be to

predict PTB with changes in anxiety, little to no adjustments should be made, as it would adjust the true effect away.

Some key demographic characteristics of the AOB sample, including age and education, were found to be representative of the Calgary, Alberta, and Canada populations (McDonald et al., 2013). There are, however, a few key characteristics of the AOB sample that differ from the compared populations (e.g., discontinued participants, who had withdrawn from the study either passively or actively, had poorer psychosocial health during pregnancy compared to those who stayed in the study) (McDonald et al., 2013). Although these characteristics differ between the sample and the Canadian population, they are unlikely to overestimate the reported measure of association between changes in anxiety and PTB. Thus, the reported estimates in the current research is still likely generalizable and valid to populations outside of the AOB cohort.

4.1.2 Implications for Practice and Policy

Current medical practice in Alberta focuses largely on management of the sequelae of PTB, rather than prevention (Alberta Health Services, 2016). Although important for the health outcomes of the infant, this current research also supports the importance of prevention of PTB. Shifting focus towards the mental health of the mother during pregnancy, and reducing anxiety may help to prevent PTB. Assessing psychosocial health during pregnancy, and at more than one time point, may help identify women at risk for PTB. Once identified, interventions that reduce levels of anxiety can be implemented, in an effort to reduce the risk of delivering preterm. Interventions that promote community engagement, resiliency, and social support are currently being designed (e.g., the Community Child Health Network), which aim to reduce allostatic load

in women and families (Ramey et al., 2015). However, effective implementation is imperative, particularly for women who are vulnerable to health risks (e.g., those living in low and middle income countries, or minority populations) (Hollon et al., 2002; Murray & Jordans, 2016).

4.1.3 Knowledge Translation Plan

The primary finding of this research was that increasing anxiety scores during pregnancy increases the risk of PTB. However, this research requires validation in a future longitudinal cohort study, and therefore knowledge translation efforts should be directed towards researchers and academics. The information generated from this study can be presented at national and international maternal and mental health conferences (e.g., Women's Mental Health Day), which will create opportunities for sharing the research with potential future colleagues. By disseminating research findings at various venues, it may be possible to promote the importance of anxiety research in the context of maternal mental health. Clinicians and other key healthcare professionals would be a potential avenue of knowledge dissemination, and it is important to collaborate with these professionals in research studies to provide clinical perspectives. The knowledge translation plan for the current research should ultimately aim to design and conduct a longitudinal cohort study that addresses unanswered questions resulting from the current study, which are discussed in the following section.

4.1.4 Future Research Directions

The results from this research suggest that there is a significant association between an increase in anxiety scores throughout pregnancy and an increased risk of PTB. However, this study possessed some limitations, which did not allow for the establishment of causality between

changes in anxiety and depression during pregnancy, and PTB. A prospective cohort study design that replicates these findings, and addresses the limitations of this thesis, would better inform future research studies by establishing a causal relationship. This research was unable to clarify some gaps in this field, including: 1) the relationship between depression, comorbid depression and anxiety, and PTB; 2) how certain covariates, such as chronic stress, may influence the relationship between anxiety and PTB; 3) the relationship between pregnancy-specific anxiety and PTB; and 4) how the pattern of anxiety influences PTB, with several time points throughout pregnancy that are measured from the first trimester.

The sample size of the AOB cohort study was large (3388), however it lacked sufficient power to fully rule out the possibility that depression, and comorbid anxiety and depression influence the risk of PTB. A future longitudinal cohort study would require a large enough sample of women to fulfill the power necessary for the analysis. The future cohort should also include various sample characteristics (psychosocial, medical etc.) to account for as many potential covariates as possible. Poor control of confounding variables may invalidate study findings, and therefore are less likely to demonstrate a causal relationship (Patten, 2015). Future longitudinal studies should therefore include a validated psychosocial measure of chronic stress, or assess PSS at multiple time points during pregnancy. A validated scale should also be used to measure changes in pregnancy-specific anxiety, to better understand the association of changes of various types of anxiety with PTB. Further, because the current study sample was more affluent than the Canadian population, a different sampling procedure should be used to collect study participants. This procedure, such as sampling various clinics that serve women of diverse socioeconomic status, may help improve generalizability and external validity of the sample. Finally, this future

study would measure anxiety and depression at multiple time points throughout pregnancy (beginning in the first trimester of pregnancy), in order to map a more accurate trajectory of these constructs. This would allow researchers to understand particular trends and responses to stressors in the environment.

Various biomarkers have been proposed to explain the relationship between psychosocial health and PTB within the framework of allostatic load, including cortisol, CRH, C-reactive protein, cytokines, and immunoglobulin G (Premji and MiGHT Group, 2014). Emerging research has also shown that there are genetic predispositions to spontaneous PTB, and that these genetic biomarkers can predict PTB with a high sensitivity and specificity (Heng et al., 2016). A future prospective cohort should consider measuring physiological responses to anxiety, in order to develop a more comprehensive strategy of predicting PTB. Measuring physiological responses to anxiety would also help establish biological plausibility of this relationship, which is a causal criteria defined by Bradford Hill (Hill, 1965). Care should be taken into recording the time of data collection, as some biomarkers are time-sensitive and exhibit diurnal fluctuations throughout the day (Katz et al., 1975). The biomarker and questionnaire collection should be simultaneous for each time point.

4.2 Conclusions

The current study demonstrated that the pattern of anxiety during pregnancy is significantly associated with PTB, as both a continuous and categorical variable. Furthermore, consistently low levels of depression are protective from PTB, however a worsening of depression did not appear to significantly increase the odds of PTB. Chronic stress did not modify any of these

relationships. A future longitudinal cohort study with a large sample size and heterogeneous population may help to better understand the influence of changes in anxiety, chronic stress as a modifier, and PTB. These findings are necessary in the advancement of research and the improvement of primary prevention. Interventions should focus on reducing anxiety earlier on in pregnancy, to prevent preterm delivery.

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Appendices

Appendix 1: Spielberger State Anxiety Scale

The Speilberger State Anxiety Scale was not included in this appendix, due to copyright.

Appendix 2: Edinburgh Postnatal Depression Scale

Check the answer that comes closest to how you have felt in the past 7 days, not just how you felt today.	Never	Almost Never	Sometimes	Fairly Often	Often
In the past 7 days, I have been able to laugh and see the funny side of things	○	○	○	○	○
In the past 7 days, I have looked forward with enjoyment to things	○	○	○	○	○
In the past 7 days, I have blamed myself unnecessarily when things went wrong	○	○	○	○	○
In the past 7 days, I have been anxious or worried for no good reason	○	○	○	○	○
In the past 7 days, I have felt scared or panicky for no very good reason	○	○	○	○	○
In the past 7 days, things have been getting on top of me	○	○	○	○	○
In the past 7 days, I have been so unhappy that I have had difficulty sleeping	○	○	○	○	○
In the past 7 days, I have felt sad or miserable	○	○	○	○	○
In the past 7 days, I have been so unhappy that I have been crying	○	○	○	○	○
In the past 7 days, the thought of harming myself has occurred to me	○	○	○	○	○

Appendix 3: Perceived Stress Scale

In the past month, how often have you...	Never	Almost Never	Sometimes	Fairly Often	Often
Felt upset by something that happened unexpectantly	○	○	○	○	○
Felt unable to control important things in your life	○	○	○	○	○
Felt nervous or stressed	○	○	○	○	○
Felt confident in your ability to handle your personal problems	○	○	○	○	○
Felt that things were going your way	○	○	○	○	○
Felt unable to cope with all the things you had to do	○	○	○	○	○
Felt able to control irritations in your life	○	○	○	○	○
Felt on top of things	○	○	○	○	○
Felt angry because of things that happened that you couldn't control	○	○	○	○	○
Felt that difficulties were piling up so high that you couldn't overcome them	○	○	○	○	○

Appendix 4: Approval from Manuscript Co-Authors to Submit to U of C Electronic Vault

Suzanne C. Tough
Sent: Thursday, January 19, 2017 at 4:45 PM
To: Tyler Williamson
Cc: Donna M. Slater; Chelsea Tai Alexandra Doktorchik

I confirm that Chelsea Doktorchik can submit her thesis to the U of Calgary electronic archives
Suzanne

Donna M. Slater
Sent: Thursday, January 19, 2017 at 4:03 PM
To: Chelsea Tai Alexandra Doktorchik

Dear Chelsea,

I confirm that Chelsea Doktorchik can submit her thesis to the University of Calgary electronic vault.

Sincerely,

Donna Slater

Tyler Williamson
Sent: Thursday, January 19, 2017 at 4:12 PM
To: Donna M. Slater; Suzanne C. Tough; Chelsea Tai Alexandra Doktorchik

I confirm that Chelsea Doktorchik can submit her thesis to the U of Calgary electronic archives.

Do I need to send this to anyone besides you Chelsea?

Tyler

Tyler Williamson, PhD