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Association of Post-Traumatic Stress Disorder Exposure and Treatment in Pregnancy with Pregnancy, Obstetric and Neonatal Outcomes

Natalie Zitoun,

Supervisor: Bournissen, Garcia-Facundo, *The University of Western Ontario*
: Campbell, Karen M., *The University of Western Ontario*
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Abstract

A particular condition for which there is a dearth of pregnancy information is Post-Traumatic Stress disorder (PTSD). This thesis aimed to evaluate PTSD exposure and treatment in pregnancy. Our first study was a systematic review, meta-analysis, and GRADE assessment that reported associations between maternal PTSD exposure with pregnancy, obstetric, and neonatal outcomes. Our second study was a prospective evaluation of pregnancy outcomes after prazosin exposure in the first trimester of pregnant patients who were counselled at the Fetal Risk Assessment from Maternal Exposures (FRAME) clinic. Our review and analysis found positive associations between PTSD in pregnancy and some adverse pregnancy outcomes including conflicting evidence suggestive that maternal PTSD was associated with increased odds of having a low birthweight infant and preterm birth. Our prospective study found that pregnancy outcomes after prazosin exposure appeared to align with unexposed pregnancy outcomes. Together, these findings contribute to providing information to improve perinatal and neonatal health.

Keywords

Post-traumatic stress disorder (PTSD), pregnancy, fetal risk assessment from maternal exposures (FRAME), prazosin, perinatal health, neonatal health.

Summary for Lay Audience

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that usually results after exposure to a traumatic event. It is well-documented that females are more likely to develop PTSD than males. This motivates studying PTSD in pregnant populations. PTSD exposure in pregnancy may have adverse effects on perinatal and neonatal health. Some medications, such as prazosin, are effective in treating PTSD. To date, there is limited research on how PTSD exposure affects perinatal and neonatal health, as well as very limited research on prazosin safety when used during pregnancy. This limit in research limits lowers the quality of care that pregnant patients receive. Therefore, it is important to address the lack of research so that pregnant patients can receive a better level of care throughout their pregnancies.

We conducted a systematic review, meta-analysis and GRADE assessment on studies that assessed associations between maternal PTSD with adverse pregnancy, obstetric or neonatal outcomes. Our review found that maternal PTSD was positively associated with infant head circumference, infant sleeping & eating difficulties, reduced breastfeeding, and lower infant salivary cortisol levels. We also found that PTSD exposure in pregnancy may be associated with increased odds of having a preterm birth or a low birthweight infant. We also evaluated fetal and pregnancy outcomes in a sample of pregnant patients exposed to prazosin during the first trimester of their pregnancies. We found that pregnancy and fetal outcomes were consistent with normal pregnant populations that did not have prazosin exposure. In conclusion, PTSD exposure in pregnancy was associated with specific adverse pregnancy, obstetric and neonatal outcomes whereas prazosin exposure in a small number of pregnancies did not demonstrate any adverse pregnancy, obstetric or neonatal outcomes.

We expect that the information obtained will help provide guidance on PTSD exposure in pregnancy and on the safety of prazosin exposures in early pregnancy for healthcare providers to better care for pregnant patients. We expect that our findings will contribute to better standards of care in perinatal and neonatal health. Future research should examine the effects of untreated PTSD in pregnancy and examine the effects of prazosin treatment in pregnancy to allow for more official conclusions and to help fill the gaps that currently exist on this topic.

Co-Authorship Statement

This thesis includes two integrated articles, each of which has been or will be submitted for publication in a peer-reviewed journal. The co-author details are presented below.

Chapter 3: Natalie M. Zitoun, M. Karen Campbell, Yasaman Mohamadi-Kamalabadi, Joel Gagnier, Facundo Garcia-Bournissen. Post-Traumatic Stress Disorder and Pregnancy Outcomes: A Systematic Review, Meta-Analysis and GRADE Assessment

Natalie Zitoun, Dr. Facundo-Garcia Bournissen and Dr. M Karen Campbell contributed to the conception and design of the study. Natalie Zitoun, Dr. Facundo-Garcia Bournissen Dr. M. Karen Campbell, and Dr. Joel Gagnier contributed to the interpretation findings. Natalie Zitoun performed the scoping search. Natalie Zitoun and Yasaman Mohamadi-Kamalabadi contributed to the study screening and selection, data extraction, and risk of bias assessment. Natalie Zitoun and Dr. Facundo-Garcia Bournissen contributed to conducting the meta-analysis. Natalie Zitoun and Dr. Joel Gagnier contributed to conducting the sensitivity analyses and GRADE assessment. Natalie Zitoun, Dr. Facundo-Garcia Bournissen Dr. M. Karen Campbell, and Dr. Joel Gagnier contributed to interpretations of the analysis and witting of the manuscript. Dr. Facundo-Garcia Bournissen Dr. M. Karen Campbell and Dr. Joel Gagnier contributed to the subsequent revisions of the draft and approved the final manuscript.

Chapter 4: Natalie Zitoun, M. Karen Campbell, Doreen Matsui, Facundo Garcia-Bournissen. Prospective Evaluation of Pregnancy Outcomes after Gestational Exposure to prazosin

Natalie Zitoun, Dr. Facundo-Garcia Bournissen and Dr. M Karen Campbell were involved in the conception of the study design. Natalie Zitoun and Dr. Facundo-Garcia Bournissen were involved in the recruitment of patients. Natalie Zitoun, Dr. Facundo-Garcia Bournissen and Dr. M Karen Campbell were involved in establishing the data collection variables. Natalie Zitoun and Dr. Facundo-Garcia Bournissen were involved in data collection. Natalie Zitoun, Dr. Facundo-Garcia Bournissen, Dr. M Karen Campbell, and Dr. Doreen Matsui contributed to interpretations of the data and witting of the manuscript. Natalie Zitoun, Dr. Facundo-Garcia Bournissen, Dr. M Karen Campbell, and Dr. Doreen Matsui contributed to the subsequent revisions of the draft and approved the final manuscript.

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List of Abbreviations

PTSD- Post-Traumatic Stress Disorder

LBW- Low Birthweight

PTB- Preterm Birth

GA- Gestational Age

SGA- Size for Gestational Age

DSM- Diagnostic and Statistical Manual of Mental Disorders

PCL- Post-traumatic Stress Disorder Checklist

PDS- Perinatal Posttraumatic Diagnostic Scale

IES- Impact of Event Scale

PPQ- Perinatal Post-Traumatic Stress Disorder Questionnaire

PTSDQ - Postpartum PTSD questionnaire scores

MINI - Mini International Neuropsychiatric Interview

PSS-SR- PTSD Scale-Self Report for DSM-5

CIDI- Composite International Diagnostic Interview

SRQ-20- The Self-Reporting Questionnaire 20-item

PC-PTSD - Primary Care PTSD Screen for DSM-5

ICD-9- International Diagnostic Code Descriptions

ROB- Risk of Bias

CI- Confidence Interval

OR- Odds Ratio

GRADE- Grading of Recommendations Assessment, Development and Evaluation

FRAME- Fetal Risk Assessment from Maternal Exposures

LHSC- London Health Sciences Centre

NICU- Neonatal Intensive Care Unit

Chapter 1

1 Thesis Overview

1.1 Summary

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that causes substantial functional disturbances in one's life (1). While any individual can suffer from PTSD, studies consistently confirm that sex and gender differences exist in PTSD; women have a higher prevalence of (PTSD) and experience greater symptom severity and chronicity when compared to males (2). It is estimated that women have approximately two to three times a higher risk of developing PTSD when compared to men (3–6) The higher prevalence, risk symptom severity and chronicity of PTSD in women becomes an even greater issue of importance when observing pregnant populations and there is evidence that shows that PTSD may be a significant underlying mechanism in obstetric health outcomes and may contribute to adverse pregnancy and birth outcomes (7–10) when left untreated.

In the general population, PTSD can be managed through pharmacological intervention. Such medications include prazosin, which is a well-tolerated and generically available medication that has shown evidence to be effective in treating PTSD-associated symptoms and has shown to be safe for use in the general population field (11,12). Using medications such as prazosin during pregnancy could potentially minimize the risk of adverse pregnancy and birth outcomes associated with PTSD in pregnant patients, by eliminating the risks associated with untreated PTSD. But it is unknown whether exposure to such medications may carry their own risks. There is limited research on how PTSD exposure affects pregnancy and birth outcomes, as well as very limited research on prazosin safety when used during pregnancy. This thesis aimed to explore PTSD exposure and PTSD treatment with prazosin in pregnancy and how they relate to pregnancy and birth outcomes.

Our systematic review, meta-analysis, and GRADE assessment (**Post-Traumatic Stress** Disorder and Pregnancy Outcomes: A Systematic Review, Meta- Analysis and GRADE Assessment) synthesized previous literature that assessed associations between maternal PTSD and pregnancy obstetric and neonatal outcomes. We found that there was evidence for an association between maternal PTSD with reduced infant head circumference, infant sleeping

& eating difficulties, reduced breastfeeding, and lower infant salivary cortisol levels. There is conflicting literature regarding an association between PTSD and low birthweight (LBW) and preterm birth (PTB). Our meta-analyses of studies for which data were available revealed a pooled OR of (OR, 2.05; 95%CI: [1.27, 3.33]) with LBW and a pooled OR of 1.23; 95%CI: [1.11, 1.37]) with PTB.

We then evaluated fetal and pregnancy outcomes in a sample of 11 pregnant patients exposed to prazosin during the first trimester of pregnancy who were counselled at the Fetal Risk Assessment from Maternal Exposures (FRAME) clinic in the London Health Sciences Centre (Ontario, Canada) between January 1, 2000, to December 31, 2021 (**Chapter 4**). Our findings revealed that 6 /11 (54.5%) subjects did not report any adverse outcomes. We also reported 2 miscarriages. Further observation showed that the infant's birthweights were within the normal range for the remaining 9 pregnancies. We also found that the adverse effects we observed in this sample were consistent with background population norms this included: one case of postpartum hemorrhage, one case of preeclampsia, one case of preterm birth, two NICU admissions, and 2 cesarean sections. Furthermore, we reported that there were no fetal malformations for any of the pregnant patients enrolled in this study. While conclusions can't be drawn regarding safety due to the small number of exposed individuals, the data provide incremental information in an area where there is limited data.

1.2 Thesis Structure and Student's Role

I conducted the research reported in this thesis under the supervision of my supervisory committee. I wrote all chapters of this thesis as partial fulfillment of requirements for the Master of Science degree in Epidemiology and Biostatistics. Feedback was incorporated from Drs. Garcia-Bournissen, Campbell and Gagnier and, where appropriate, others as cited below.

Literature Review presents a detailed literature review regarding PTSD: its prevalence, risk factors, sex and gender differences, effects on pregnancy and birth outcomes, assessment Tools, and PTSD Treatment. Available information on prazosin safety and prazosin safety in pregnancy is also reviewed. **Post-Traumatic Stress Disorder and Pregnancy Outcomes: A Systematic Review, Meta- Analysis and GRADE Assessment** presents a systematic review, meta-analysis and GRADE assessment of prior literature examining associations between maternal PTSD and pregnancy, obstetric and neonatal outcomes. A

version of this chapter will be submitted to a peer-reviewed journal with authors: Natalie M. Zitoun, M. Karen Campbell, Joel Gagnier, Yasaman Mohamadi-Kamalabadi and Facundo Garcia Bournissen. This study was conceptualized under the advice of my supervisory committee. I conducted the scoping search for the systematic review using, screened the studies, extracted data, performed, and interpreted the results of the meta-analysis and conducted two GRADE assessments. Yasaman Mohammadi was a secondary reviewer of the studies. Drs. Garcia, Campbell and Gagnier provided advice and feedback during the conduct of the study. Feedback on the written manuscript was sought, and incorporated, from Yasaman Mohammadi and the members of the supervisory committee (Drs. Garcia Campbell, and Gagnier). **Prospective Evaluation of Pregnancy Outcomes after Gestational Exposure to Prazosin** presents an observational study describing the fetal and pregnancy outcomes in a small sample of women with prazosin exposures in early Pregnancy. A version of this manuscript is currently undergoing peer review with authors: Natalie M. Zitoun, M. Karen Campbell, Doreen Matsui and Facundo Garcia Bournissen. The question arises from Dr. Garcia's research focus. Data sources included hospital chart data from LHSC as well as information from telephone interviews. In collaboration with Drs. Garcia and Campbell, I created the variables we would be recording as well as developed questions for the telephone questionnaire conducted with these patients. Recording, storage, and assessment of this data, interpretation of results, and writing of the findings was conducted with feedback from Drs. Garcia and Campbell as well as with Dr. Doreen Matsui. **Summary, Conceptualization and Conclusion** integrates findings from these two integrated articles and concludes this thesis.

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Chapter 2

2 Literature Review

2.1 Post-Traumatic Stress Disorder: Background and Diagnostic Definitions

Post-Traumatic Stress Disorder (PSTD) is a psychiatric condition that most frequently results from exposure to severe stressors or traumatic events. (1). PTSD became recognized as an official diagnosis in 1980 via its addition to the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) (2). Although officially recognized as an official mental health diagnosis in 1980, PTSD has been described under different terms such as "shell-shock", or "battle fatigue" in various medical & general literature for centuries, and its presence in literature dates as far as 4000 BC and can therefore, be thought of as a timeless condition (3). Although trauma exposure is required to develop PTSD, and is, therefore, a necessary cause (4) in PTSD, it is not a sufficient cause as this complex disorder is caused by a combination of neurological, psychological, environmental, social and genetic factors. Therefore, the combination of these various factors alongside trauma exposure makes up the causal pie i.e., the sufficient cause, in the causal pathway for developing PTSD (5,6).

Because the indication and etiology are complex, PTSD, and its definition, have been a topic of controversy since its introduction as an official psychiatric illness in the DSM-III (2). Since the release of the DSM-III, various revisions have been made: the DSM IV (DSM-4) in 1995; and the DSM V (DSM-5) in 2013, which is the current version of the DSM that is currently used (7). With each revision of the DSM, the criteria for PTSD have changed considerably (8). Unlike the DSM-4, which places PTSD in the anxiety disorder category, the DSM-5 has PTSD placed in a new diagnostic category named "Trauma and Stressor-related Disorders" which recognizes that the focus of PTSD relates to traumatic events (9). The DSM-5 looks at PTSD in the context of 5 clusters of characteristics: A) stressor; B) intrusion; C) symptoms; D) avoidance, negative alterations in cognitions and mood; and E) alterations in arousal and reactivity. To meet the diagnostic criteria for PTSD according to the DSM-5, these criteria

must last for a minimum of a month, must cause distress or functional impairment, and cannot be a result of medication use, substance abuse or any other illness (10)

The second major diagnostic definition is the World Health Organization's International Classification of Diseases (ICD). The ICD usually adopts a simpler approach to psychiatric diagnoses than the DSM to have less of a burden on diagnosticians in poorly resourced settings, who often cannot assign lengthy assessments for their patients (11). A central aspect of the ICD-11 diagnostic definition is re-experiencing memories of the previous trauma or stressor in the present time (12). Additionally, the ICD-11 has a subcategory of PTSD termed complex PTSD, which is a new disorder that describes the more complex reactions that are usually experienced by individuals exposed to chronic trauma stressors. The addition of complex PTSD as distinctively from PTSD in the ICD-11 is in the anticipation of providing enhanced precision when providing a diagnosis in populations that are a greater likelihood of being exposed to chronic trauma (13).

2.2 PTSD Risk Factors

Risk factors associated with the development of PTSD can be grouped as sociodemographic, pretrauamatic, peritraumatic and posttraumatic factors. Sociodemographic factors, include the demographic characteristics of individuals that are associated with an increased likelihood of experiencing PTSD (14). Pretraumatic risk factors include risk factors associated with cognitive characteristics, neurological characteristics, or other relevant health characteristics that can predispose one in developing PTSD after trauma exposure. (15). Peritraumatic risk factors include how one perceives the trauma and how it is experienced by the individual on a cognitive level as well as on a biological level in terms of the one stress response (16,17). Finally, posttraumatic risk factors reflect the long-standing response to trauma exposure and include factors like one's perception of an ongoing threat to their safety (18,19). An umbrella review conducted by Tortella-Feliu et al. (2019) remains to be the biggest conceptualization of evidence to date of suggested risk factors for PTSD (20) and includes thirty-three systematic reviews and meta-analyses. In this umbrella review, the evidence between the four categories of risk factors and PTSD is placed into four classes: Class I (convincing), Class II (highly suggestive), Class III (suggestive), and Class IV (Weak). When looking at sociodemographic risk factors for PTSD, the umbrella review found that Being Indigenous had Class I evidence

(convincing), and being a female had Class II (highly suggestive) evidence for being a risk factor for PTSD. The risk factor evidence found for being a female will be discussed further in Section 2.4 of this literature review. When exploring pre-traumatic risk factors, this umbrella review found that a history of the disease, including chronic or other major physical illness as well as a family history of previous psychiatric disorder, revealed class I (convincing) evidence for being associated with pre-trauma risk factors in developing PTSD. Additionally, the umbrella review found that a history of any previous psychiatric disorder revealed Class III (suggestive) evidence of being a risk factor for PTSD. When exploring peritraumatic risk factors, the umbrella review showed that severity and being trapped during an earthquake, as well as exposure to potentially traumatic experiences, showed class II (highly suggestive) evidence for being a PTSD peritraumatic risk factor. Moreover, this review found that torture among survivors of war or mass violence showed class III (suggestive) evidence of being a risk factor for PTSD. Regarding posttraumatic factors, the umbrella review found Class IV (weak evidence) in any potential posttraumatic risk factors, this included symptoms of anxiety, avoidance, and depression.

2.3 PTSD Prevalence

When exploring the worldwide prevalence of PTSD, comprehensive population-based cross-national studies on the epidemiology prevalence of PTSD have revealed that the cross-national lifetime prevalence is estimated to be around 3.9% in total samples (21). Interestingly, World Mental Health Surveys have observed higher 12-month prevalence rates in high-income countries such as the U.S. and Canada than in low- and middle-income countries (22). According to the National Comorbidity Survey Replication (NCS-R), which is one of the largest epidemiological studies of mental disorders conducted in the United States general population, the lifetime prevalence of PTSD in adults is estimated to be 6.8% and the annual prevalence is estimated at to be 3.5% in the US general population (23,24). Other studies have shown similar estimates for the U.S. and Canada that range between 6.1-9.2% in Canada and U.S., with one-year prevalence rates ranging between 3.5-4.7% (21,25–27). When looking specifically at Canada alone; Statistics Canada published a report from a 2021 Survey on Mental Health and Stressful Events, (Record #5341) indicating that 5% of Canadians reported having a PTSD diagnosis by a health professional and 8% of Canadians met the criteria of

having probable PTSD-based symptoms when looking at symptoms they experienced in the past month (28).

2.4 PTSD Sex Differences

There are sex and gender differences in PTSD prevalence. For this review, we note that most studies report differences about biological sex as opposed to gender and acknowledge that our reference to women is in reference to literature that exists on biological sex due to the limitations in studies that do not fully encompass gender differences and primarily refer to women on the basis sex and not gender. Studies have shown that the prevalence of PTSD is higher in females than in males. These findings are consistent, as most studies and reports show that women disproportionately have higher rates of (PTSD) and experience greater symptom severity and chronicity when compared to males (29). When exploring general populations, it is estimated that females have a least two to three times a higher risk of developing PTSD when compared to males (30–33). In the U.S., the NCS-R revealed that the past year's prevalence of PTSD among adults was higher for females (5.2%) than for males (1.8%) (23). When looking at PTSD prevalence in Canada based on sex, statistics in Canada revealed that 10% of females met the criteria for probable PTSD, which is almost twice as high as males (6%) (28). Research supports that a higher risk of PTSD in females is not the product of error or bias or reporting bias but is a result of sex differences. As mentioned in section 2.2, due to consistent findings of higher PTSD prevalence in females than males. Being female is considered to be a demographic risk factor for developing PTSD. Studies have further investigated the increased risk of PTSD and being a female and some studies have postulated the mediation hypothesis: which suggests that sex differences in PTSD are related to sex differences in other associated risk factors (30). Although the exact reasons and mechanisms are still not fully understood, studies have shown that males and females respond to trauma differently (34). Furthermore, multi-variable mediation models conducted have also revealed that the combination of PTSD risk factors does appear to mediate the association between sex

and PTSD, suggesting that females report more PTSD symptoms because they experience higher levels of associated PTSD risk factors. (35)

2.5 PTSD in Pregnant Women & Adverse Birth Outcomes

The increased risk of PTSD in females becomes a further concern when looking at pregnant populations. Studies have shown that PTSD might contribute to adverse pregnancy and birth outcomes. The full mechanism by which this happens is still not fully known. Some studies have suggested that the association between adverse pregnancy and birth outcomes in mothers with PTSD is a result of direct physiological associations (36,37). Other studies have shown that these adverse outcomes may be a result of mothers with PTSD engaging in riskier behaviours such as smoking, substance use, alcohol consumption or other high-risk factors such as poor eating habits, excessive weight gain, and lack of prenatal care (38,39). Despite the significance of this issue and the growing body of literature on antenatal PTSD and adverse pregnancy and birth outcomes, there is still a lack of comprehensive reviews and analyses and assessments on this topic. This gap will be addressed in **Post-Traumatic Stress** Disorder and Pregnancy Outcomes: A Systematic Review, Meta- Analysis and GRADE Assessment: which is a systematic review, meta-analysis and GRADE assessment that investigates the association of maternal PTSD exposure and fifteen outcomes among 40 studies.

2.6 PTSD Assessment Tools

PTSD assessment requires a comprehensive evaluation of an individual's trauma history, presenting symptoms and other relevant features. Various assessment tools can be utilized to assess PTSD including self-report measures, clinical interviews, and even neurological or physiological equipment.

Clinical interviews, normally conducted by trained healthcare professionals involve asking the patient about their symptoms, history of trauma and other applicable features. The interviews are conducted and scored using scales such as the Clinician-Administered PTSD Scale (CAPS), the PTSD Symptom Scale Interview (PSS-I and PSS-I-5), the Structured Clinical Interview; PTSD Module (SCID PTSD Module), the Structured Interview for PTSD (SIP or SI-PTSD) and the Treatment-Outcome Posttraumatic Stress Disorder Scale. The Clinician-

Administered PTSD Scale (CAPS) is considered the gold standard interview method for assessing PTSD symptoms in clinical trials and is the clinical interview assessment method used to assess PTSD (40). It consists of 30 items and was created by the U.S. Department of Veterans Affairs National Center for PTSD staff. The CAPS can be used to give PTSD diagnosis, assess symptoms of PTSD and help determine lifetime diagnosis. It can be administered generally around 30 minutes to 60 minutes (41). The CAPS has been shown to have good sensitivity (94.4%-98.2%), specificity (91.7%-92.8%), and interrater reliability, (κ = 0.86-0.91,) for both men and women (42). All in all, the CAPS has proven itself to be an exceptional assessment tool that is extensively validated. (43).

Self-report tools are also utilized in assessing PTSD. Self-report measures require the individual to assess their symptoms and score or rate the severity of their symptoms in a standardized questionnaire (44). These self-report tools include the PTSD Checklist (PCL), the Impact of Event Scale (IES), the Davidson Trauma Scale (DTS), the Mississippi Scale for Combat-related PTSD (MISS or M-PTSD), the Modified PTSD Symptom Scale (MPSS-SR), TSD Symptom Scale Self-Report Version (PSS-SR), Short PTSD Rating Interview (SPRINT). The most common self-report measure utilized to assess PTSD is the PCL (45). The PCL consists of 20 items and was developed by the VA National Center for PTSD. It is typically used to screen individuals for PTSD diagnosis, it can also be used to monitor symptom changes during and after treatment (46,47). The PCL has been shown to have good reliability and validity, making it an effective tool in assessing PTSD (48).

Although not as frequently utilized as self-report measures or structured interviews, in some cases, neurological or physiological equipment can also be utilized to assess PTSD. Such methods include electrocardiograms (ECGs), Galvanic Skin Response (GSR) Appliances, Magnetic Resonance Imaging (MRI) or Functional Magnetic Resonance Imaging (fMRI) (49–51).

Every tool comes with its assets and flaws. Therefore, the choice of which tool to use depends on the specific needs of the health care provider or investigator. It is essential to utilize

appropriate assessment tools when diagnosing PTSD to ensure accuracy in PTSD diagnosis and subsequent treatment.

2.7 PTSD Treatment

Once PTSD is assessed and diagnosed, it can be managed or treated with psychological treatment and/or pharmacological interventions. (11) The main psychological treatments utilized for PTSD are Trauma-focused Psychological Therapies (TFPTs). One form of TFPTs is Trauma Focused Cognitive Behavior Therapy (TF-CBT) which is suggested in most treatment guidelines and concerned to be the first-line treatment for PTSD. (52) CBT/TF-CBT has been shown to be effective in PTSD treatment and has been well-documented in reducing PTSD symptoms (53–55). Other common TFPTs include eye movement desensitization and reprocessing (EMDR) and Exposure therapy. Both of these therapies also display empirical evidence for alleviating PTSD (56) (57). Although TFPTs exhibit a high amount of empirical evidence for PTSD treatment, they do have limitations (54). Firstly, clinical trials of TFPT have shown to have high dropout rates (58). Secondly, TFPTs appear to be non-effective in approximately half of the patients who can tolerate it (58). When looking at TF-CBT treatment specifically, which is considered to be the first line of treatment for PTSD, only about two-thirds of individuals appear to respond effectively to this intervention (59). Studies have also shown that those with higher PTSD severity are more likely to have poorer responses to TFPT's (60). Another limitation is lack of access as waiting lines for TFPTs continue to increase. The lack of access is especially concerning in areas of the world that do not have the ability or resources to do these therapies. (61). The limitations in TFPTs alone have highlighted the need for healthcare professionals to supplement treatment with pharmacological interventions and have applied guidelines for healthcare professionals to use TFPTs, as a first treatment option, and pharmacological treatment as an addition to the psychological treatment or as a second option (62).

The first-line pharmacological treatments recommended for PTSD are antidepressant medications and more specifically selective serotonin reuptake inhibitors (SSRIs) (63). In Alternate drug types, including benzodiazepines, anticonvulsants, atypical antipsychotics, and adrenergic inciting agents have also shown effectiveness in treating PTSD and have been used in pharmacological interventions (64). Specific drugs that have shown the strongest evidence

in PTSD pharmacotherapy include fluoxetine, paroxetine, sertraline, venlafaxine, risperidone and prazosin. (65).

Over recent years, many studies have shown that prazosin is effective in treating symptoms of PTSD. Additionally, prazosin in particular consistently shows positive results for reducing nightmares and hyperarousal associated with PTSD, which are PTSD-associated symptoms that are often present in individuals that are more often treatment-resistant (66,67).

2.8 Prazosin Safety & Efficacy

Prazosin has FDA approval in treating hypertension (on-label use), but is currently prescribed for off-label use in the PTSD management (68). Because prazosin is an alpha1-antagonist it acts by reducing CNS activation through its antagonistic effect on alpha 1 receptor. Through this mechanism, it is proposed that prazosin reduces REM sleep disintegration which in this improves sleep, reducing PTSD-associated nightmares and diminishing dysfunctional fear habituation (69). The safety and efficacy of prazosin for treating PTSD have been documented in general populations. For example, a study conducted by Hudson et al. (2012) concluded that prazosin had good clinical efficacy and was found to be safe in relieving PTSD-associated nightmares (70) Furthermore, a meta-analysis of six studies concluded that prazosin was well tolerated and showed no significant sustained effect on blood pressure, which was originally a potential cause of concern given its primary use in treating hypertension (71).

2.9 Prazosin Safety in Pregnancy

Even though research shows that pregnancy drug safety cannot be inferred reliably through animal studies or non-pregnant patient information due to the physiological differences that exist in pregnant humans (72,73), there remains to be a severe under-representation of pregnant women in drug safety trials. Thus, the scarcity of adequate drug safety information in pregnancy continues to be an on-going issue for health-care providers (74,75). This is exemplified by the lack of safety information regarding prazosin use during pregnancy. prazosin is a pregnancy category C drug, which states that risk cannot be ruled out (76). There is very little literature on prazosin safety in pregnancy. One small systematic review exists on the topic, and it specifically evaluates its use in the third trimester. However, this review did not include any reports on prazosin use in pregnancy for PTSD specifically, and the review

concluded that it is best to avoid prazosin information purely due to a lack of safety information (77). The lack of information means that healthcare providers are unable to fully advise pregnant patients who suffer from PTSD on the potential risk prazosin may have on them or their fetuses. This limits such patients from having a pharmacology option that has been well-documented as being effective in alleviating PTSD (66). This will be addressed further in **Chapter 4**.

2.10 Literature Gaps to be addressed in this Thesis

Although various studies show that women are at higher risk of developing PTSD and many studies reveal that PTSD can have adverse birth and health outcomes, there is still a lack of comprehensive reviews to summarize and evaluate evidence related to PTSD exposure and adverse birth outcomes. Therefore, this thesis aims to conduct a comprehensive review, analysis and assessment of maternal PTSD exposure and adverse birth outcomes to provide important evidence that will help guide healthcare professionals and officials. Secondly, even though many studies have shown that prazosin is effective in treating PTSD and has a tolerable safety profile in general populations, very little to no research has been conducted on the safety of prazosin use for PTSD during pregnancy. This thesis aims to provide more data regarding fetal and pregnancy outcomes associated with prazosin exposures in early Pregnancy. Thus this thesis strives to improve overall care for pregnant patients with PTSD by accomplishing these objectives.

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Chapter 3

3 Post-Traumatic Stress Disorder and Pregnancy Outcomes: A Systematic Review, Meta- Analysis and GRADE Assessment

3.1 Abstract

Introduction: Post-Traumatic Stress Disorder (PTSD) is a prevalent and typically debilitating psychiatric syndrome. The prevalence of PTSD in pregnant populations is comparable to general populations. PTSD experienced in pregnant pregnancy may be an important underlying mechanism in pregnancy complications or adverse neonatal outcomes. **Objective:** The goal of this study is to review, meta-analyze & GRADE the quality of evidence for studies that evaluate associations between perinatal PTSD and pregnancy outcomes. **Methods:** A literature search was implemented using the following databases: Google Scholar, PubMed, and EMBASE. The overall quality of evidence across included papers using the GRADE guidelines. Meta-analysis was conducted using statistical R version 3.6.2**. Results:** 40 studies were included in the review: 27 prospective cohort studies, 5 retrospective cohort studies, 4 cross-sectional studies, and 4 case-control studies, including in total 157,708 pregnancies. Out of these, 11,750 had PTSD symptomatology. Associations were found between maternal PTSD with reduced infant head circumference, infant sleeping & eating difficulties, reduced breastfeeding, & lower infant salivary cortisol levels. There is conflicting literature regarding an association between PTSD and low birthweight (LBW) and preterm birth (PTB). Our meta-analyses of studies for which data were available revealed a pooled OR of (OR, 2.05; 95%CI: [1.27, 3.33]) with LBW and a pooled OR of 1.23; 95%CI: [1.11, 1.37]) with PTB. GRADE analysis revealed a low-quality of evidence for LBW and PTB. **Discussion & Conclusion:** Our findings reveal evidence that PTSD in pregnancy is associated with some adverse outcomes. Additional studies, including studies of whether treatment during pregnancy could improve adverse birth outcomes, are needed to draw more definitive conclusions.

3.2 Introduction

Posttraumatic stress disorder (PTSD) is a well-recognized chronic clinical disorder that most often occurs as a response to severe stressors or traumatic events. PTSD is a prevalent and typically debilitating psychiatric syndrome with that can cause significant functional disturbances in one's life (1). According to the DSM-5, PTSD consists of 5 sets of the following symptom clusters: stressor, intrusion symptoms, avoidance, negative alterations in cognitions and mood, & alterations in arousal and reactivity (2). To meet the DSM-5 criteria for PTSD, these symptoms must have lasted for at least one month, cause distress or functional impairment & cannot be due to medication, substance abuse or any other illness (2).

Pregnant women can have PTSD in the prenatal period which is defined as the fetus' developmental period between conception and birth (3), as well as the postnatal period after delivery. The perinatal period is the period before and after delivery, however in the study of maternal PTSD some authors look more broadly at the period which extends from when pregnancy begins up to one year following childbirth (4). Studies estimated that the mean prevalence of PTSD in pregnant women is around 3.3% (5). Recently, even higher PTSD prevalence estimates have been reported in the literature. One such study includes the Padin et al. (2022) study, which found that 11.1% of pregnant patients screened positive for PTSD (6). PTSD experienced in pregnant populations may pose additional risks in pregnancy and be an important underlying mechanism in pregnancy complications and adverse birth outcomes.

Poorer outcomes could indirectly result from associated harmful or risky behaviours as women with PTSD may have an increased risk of engaging in high-risk health behaviours (7). Direct pathways leading from PTSD to poorer outcomes might include direct physiological associations via neural pathways and other signaling cascades (8). Despite this, there is limited studies that explores PTSD in pregnancy and pregnancy, obstetric, or neonatal outcomes. A study that did explore PTSD in pregnancy was a systematic review conducted by Cook et al. (2018), which reviewed 21 studies and had a particular focus on postpartum PTSD. This review concluded that there was evidence suggesting an association between maternal PTSD and low birthweight (LBW) and reduced breastfeeding frequency. Inconclusive results were found for associations between maternal PTSD with preterm birth (PTB), fetal growth, head circumference, mother-infant interaction, mother-infant relationship, or child development (9).

One recent meta-analysis conducted by Sanjuan et al. (2021) found that amongst 16 studies, maternal prenatal PTSD was associated with a higher risk of low birthweight (LBW) as well as preterm birth (PTB) (10).

There is a lack of consistency in these recent findings and an absence of comprehensive reviews or meta-analyses conducted on the birth outcomes of perinatal PTSD. Such a review would allow the summary of many studies and many birth outcomes while exploring quality of evidence of the studies. Therefore, this present study aims to systematically review, meta-analyze and GRADE the quality of evidence for studies that evaluate associations between perinatal PTSD and pregnancy, obstetric and neonatal outcomes.

3.3 Methods

The protocol for this systematic review and meta-analysis is registered with the International Prospective Register of Systematic Reviews, PROSPERO (ID: (CRD42022358818). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to frame this systematic review and meta-analysis (11) this checklist is provided in **Figure 3.1 PRISMA Diagram of Study Identification and Selection**

Appendix A: PRISMA Checklist

3.3.1 Literature search

Studies were identified by searching the following databases: Google Scholar, PubMed, and EMBASE to identify relevant keywords contained in the title, abstract, and body of the articles. Keywords were identified in this way, synonyms used in each respective database were also utilized in a comprehensive literature search. The initial search terms were 'Post-Traumatic Stress Disorder', 'Trauma', 'PTSD', 'pregnancy outcomes, 'pregnancy', and 'birth outcomes' A comprehensive search was applied by utilizing Medical Subject Headings (MeSH terms) to encompass all possible synonyms in the initial search. The search was restricted to English language but wasn't limited to any specific period. Forward citation was also implemented to identify any articles missed from database searching. The search strategy for these databases is provided in **Appendix B: Search Strategy.**

3.3.2 Inclusion & Exclusion Criteria

Inclusion criteria were the following: the participants had to be human subjects who had PTSD while they were pregnant and subsequently gave birth; if there were comparison groups, the comparison groups had to be healthy pregnant participants without PTSD; the exposure had to be PTSD, or other classifications indicative of PTSD (trauma, night terror cases caused by trauma, hysteria in older studies); and finally, the outcome had to be pregnancy outcomes which were measured through the following variables: low birthweight (LBW), preterm birth (PTB), gestational age (GA), amount of breastfeeding, pre-eclampsia, gestational diabetes, mother-infant interaction, infant head circumference, infant development, infant temperament, and infant cortisol production. A meta-analysis was conducted for the association between maternal PTSD and: LBW, gestational age, and PTB.

3.3.3 Study Selection

Two reviewers (NZ and YMK) screened articles in each database against the inclusion criteria. Discrepancies between reviewers regarding study selection were resolved during the review

stage. The initial search terms produced 409 articles: 200 from PubMed, 167 from Google Scholar and 42 from EMBASE Fifty-seven duplicates were removed, and the 352 remaining articles were screened for according to the inclusion criteria. Forward citation searching lead to the identification of an additional 17 articles, resulting in a total of 369 articles. These articles went through title and abstract screening, which then resulted in 51 articles undergoing full-text review, 40 of the articles were found to be eligible for data extraction (**Figure 3.1).**

3.3.4 Risk of Bias Assessment

To ascertain the validity of the included studies, the risk of bias was assessed by "Tool to Assess Risk of Bias in Case-Control studies", "Tool to Assess Risk of Bias in Cross-Sectional studies" and "Tool to Assess Risk of Bias in Case-Control studies". These tools were devised by the CLARITY Group at McMaster University (12–14) and comprises a set of questions for each appropriate study design, each of these question sets addresses a different type of bias and has four possible answers: Definitely yes (low risk of bias); Probably yes, Probably no, and Definitely no (high risk of bias). According to the answers to each question, the studies were assigned to high, moderate, or low risk of bias. The risk of bias assessment was performed independently by two authors (NZ and YMK).

3.3.5 Meta-Analysis

The meta-analyses were conducted using statistical R version 3.6.2 using the "metafor" package. Studies were qualified for pooling in meta-analyses if point estimates of odds ratio were provided or if enough information was provided to be able to calculate odds ratios. A random effects model was to estimate the pooled odds ratios (OR) and their 95% confidence intervals (CI). Estimates from the most fully adjusted model were used. Meta-analyses were conducted for the following outcomes: LBW (defined as birth weight <2500g), gestational age and PTB (defined as <37 completed weeks gestation). The heterogeneity between the study findings was assessed using the Cochran's Q test at $p < 0.05$ and calculating I2 values, with I2 values 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively

(15). For the studies that looked at LBW, sensitivity analysis was done using a mixed-effects model for both LBW and PTB outcomes to see the influence of study design, PTSD assessment tool and country in which the study was conducted in, the codes for these analyses can be found in **Appendix E: Codes for Analyses**

3.3.6 Quality Assessment: Grading the evidence (GRADE)

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for systematic reviews and implemented using GRADE Pro GDT software (http://tech.cochrane.org/gradepro) to determine the quality of the overall evidence for the two outcomes analyzed : LBW and PTB. GRADE consists of the following domains (risk of bias, inconsistency, indirectness, imprecision and publication bias) to rate the quality of evidence as high, moderate, low or very low (16) .This assessment was performed by two authors (NZ and YMK).

3.4 Results

3.4.1 Study Characteristics:

A total of 40 studies of various study designs were included in the review: 27 prospective cohort studies, 5 retrospective cohort studies, 4 cross-sectional studies, and 4 case-control studies. The studies enrolled participants from a range of different countries including the USA (n= 23), the United Kingdom (UK) (n = 7), Canada (n=1), Brazil (n=1), Peru (n=1), South Africa (n=2), Pakistan (n=1) , Israel (n=1), Switzerland (n=2) and Italy (n=1). The total number of pregnancies included for analysis was 157,708 across the 40 studies. Out of these 157,708 pregnant participants, 11750 had PTSD symptomology. It is worth noting that six papers did not report the prevalence of PTSD (17–22). The studies included were published between 2001-2022. Across all these studies the mean age of participants ranged between 23.3 years to 33 years old. The studies varied in which tools they used to assess maternal PTSD or Trauma and varied in the tools they used to assess outcomes. A summary the study designs used, country of origin, age, number of participants with PTSD in each study as well as the

statistical test used for each study is **Table** 3-1 (n=40). Summary tables of what tools and outcomes each study used is also provided in **Table** 3-1**.**

3.4.2 Outcomes

Outcomes studied included LBW, PTB, gestational age, mother-infant interaction, infant development, infant cognition, infant negative affectivity, head circumference, infant temperament, breastfeeding duration and sleeping and eating patterns in infants. Obstetric complications included gestational diabetes, and preeclampsia. Most studies looked at multiple infant outcomes simultaneously. The most common outcomes studied were infant LBW (n=15), PTB (n= 14), Gestational age (9) and mother-infant interaction (n= 10) . Fewer studies looked at obstetric complications (n= 5), head circumference (n=3), infant temperament (n=2), infant negative affectivity (n= 2), breast-feeding behaviour (n=2) infant development (n=1), infant cognition (n=3), as well as sleeping and eating patterns in infants (n=1). Summary for each outcome sub-category is provided in **Appendix C** : Main Findings for Subcategories

3.4.3 Low Birthweight (LBW)

Evidence for a relationship between PTSD exposure during pregnancy and low infant birthweight was inconsistent among the 15 studies. The study characteristics and main findings related to infant LBW are displayed in **Table C1**: Main Findings for Low Birthweight (n=15)**.** A total of seven studies found that maternal PTSD was positively associated with LBW (n = 8), (23–28, 30). Contrary to these seven studies, eight (n=8) studies found no statistically significant association between maternal PTSD and low infant birth weight (7, 29, 31–36).

3.4.4 Gestational Age (GA)

Evidence for a relationship between PTSD exposure during pregnancy and gestational age was inconsistent (n =9). **Table C2** presents the findings for all nine studies. One study found that maternal PTSD was associated with reduced gestational age (37) . The remaining eight (n=8) studies found no association between antenatal PTSD and gestational age (31–36,38).

3.4.5 Preterm Birth (PTB)

Evidence for a relationship between PTSD exposure during pregnancy and infant PTB was inconsistent among the 14 studies which considered this dichotomous outcome. Seven of these studies were among the nine studies assessing GA as a continuous variable (n=7) (25,33–38). The findings for the 14 studies are presented in **Table C3**. Six out of these fourteen studies (n=6) found that maternal PTSD was associated with PTB (25,33,34,37,39,40). The remaining eight studies (n=8) found no association between antenatal PTSD and PTB (7,28,29,35,36,38,41,42).

3.4.6 Mother-Infant Interaction

Evidence for a relationship between perinatal PTSD and mother infant-interaction was inconsistent among 12 studies. The findings for these 12 studies are presented in **Table C4.** For two of these studies (n=2), breastfeeding duration was included as a sub-category of mother-infant interaction. Eight of these twelve studies (n=8) found that maternal PTSD was associated with hindered mother-infant interaction (20,30,43–48).

3.4.7 Mother Infant Interaction: Breastfeeding Duration

When looking at breastfeeding as a sub-category of mother-infant interaction, there was some evidence for an association between PTSD exposure during pregnancy and reduced breastfeeding as all the studies (n=2) that examined breastfeeding behaviour found that maternal PTSD led to reduced breastfeeding in infants (43,45) **(Table C4).**

3.4.8 Infant & Neonatal Complications

Evidence for a relationship between perinatal PTSD and neonatal complications was inconsistent in the 9 studies (n=9). The findings are summarized in **Table C5.** Infant

complications studied included: Infant negative affectivity (NA) (n=2); Infant temperament (n=2); Infant Cognition & Development (n=4); Infant Sleeping/Eating Behaviour (n=1); and Lower Infant Cortisol levels (n=1). Associations were found between maternal PTSD and infant & neonatal complications in five of these nine studies (n=5) (17,19,21,44,49). When looking at sleeping/eating behaviour and was some evidence that maternal PTSD was associated with sleeping and eating difficulties in premature infants. There was also some evidence that maternal PTSD was associated with lower infant cortisol levels (19,21).

3.4.9 Neonatal head Circumference

Three studies explored an association between PTSD exposure during pregnancy and neonatal head circumference. As presented in **Table C6**, all three studies found some degree of association between antenatal PTSD or symptoms of antenatal PTSD and reduced infant head circumference (32,34,42).

3.4.10 Obstetric Complications

Evidence for a relationship between PTSD exposure during pregnancy and obstetric complications was inconsistent in the five studies which studied this (n=5). The findings are presented in **Table C7**. Three of these five studies found associations of maternal PTSD with obstetric complications (22,50,51).

3.4.11 Overall Associations

Overall, the evidence in the papers reviewed supported an association between maternal PTSD with infant sleeping & eating difficulties, lower infant salivary cortisol levels, reduced breastfeeding, and reduced infant head circumference, this is highlighted in **Table C8**.

3.4.12 Risk of Bias

Figure 3.2 shows the findings from the risk of bias (RoB) assessment of the included case-control studies (n=4), **Figure 3.3** shows the findings from the risk of bias (RoB) assessment of the included cross-sectional studies (n=5) and **Figure 3.4** shows assessment of the included cohort studies (n=31). None of the studies included were found to have a certain low risk of bias in any domain across any study design tool. Two additional domains were implemented "not applicable," and "unclear." Not applicable was stated for the third question in the CLARITY assessment tool for cohort studies, "Can we be confident that the outcome of interest was not present at start of study?" due to the nature of the outcome being birth outcomes and therefore inapplicable in this scenario. A domain was marked "unclear" for a study if the related information was not clearly or well communicated by the authors. According to our assessments, the majority (n=3, 75%) of the case-control studies did not appropriately match or adjust for cases according to appropriate prognostic variables. Further assessment showed that all of the cross-sectional studies (n=4, 100%) did not have a representative source population. The Ayers et al. (2007) study also had an overall high risk of bias, as it had a high risk of bias in all five questions of the cross-sectional bias assessment (52). For the cohort studies, the majority of the studies (n=29, 91%) showed a higher intermediate risk of bias when assessing confidence in the assessment of the exposure, as PTSD being the exposure made studies subject to recall bias, and self-reported measures. Most of the cohort studies showed a low intermediate risk of bias in the following categories: appropriately selecting for exposed and unexposed cohorts from the same populations (n=20, 63%) assessing for the presence of prognostic factors as (n=30, 94%), and having similar co-interventions between groups (n=25, 78%).

3.4.13 Meta-Analysis and Heterogeneity

Pooled OR estimates from the mixed effects meta-analysis showed a statistically significant association between perinatal PTSD exposure and LBW (OR, 2.05; 95%CI: [1.27, 3.33]) across 10 of the included studies. There was high heterogeneity amongst these studies ($Q(df = 9) = 28.45$, $P < 0.05$, $I2 = 74.54\%$) (**Figure 3.5).** The meta-analysis also showed a statistically significant association between perinatal PTSD exposure and PTB OR, 1.23; 95%CI: [1.11, 1.37]) across 9 of the included studies. There was no heterogeneity amongst these studies (Q(df

= 8) = 8.98, p= 0.34, I2 =0%) (**Figure 3.6)**. Sensitivity analyses were conducted for both outcomes (LBW and PTB). The sensitivity analysis for LBW indicated that there was no significant residual heterogeneity, QE (df = 1) = 0.4065 (p-value =0.5237). In conducting a test of moderators, the analysis revealed there was significant heterogeneity between the moderators QM (df = 8) = 28.0447, (p<0.05). Further analysis revealed the study conducted in the country Pakistan has a significant effect on the LBW outcome (p=0.0021). The analysis also revealed that the study design of Case-Control (p=0.0315) and Prospective Cohort (p=0.0086) also had significant effects on the low-birth-weight outcome. These findings are further displayed in **Table D1** and **Figure 3.7.** The sensitivity analysis for PTB indicated that there was no significant residual heterogeneity in the model (p=0.4858). The test of moderators (QM) for PTB was also not statistically significant (p=0.2570). These findings are further displayed in **Table D2** and **Figure 3.8 Preterm Sensitivity Analysis Forest Plot (n=14)**

A GRADE assessment was conducted, revealed that these studies had overall low quality of evidence for birthweight and PTB. Among the greatest threats to the validity for both LBW and PTB outcome were bias due to most of these studies having an intermediate risk of bias, indirectness due to the studies using different PTSD assessment tools and different pregnant populations from differing sources, and imprecision (wide confidence intervals). Inconsistency was an additional threat to validity for the LBW outcome due to a high calculated heterogeneity score amongst these studies (>70%). Furthermore, the results revealed an adverse effect of PTSD in increasing the odds of LBW (OR= 2.05; 95% CI 1.27-3.33) among a total of 11798 participants **(Table** 3-2**)** And an adverse effect of PTSD increasing the occurrence of and PTB OR=1.23; 95% CI 1.11–1.37) among a total of 128533 participants **(Table** 3-3**).**

3.5 Discussion:

This systematic review, meta-analysis and GRADE assessment investigated the association of maternal PTSD exposure and the following outcomes: infant birthweight, PTB, gestational age, mother-infant interaction, infant development, infant cognition, obstetric complications, infant negative affectivity, gestational diabetes, preeclampsia, head circumference, infant temperament, breastfeeding duration and sleeping and infant eating patterns. This discussion will summarize the findings within the context of the potential consequences of maternal PTSD exposure and adverse pregnancy obstetric or neonatal outcomes. We have included a total of

40 studies, two meta-analyses and two GRADE assessments, to our knowledge, this is the first systematic review and analysis to integrate 40 studies that look at the 15 outcomes we have listed above while also incorporating a meta-analysis and GRADE assessment.

We note that at least one study in each pregnancy/birth outcome found an association between maternal PTSD and the outcome. We will further discuss each outcome below.

Shorter gestational period has been shown to have significantly adverse long-term effect on infants (20,53,54). Our findings for reduced GA outcome displayed that 1/9 (11%) studies that explored reduced GA outcome found an association between perinatal PTSD and reduced gestational age. When comparing our findings to those in the Cook et al. (2018) systematic review, our findings are comparable in the sense that we also concluded that evidence of reduced GA due to PTSD exposure was inconsistent, but that there were studies that showed an association between maternal PTSD and shorter gestational age. When further comparing our findings, it is worthy to note that our review on GA outcome summarized findings from nine studies whereas they summarized three studies exploring GA outcome (9). The Sanjuan et al. (2021) study also explored reduced GA outcomes and found that PTSD exposure was associated with shorter GA in their seven included studies. Taking this all together, this suggests that there is potential evidence for an association between maternal PTSD and shorter gestational age, however, more studies are required for a more conclusive statement.

Various studies have shown negative mother-infant interaction, or mothers reduced engagement with their children, is associated with a negative impact on their child's development and cognitive skills that can go very well into their child's adulthood (55–57). One form of mother-infant interaction is breastfeeding, and various studies have shown that reduced breastfeeding can have negative consequences for an infant, and in some cases even lead to morbidity when paired with inadequate use of formula (58). Our findings revealed that eight out of the twelve studies (67%) found an association between perinatal PTSD and reduced mother-infant interaction, in which a subcategory was breastfeeding duration. In comparing the findings to that of the Cook et al. (2018) review, the results of this study are aligned in that we also found miscellaneous results with the majority of the studies suggesting a negative association between PTSD and hindered mother-infant interaction (9). Our study summarized twelve studies for this outcome compared to their eleven. Furthermore, when looking at the

breastfeeding duration subcategory on its own, 100% (2/2) of the studies that explored this outcome reported an association between maternal PTSD and shorter breastfeeding duration, this also aligns with their studies findings, which had the same findings that suggested evidence for an association between maternal PTSD and shorter breast-feeding duration (9).

Infants with smaller head circumference are at risk for developmental delays, ophthalmologic disorders, audiological disorders, intellectual disorders or disability, and neurological disorders (59). We found that all three studies which examined the association of perinatal PTSD with smaller infant head circumference demonstrated an effect. In comparing our study to the Cook et al. (2018) review, our findings differed as they had reviewed only one of the three studies we reviewed (9) (32). Although they reported no association in the included Engel et al (2005) study, they did find that Post-Traumatic Symptom Symptomology (PTSS) was inversely associated with infant head circumference at birth. As per our inclusion criteria, PTSS was allowed to be assessed as an indicator of PTSD exposure, which could have caused the inclusion of cases not strictly diagnosed as PTSD (32). Although our wider inclusion margin may have led us to different results, it also exemplifies the limitation of restricting inclusion to strict PTSD diagnosis as exposure. It should also be noted that the diagnostic criteria for disorders such as PTSD are consistently being updated/revised, and there could be resulting temporal variation in whether specific mothers would have qualified for official PTSD diagnosis if studied later with the same symptoms (60).

Our findings revealed that six out of the nine studies (67%) had an association between maternal PTSD and postpartum neonatal & infant complications. In this outcome cluster, we considered studies with endpoints of infant negative affectivity (NA), infant temperament, infant cognition, infant development, infant sleeping/eating behaviour, and infant cortisol levels. The following text will further discuss the findings for neonatal and infant complications in each of their respective sub-categories.

Infant Negative Affectivity (NA) and more difficult infant temperament is correlated with later challenges including frustration, anxiety, job dissatisfaction, and somatic disorders (61). One of the two studies (50%) included in our review found a significant positive association between maternal stress and infant negative affectivity. One out of two studies of associations between maternal PTSD and infant temperament demonstrated that maternal PTSD was

associated with poorer infant temperament (44). The Cook et al. (2018) review did not explore infant NA or temperament as individual outcomes (9). There is sparse literature on maternal PTSD and infant NA. The preliminary evidence reported in our study highlights the need for more studies to explore this association.

Cognitive abilities are an important predictor of health, survival skills, academic performance, and overall health. In infancy, cognition shapes how an infant begins to see and understand the world around them (61,62). Our findings revealed that one of the three studies (33%) we included detected a moderate association between antenatal PTSD and poorer infant cognitive outcomes. Our results are comparable to Cook et al. (2018), as they include two of the three studies we summarized for infant cognition (17,30), but they did not include the MacGinty et al. (2020) study (42).

Eating and sleeping difficulties in infancy has been shown to have future health implications (63,64). The one study investigating this outcome found a that there was significantly more sleeping and eating difficulties in infants of mothers who had PTSD exposure (19). Our results are comparable to that of the Cook et al. (2018) review, which included the same study and concluded a similar finding (9).

Studies in infants have shown that cortisol deficiency can lead to serious health complications (65). The one study which investigated this outcome found that the salivary cortisol of infants was lower for infants who had mothers with antenatal PTSD (21). Our findings are comparable to the Cook et al. (2018) review, which included the same study and concluded a similar finding (9).

Obstetric complications in pregnancy have been shown to have serious as well as potentially life-threatening implications for both mothers and infants. (66–69). Our findings showed that three out of the five studies (60%) revealed a positive association between maternal PTSD and obstetric complications. The Cook et al. (2018) review included one of the same studies (50), but did not include the remaining four studies summarized in our review (9,22,31,38,51). This highlights why systematic reviews and analysis should be frequently updated considering new literature. The findings from our review considering recent literature demonstrate increasing evidence of an association between maternal PTSD and obstetric complications. We note that

although excessive fetal growth and birth defects are not obstetric complications, we included them as such in this review due to the methods of the Seng et al., (2001) study exploring obstetric complications as an outcome in which they included excessive fetal growth and birth defects as a sub-category (50).

Studies have shown that LBW infants have a higher risk of death and illness and other infants after birth (70–75). Eight of the fifteen studies (53%) investigating the association of perinatal PTSD and LBW observed an association. Seven of these were statistically significant associations. Our findings are comparable to those of the Cook et al. (2018) review which reported that about half of their included studies showed evidence for an association between maternal PTSD and infant LBW (9). Although they summarized nine of the studies we included (7,23,25,28–30,32,35), they did not include five others (24,26,27,33,36). This exemplifies why it is beneficial for multiple reviews to be conducted on similar research questions, as it increases the confidence of conclusions and fully encompasses the plethora of research results that may not be garnered by the search strategy in one systematic review alone.

Our meta-analysis of 10 of the 15 (67%) studies exploring LBW revealed mothers with PTSD exposure had more than two times the odds of delivering a LBW infant when compared to mothers without PTSD exposure. When comparing this analysis to the Sanjuan et al. (2021) analysis, our findings were comparable in that they also found that maternal PTSD versus no PTSD was associated with greater odds of LBW (10). The studies included in our analysis consisted of cohort studies and case-control studies. Because most studies report a prevalence's of under 10% for LBW and for and PTB in normal pregnant populations, the rare disease assumption can be utilized, thus allowing us to use the odds ratio as a proxy for risk ratio (77). Our sensitivity analysis showed that there was no significant heterogeneity, which suggested that the variation amongst the included studies was not significantly different from expected due to chance. However, our test of moderators indicated that there was significant heterogeneity among the moderators, which suggested that there were factors contributing to the variability between the studies that were not reported in our model. These moderators included place of study as Pakistan, being a case-control study, and being a prospective cohort study. GRADE analysis on PTSD exposure and LBW outcome revealed a low quality of evidence, meaning we cannot confidently conclude the results found between the increased

odds of LBW due to perinatal PTSD exposure. We note that only 10 out of the 15 studies included in the systematic review were able to be included in this analysis and therefore potential for bias cannot be over-ruled. We also note that we were unable to observe early PTB (<34 weeks) to see if a difference in effect due to the studies using standard definitions of PTB (<37 weeks). All of this should be considered when making decisions about how antenatal PTSD is associated with LBW infants.

Preterm infants have a higher risk of developing health complications (78). Six out of fourteen (43%) of the studies that examined this outcome found a positive association between perinatal PTSD and PTB. In comparing our findings to that of the Cook et al. (2018) review, our results are comparable in that half of their included studies (50%) showed evidence for an association between maternal PTSD and PTB. They had included six of the articles which we included (25,28,29,32,35,40). However, they did not include eight studies we had in our review (33,34,36–39,41,42), three of which revealed an association between maternal PTSD and low infant birthweight (34,37,39). This again illustrates the importance of conducting more than one systematic review on research questions of interest so clinical decisions can be more easily and confidently interpreted within the context of the search strategies and definitions imposed by various reviews.

Our meta-analysis of 9 of the 14 (64%) studies exploring PTB revealed there was a statistically significant increase in the odds of having a preterm baby for mothers with PTSD exposure. When comparing this analysis to the Sanjuan et al. (2021) analysis, our findings were comparable in that this study also found that maternal PTSD was associated with greater odds of PTB (10). Our sensitivity analysis revealed that there was no residual heterogeneity which suggested that the variation amongst the included studies was not significantly different from expected due to chance. We also found that there was no effect of moderators on the odds of PTB which suggested that effect sizes were stable across distinctive subgroups of studies. We do note that only nine studies were analyzed and that it has been shown that the risk of undetected heterogeneity is much higher when the number of studies to be meta-analyzed is small (79). GRADE analysis on perinatal PTSD and LBW outcome revealed a low quality of evidence, meaning we cannot confidently conclude the results found between the increased odds of PTB due to maternal PTSD exposure. We also note that only 9 out of the 14 total

studies included in the systematic review were able to be included in this analysis and the 14 studies yielded conflicting findings. All of this should be taken to account when interpreting how antenatal PTSD is associated with preterm birth.

3.5.1 Strengths & Limitations

This review and analysis were intended to gather and evaluate evidence to draw research and clinical conclusions. We believe that this is the first study to include a meta-analysis and GRADE assessment in a systematic review of maternal PTSD exposure and adverse pregnancy, obstetric, and neonatal outcomes. However, we also note the following limitations.

First, we note the limitation imposed by the available study designs. When conducting systematic reviews, meta-analyses and grading recommendations randomized controlled trials (RCTs) are the best study designs to include and therefore given the highest level because they are designed to be unbiased and have less risk of systematic errors (80). Due to the fact that, in this case, exposure is a psychiatric disorder (PTSD), then studies are observational by design. In observational studies it is not possible to control for all potential confounding variables that may influence the associations between PTSD exposure and birth outcomes. Even though many of the studies did attempt to adjust for potential confounding factors through statistical analysis, there is still a potential for residual confounding in these studies and therefore the potential for bias.

We also note a second limitation is the variation in the assessment of PTSD exposure in these studies. Various tools were utilized to assess PTSD and those will be differentially subject to measurement error and bias. The accuracy of the estimated association between PTSD and the key outcomes will be influenced by the accuracy of the assessment tool. Studies have shown that the PCL, PDS, and PTSDQ are the most validated measures for assessing PTSD symptoms (83–85). Although most studies used valid and reliable assessment tools some studies, such as the Ferri et al. (2007) study, used less valid measures such the Composite International Diagnostic Interview (CIDI), which has been shown to give a high number of false-negative cases (23,81).

A third limitation of our study is the differences in how studies reported outcomes, and how these outcomes were assessed. For instance, mother-infant interaction is often measured

qualitatively and therefore is more difficult to quantitively analyze. The variation in outcomes assessment among studies limited our ability to appropriately meta-analyze some outcomes. Furthermore, even amongst carefully defined outcomes, the outcome assessment tools will have varied. Fortunately, outcomes based on birthweight and gestational age will have had similar assessment properties from study-to-study and often were extracted from medical records. The differences in outcome measurement tools may have been have led to measurement errors in certain outcomes, which may have biased our results and reduced our precision. Studies that utilized self-reported measures of the birth outcome may have been subject to recall bias or social desirability bias, which may have led to over- or underestimation of the true birth outcome effects (82).

A fourth limitation arises from the sparsity of research on this topic, which led to our decision to include all studies we found regardless of sample sizes. The inclusion of smaller studies in our meta-analyses may have limited our summary estimates (83), as we noted imprecision and wide confidence intervals in both our meta-analyses, making it difficult to draw conclusions.

A fifth limitation is the risk of bias introduced into the meta-analyses for LBW and PTB outcome respectively. As we noted, 10 out of the 15 total studies examining LBW were included in the meta-analysis for LBW, in which 6 out of these 10 studies had a statistically significant association with PTSD and LBW in the review. We additionally noted that 9 out of the 14 total studies examining PTB were included for meta-analysis, in which 5 out of these 9 studies had a statistically significant association with PTSD and PTB in the review. These selective samples may have implicated or introduced a risk of bias in the meta-analyses.

3.5.2 Conclusion

The evidence revealed in our systematic review supported an association of maternal PTSD with reduced infant head circumference, infant sleeping & eating difficulties, reduced breastfeeding, and lower infant salivary cortisol levels. Findings regarding association between PTSD and increased risk of LBW and PTB were conflicting. However, meta-analyses of those studies for which data were available yielded an estimate of an association between maternal PTSD and an increased risk of infant LBW and PTB. Evidence for an association between maternal PTSD and reduced gestational age, as a continuous variable, was inconsistent as was

the evidence associated with poorer mother-infant interaction, infant negative affectivity, infant temperament, infant cognition and development and obstetric complications was inconsistent. The association between maternal PTSD and reduced infant salivary cortisol level and maternal PTSD and infant sleeping/eating difficulties were based on single studies, so more studies are needed before reaching conclusions for these two outcomes. This review and analysis further advance the understanding and comprehension of how maternal PTSD affects pregnancy, obstetric and neonatal outcomes. Based on our findings, we speculate that PTSD screening and treatment during pregnancy could potentially improve birth outcomes. However, our research also shows the dearth of consistent evidence in some areas and points to the need for further research with more studies characterized by larger sample sizes, and with high validity reliability and generalizability. Such further research is critical and necessary to draw more interpretable conclusions.

3.6 Tables and Figures

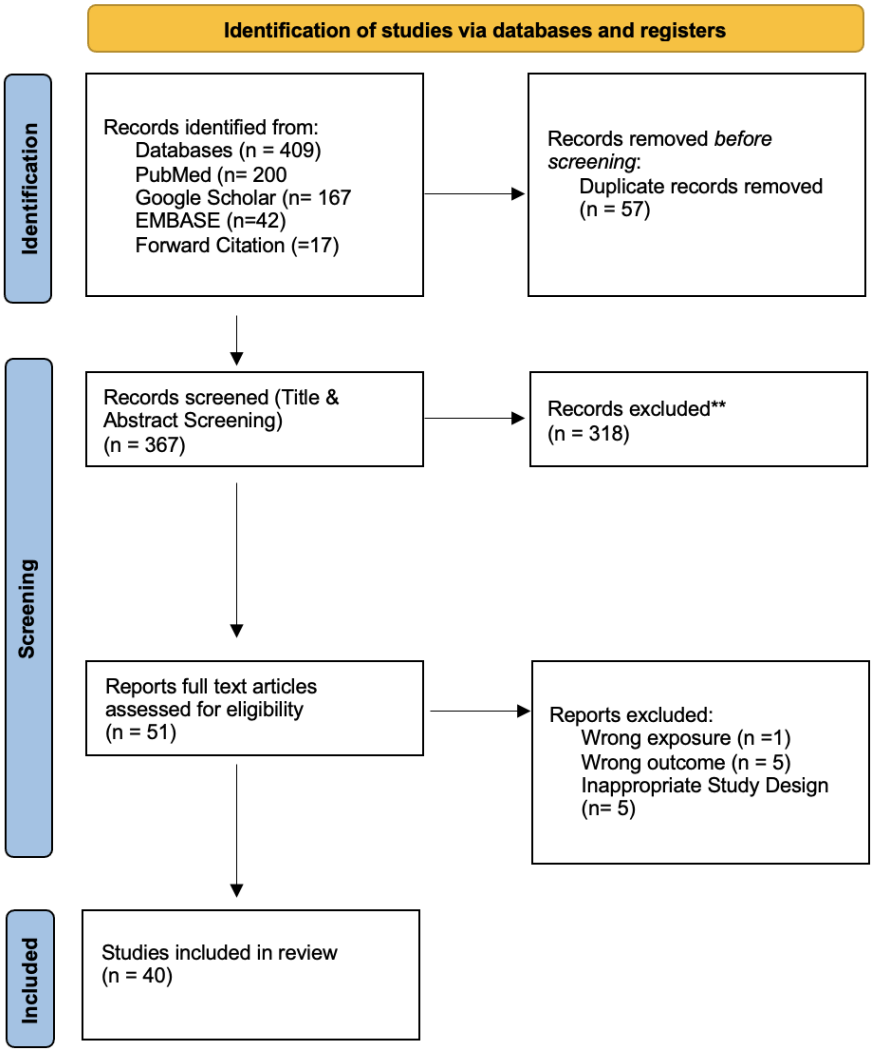

Figure 3.1 PRISMA Diagram of Study Identification and Selection

Table 3-1 Summary Table of Studies (n= 40)

Study	Study Design	Country	Age	Sample Size	N (%) PTSD	PTSD Tool Assessment	Birth Outcome Measurement Tool	Statistical Analysis/ Testing Method
Blackmore et al. (2016)	Prospective Cohort	USA	Mean Age 24.42 (SD= 3.74)	358	139 (38.8%)	DSM	Obstetric outcomes were defined according to standard definitions and maternal and infant case notes reviewed by a maternal fetal specialist (E.K.P.)	Pearson's $\chi 2$ analysis
Engel et al. (2005)	Prospective Cohort	USA	Age Range: 18+	54	4 (7%)	PCL	Medical Records	Multivariable linear regression

Ferri et al. (2007)	**Prospective Cohort**	**Brazil**	**Age Range: 16-19**	**912**	**91 (10%)**	**CIDI**	**Hospital Interviews**	**Prevalence Ratios**
Gelaye et al. (2020)	**Prospective Cohort**	**Peru**	**Mean Age: 27.9 years (SD = 6.1)**	**4408**	**1519 (34.4%)**	**PCL**	**Medical Records**	**beta coefficients (β) odds ratios (ORs) and 95% confidence intervals (CIs)**
Koen et al. (2016)	**Prospective Cohort**	**South Africa**	**Median= 29 years**	**544**	**108 (19.9%)**	**MINI**	**Medical Records**	**Regression Models**
Lipkind et al. (2010)	**Case Control**	**USA**	**Age Range : = 18 - ≥ 35)**	**446**	**61 (12%)**	**PCL**	**Medical Records**	**multiple regression analysis**

Maslow et al. (2016)	**Prospective Cohort**	**USA**	**Age Range : 15–49 years**	**3360**	**449(13.4%)**	**PCL**	**Medical Records**	**χ2 analysis, t tests, and generalized estimating equations (GEEs)**
Morland et al. (2007)	**Prospective Cohort**	**USA**	**Mean Age = 27 Years**	**101**	**16 (16%)**	**PCL**	**A labor-and-delivery checklist, medical records**	**Descriptive and bivariate statistical analysis, including χ2 tests**
Rashind et al. (2020)	**Case control**	**Pakistan**	**Age Range : = 20-≥ 35)**	**450**	**84(18.7%)**	**MINI**	**Medical Records**	**Logistic regression analysis and univariate analysis**
Rogal et al. (2007)	**Prospective Cohort**	**USA**	**Mean Age = 24.3 years (with PTSD)** **Mean Age=**	**1100**	**31 (3%)**	**MINI**	**Medical Records**	**χ2 test for two proportions**

			24.5 (no PTSD)					
Rosen et al. (2007)	Retrospective Cohort	USA	mean age = 25.9 years	148	38(25.7%)	University of Michigan Composite International Diagnostic Interview (UM-CIDI)	Medical Records	T tests and $\chi 2$ analysis
Seng et al. (2011)	Prospective Cohort	USA	Unknown	839	98 (12%)	National Women's Study PTSD Module	Medical Records	linear regression models
Weinreb et al. (2018)	Case control	USA	Mean age= 26.3 Case Mean Age= 29.4 control	149	68(45.6%)	Four-item Primary Care-PTSD Screen	Medical Records	Propensity scores using logistic regression, Chi-square analyses, Repeated Measures

								Analyses of Variance (RM-ANOVA) and effect sizes
Xiong et al. (2008)	**Prospective Cohort**	**USA**	**Mean or range unknown (Range = 18 to ≥ 35)**	**277**	**13 (5%)**	**PCL**	**Medical Records**	**Chi-square tests and multiple logistic regression**
Feeley et al. (2011)	**Cross-Sectional**	**Canada**	**Mean Age= 31**	**21**	**5 (24%)**	**PPQ**	**Medical Records**	**Descriptive statistics were computed for all variables, and Pearson product–moment correlations .**
Harville et al. (2015)	**Prospective Cohort**	**USA**	**Age Range 18+**	**297**	**27(9%)**	**PCL**	**Medical Records**	**Bivariate and multivariable associations**

								were examined using linear (for continuous) and logistic (for dichotomous) models
Haviland et al. (2021)	Prospective Cohort	USA	Median = 33.2 years	787	157(20%)	Cohen's 4-item Perceived Stress Scale	medical records	multiple imputation
Lutgendorf et al. (2021)	Retrospective Cohort	USA	Age Range : = 17 - ≥ 35)	103,221	1657(2%)	ICD-9-CM code 309.81	medical records and ICD9CM code	Descriptive statistics and multivariable log-binomial regression
MacGinty et al. (2020)	Prospective Cohort	South Africa	26 years	961	197(20%)	The Self-Reporting Questionnaire 20-item (SRQ-20)	Medical Records ,	Linear regression models and multivariable models, Q-Q plot and Shapiro Wilk test, and VIF to

								check for multicollinearity
Yonkers et al. (2014)	Prospective Cohort	USA	Mean Unknown (Range = ≤ 25 to ≥ 35 years)	2487	129 (5%)	Antenatal PTSD MPSS	Taken from self-report questionnaire and data from medical records	recursive partitioning, simple, and multivariable logistic regression analysis
Shaw et al. (2014)	Retrospective Cohort	USA	Mean Unknown (Range = 19-40+ years)	16334	30149(19 %)	ICD-9 diagnostic codes	Medical Records	unadjusted $\chi 2$ test bivariate analysis, and adjusted multivariate logistic regression
Parfitt et al. (2013)	Prospective Cohort	UK	Mean Age= 33 years	45 dyads	Unknown	PDS	Parent-child interaction coded using CARE Index procedure	$\chi 2$ test Mann–Whitney

Parfitt & Ayers (2009)	**Retrospective Cohort**	**UK**	**Mean Age = 30 Years**	**151**	**8 (5%)**	**PDS**	**PBQ**	**Mann–Whitney U-tests , $\chi 2$ analyses, Spearman's (r) rank order correlation test**
Muller-Nix et al. (2004)	**Prospective Cohort (case-control?)**	**Switzerland**	**High preterm risk= 32 years Low preterm risk= 31 years Full term = 32 years**	**72 dyads (36 mothers, 36 infants)**	**High risk = 11(39%) Low risk = 4 (21% of mothers) Full term = 1 (4% of mothers)**	**Perinatal Posttraumatic Diagnostic Scale (PDS)**	**CARE Index procedure**	**Multivariate analysis of variance (MANOVA) Post-hoc test (Tukey). Item correlations regression analysis**

Ayers et al. (2007)	**Cross Sectional**	**UK**	**Mean Age = 32 Years**	**64 families**	**3 (5%)**	**IES**	**Bethlehem Mother-Infant Interaction Scale**	**Wilcoxon signed ranks test, Spearman's correlation. Multiple regression**
Davies et al. (2008)	**Cross Sectional**	**UK**	**Fully Symptomatic (FS)= 26 years Partially Symptomatic (PS) = 30 years Non Symptomatic (NS) = 30 years**	**211**	**FT = 8 (3.8%) PS = 45 (21.3%)**	**PDSQ**	**MORS-SF ICQ MPAS**	**Scheffe´ test, Descriptive statistics**

Seng et al. (2013)	**Prospective Cohort**	**USA**	**Mean Age = 27 Years**	**566**	**43(7%)**	**(Perinatal PTSD) National Women's Study PTSD Module**	**PBQ**	**Pearson R**
Ionio et al. (2014)	**Prospective Cohort**	**Italy**	**Mean Age= 32.63 Years**	**58 dyads (29 mothers, 29 infants)**	**2 days postpartum = 2 (10.5% of mothers) 2 months postpartum = 4 (21.2% of mothers)**	**Perinatal Post Traumatic Stress Disorder Questionnaire (PPQ)**	**SFP coded using IRSS and MRSS**	**t-test and pearsons correlation**
Parfit et al. (2014b)	**Prospective Cohort**	**UK**	**Mean Age = 33 Years**	**75 dyads**	**Unknown**	**Perinatal Posttraumatic**	**ICQ PBQ**	**Spearman's (rho) rank order correlation**

						Diagnostic Scale (PDS)		**test. Paired-samples T-tests**
Mcdonald et al. (2011)	**Cross-Sectional**	**UK**	**Mean Age= 32 years**	**81**	**14 (17%)**	**Postpartum PTSD) PTSDQ IES**	**MORS-SF PSI-SF**	**correlation and hierarchical multiple regression (HMRA). Spearman's correlation coefficient**
Beck et al. (2011)	**Cross-Sectional**	**USA**	**Unknown**	**903**	**Unknown**	**PSS-SR**	**Created questionnaire to abstract 23 new-onset physical problem after childbirth within first two months postpartum**	**Chi-square, Pearson product-moment correlation, t test, stepwise multiple regression, and hierarchical multiple regression analyses**

Halperin et al. (2015)	**Prospective Cohort**	**Israel**	**Mean Age= 28.95 years**	**171**	**16 (9%)**	**PSS-SR**	**Child birth variables collected from self-report questionnaire 24–28 h after childbirth**	**series of t-tests, haierarchical linear regression in four steps. PTSD symptoms were used as a continuous variable.**
Campbell et al. (2020)	**Prospective Cohort**	**USA**	**Age Range: 18+**	**445**	**19(4%)**	**PCL**	**Infant Behavior Questionnaire — Revised (IBQ-R)**	**Analysis of variance [ANOVA] with Bonferroni-adjusted $p < 0.05$ for all stress measures, WQS mixtures model**
Bosquet Enlow et al. (2011)	**Prospective Cohort**	**USA**	**Mean Age = 27 Years**	**52 dyads**	**14 (27%)**	**PCL-C**	**IBQ-R ITSEA SFP-R**	**Mann–Whitney U tests , SFP-R, mixed**

								models and correlaiton
Parfitt et al. (2014a)	**Prospective Cohort**	**UK**	**Unknown**	**42 families**	**Unknown**	**Birmingham Interview of Maternal Mental Health**	**ICQ PBQ**	**statistical Spearman's (rho) rank order correlation test , mean ANOVA and multiple regression methods**
Pierrehumbert et al. (2003)	**Prospective Cohort**	**Switzerland**	**Parent of high risk of preterm infant = 31 years Parent of low**	**75 families**	**Unknown**	**PPQ**	**SCL**	**r correlation coefficients and t tests**

			risk of preterm infant = 30 years Control = 32 years					
Yehuda et al. (2005)	Prospective Cohort	USA	Unknown	38 dyads	Unknown	PCL	level of cortisol	Pearson's correlational analyses, F test
Nillni et al. (2020)	Prospective Cohort	USA	Mean Age = 298 Years	318	Unknown	Primary Care PTSD Screen for DSM-5 (PC-PTSD)	Medical records	logistic regressions, one linear regression and Spearman's rho correlations
Seng et al. (2001)*	Cross-Sectional	USA	Mean Age = 23.3 years (PTSD) 24.0 years (comparison)	1093	455 (42%)	(Antenatal PTSD) ICD-9 code taken from clinical records	Rates of hospital coding for obstetric complications	logistic regression

Shaw et al. (2017)	**Retrospective Cohort**	**USA**	**19-48+**	**4408**	**1519(34%)**	**ICD-9 diagnostic codes**	**medical records**	**multivariable-modified Poisson regression**

Abbreviations: Diagnostic and Statistical Manual of Mental Disorders (DSM), Post-traumatic Stress Disorder Checklist-(PCL), Perinatal Posttraumatic Diagnostic Scale (PDS) , Impact of Event Scale (IES), Perinatal Post Traumatic Stress Disorder Questionnaire (PPQ), Postpartum PTSD questionnaire scores (PTSDQ), Mini International Neuropsychiatric Interview (MINI), PTSD Scale-Self Report for DSM-5 (PSS-SR) , Composite International Diagnostic Interview (CIDI) , The Self-Reporting Questionnaire 20-item (SRQ-20) , Primary Care PTSD Screen for DSM-5 (PC-PTSD), International Diagnostic Code Descriptions (ICD-9)

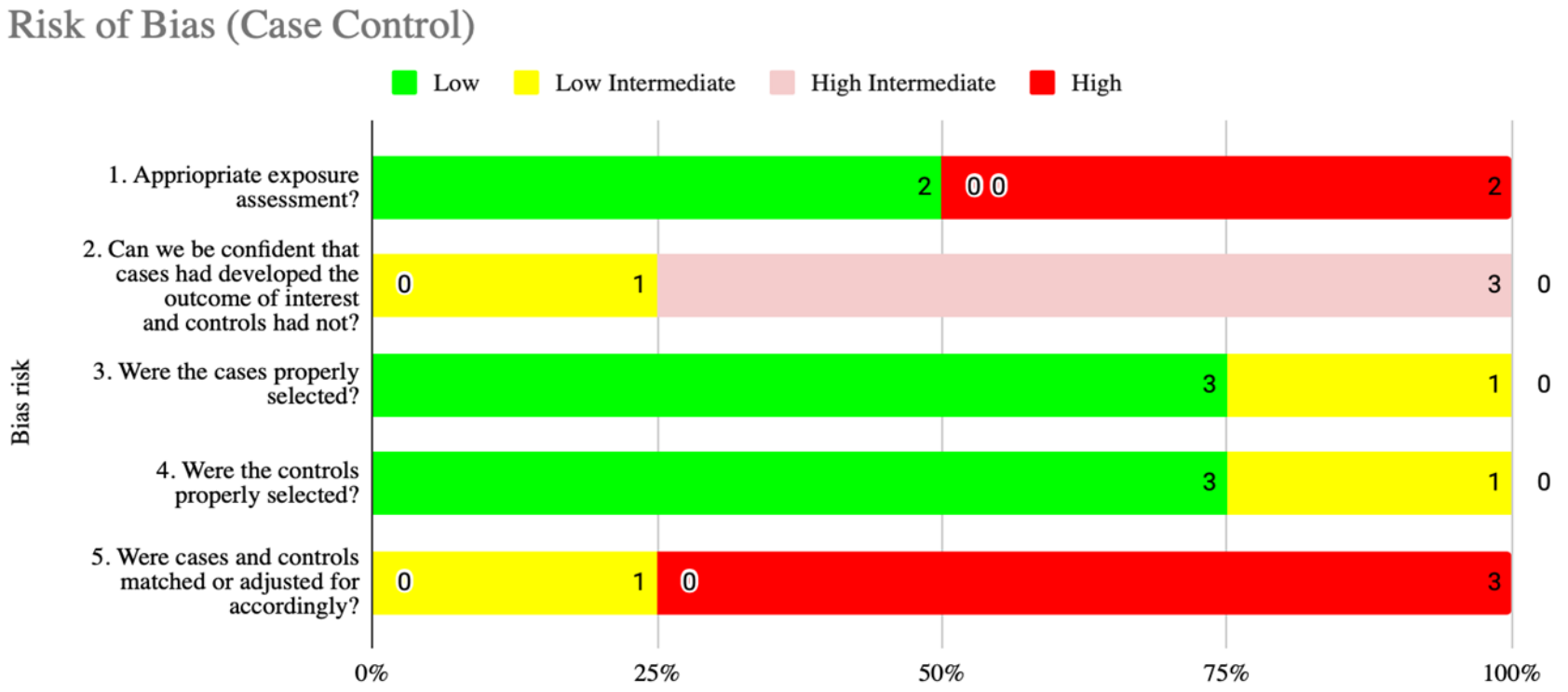

Figure 3.2: Risk of Bias Assessment for Case-Control Studies (n=4)

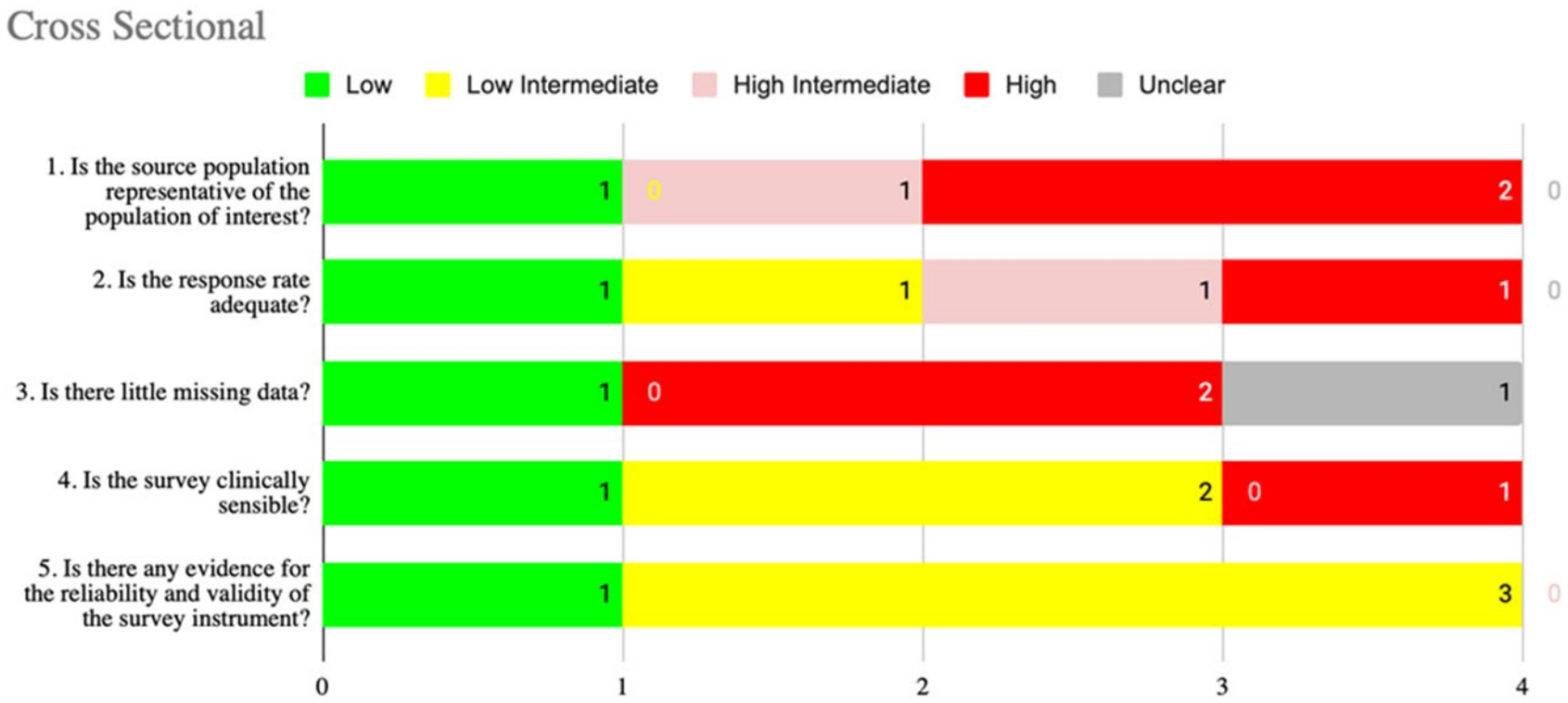

Figure 3.3 Risk of Bias Assessment for Cross-Sectional Studies(n=5)

Figure 3.4 Risk of Bias Assessment for Cohort studies(n=31)

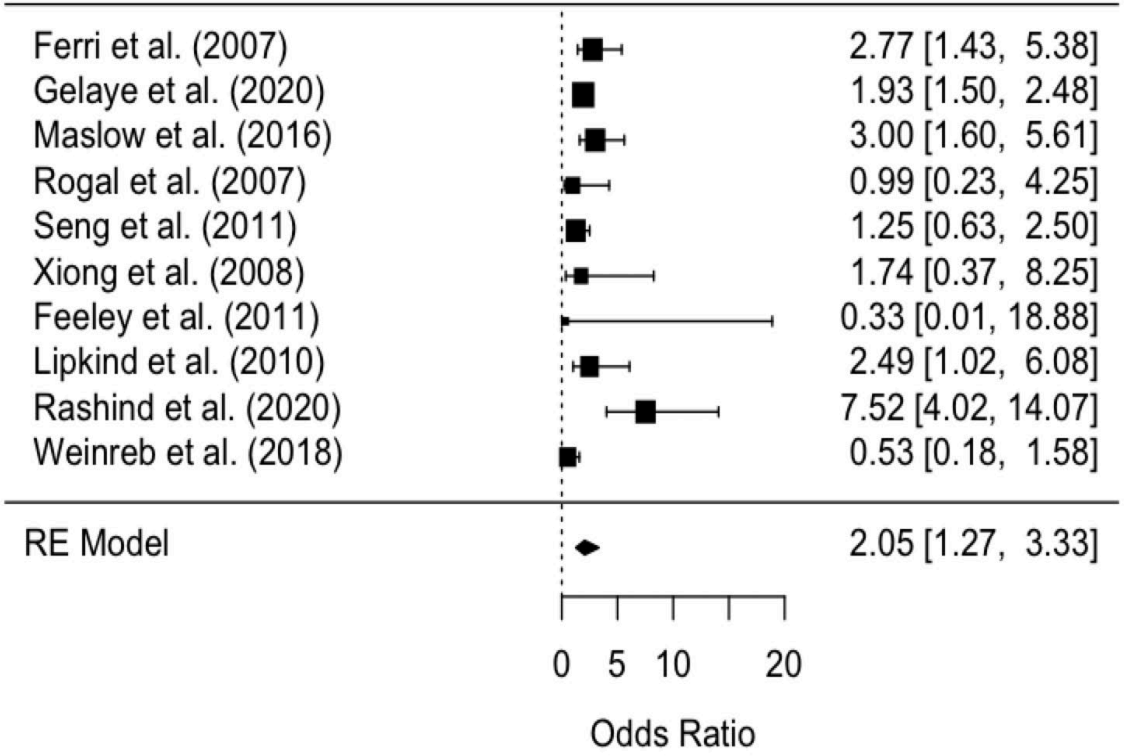

Figure 3.5 Birthweight Forrest Plot: Statistical summary and forest plot of for the association between perinatal PTSD and infant birthweight: [(P = 0.0035) ,(n=10)]

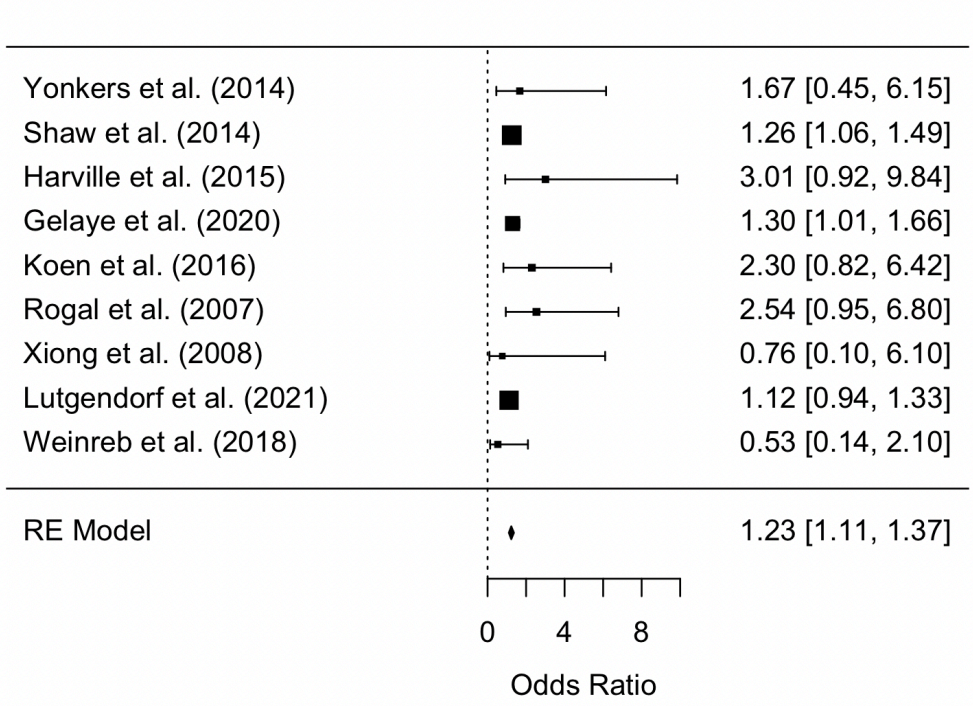

Figure 3.6 Preterm Forrest Plot: Statistical summary and forest plot of OR for the association between perinatal PTSD and preterm birth [P= 0.0002, (n=9)]

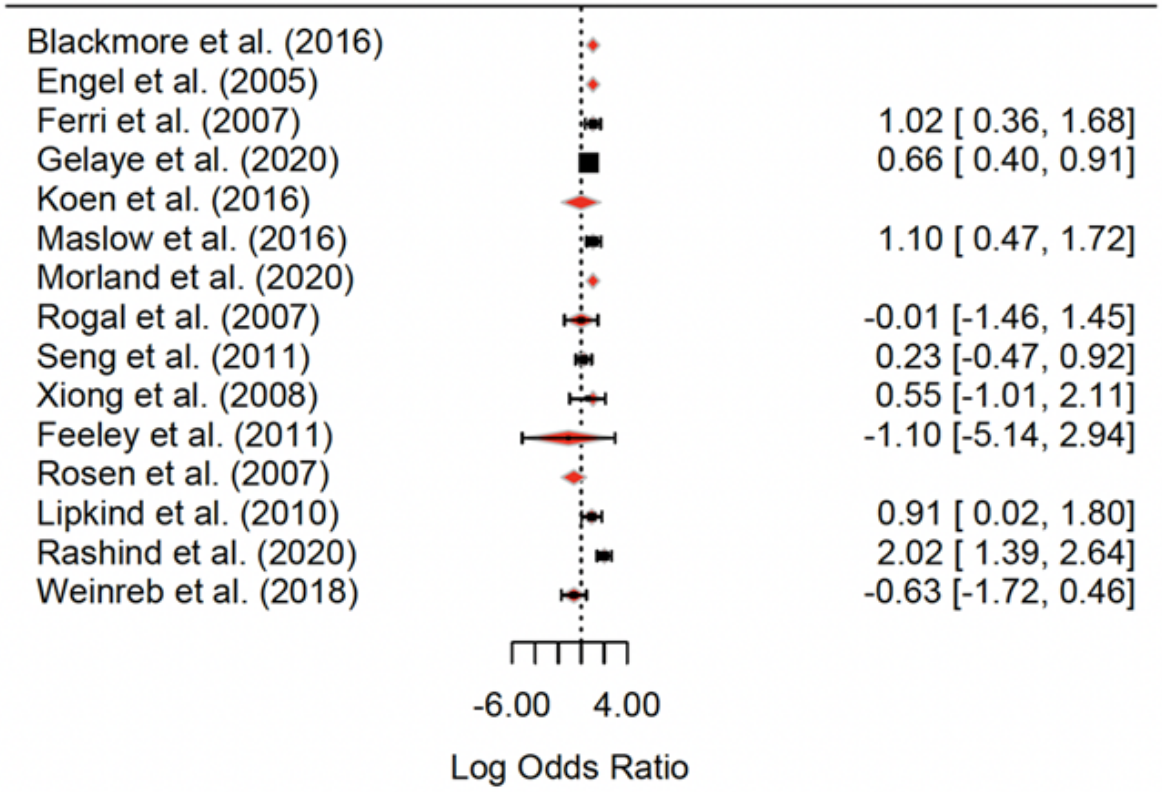

Figure 3.7 Forest Plot of BWT Sensitivity Analysis (n=15)

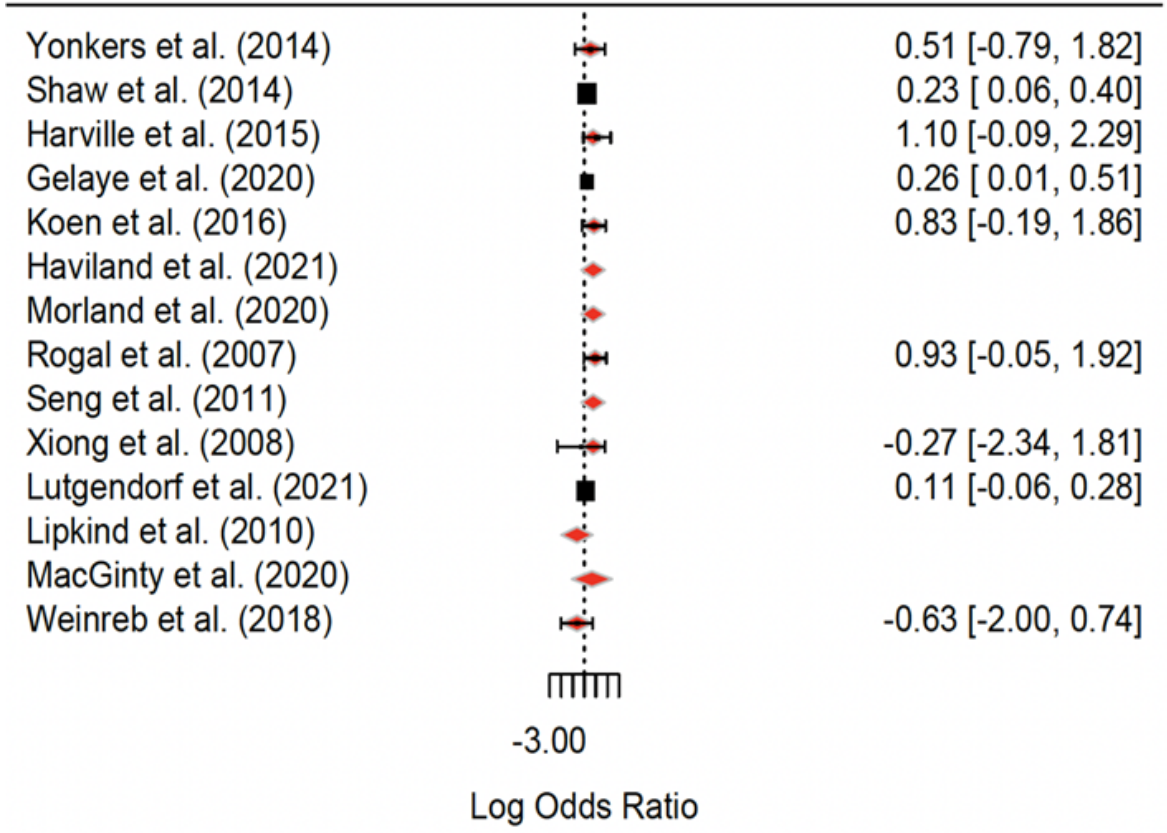

Figure 3.8 Preterm Sensitivity Analysis Forest Plot (n=14)

Table 3-2 GRADE Assessment for Low Birthweight (LBW) Outcome (n=15)

Certainty assessment						Summary of findings				
						№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**PTSD**	**No PTSD**	**Relative (95%CI)**	**Absolute (95%CI)**	
15	Observational Studies	Serious[a]	Serious[b]	Serious[c]	Serious[c]	3011/11798 (25.5%)	9382/11798 (79.5%)	OR (2.05 1.27 to 3.33)	93 more per 1,000 (from 36 more to 133 more)	⊕◯◯◯ Very low

Explanations: a. Majority of these studies have higher/intermediate risk of bias, b. high heterogeneity (>70%), c. Different populations and PTSD assessment tools used, d. Wide confidence interval

Table 3-3 GRADE Assessment for Preterm Birth (PTB) Outcome (n=15)

Certainty assessment						Summary of findings				
						№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**PTSD**	**No PTSD**	**Relative (95%CI)**	**Absolute (95%CI)**	
14	Observational Studies	Serious[a]	Not Serious[b]	Not Serious[c]	Serious[d]	5880/128533 (4.6%)	122653/128533 (95.4%)	OR 1.23 (1.11 to 1.37)	8 more per 1,000 (from 258 fewer to 12 fewer)	⨁◯◯◯ Very low

Explanations: a. Majority of these studies have higher/intermediate risk of bias, b. no heterogeneity (0%), c. Different populations and PTSD assessment tools used, d. Wide confidence interval both (from <1 to >1)

3.7 Additional Information

Supplementary information for Chapter 3 is provided in **Appendix A**: PRISMA Checklist**,** **Appendix B**: Search Strategy**, Appendix C** : Main Findings for Subcategories and **Appendix E**: Codes for Analyses

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Chapter 4

4 Prospective Evaluation of Pregnancy Outcomes after Gestational Exposure to Prazosin

4.1 Abstract

Introduction: Prazosin is an antihypertensive medication which can be used to help with post-traumatic stress disorder (PTSD) symptoms. Little data is currently available on its safety in pregnancy. **Objective**: To assess the fetal and pregnancy safety associated with prazosin exposures in early pregnancy. **Methods:** Subjects were 11 patients who took prazosin during pregnancy and were counselled at the FRAME clinic in London Health Sciences Centre (Ontario, Canada) between January 1, 2000 to December 31, 2021. Data on their other exposures and pregnancy outcomes were collected from medical records and through telephone questionnaires. **Results:** It was found that 6 /11 (54.5%) subjects did not report any adverse outcomes and were uneventful pregnancies. There were 2 miscarriages. Birthweights were within the normal range for the remaining 9 pregnancies. Adverse events reported were consistent with background population expectation, including: 1 postpartum hemorrhage, 1 case of preeclampsia, 1 preterm birth, 2 NICU admissions, and 2 caesarean sections. **Discussion / Conclusion:** For these 11 subjects, pregnancy outcomes after exposure to prazosin were consistent with typical outcomes from unexposed pregnancies. More data are needed to conclude that prazosin is safe for use in pregnant subjects. However, the lack of adverse effects above baseline is reassuring to future patients who may be unintentionally exposed to prazosin while pregnant. Therefore, this study contributes valuable data toward monitoring safety of prazosin in Pregnancy.

Keywords: pregnancy, post-traumatic stress disorder, prazosin, reproductive clinical pharmacology, drug safety

4.2 Introduction

Despite well-justified demands for research to be more inclusive and equitable, pregnancy-specific prescribing information is still greatly lacking for many drugs as pregnant women have been, and remain, consistently underrepresented in clinical research (1,2). Unfortunately, safety of drugs in pregnancy cannot be reliably inferred from animal studies, or studies in non-pregnant patient (3). This knowledge gap leaves physicians unaware, and unable to inform their patients, on potential risks or benefits certain medications will have on the patients or their fetuses if used during pregnancy (1). In the absence of formal clinical trials in pregnancy, alternative data sources need to be explored to provide accurate pregnancy-specific information, such as administrative databases or pregnant patient cohorts. (4,5).

A particular condition for which there is a dearth of pregnancy drug safety information is post-traumatic stress disorder (PTSD), even though this disorder is prevalent in young people who may get pregnant (6). prazosin, an antihypertensive medication, has recently gained popularity in the management of post-traumatic stress disorder (PTSD) symptoms, particularly vivid nightmares, and sleep-related disorders, and is currently used off-label in treating PTSD (7). Unfortunately, the use of prazosin in pregnancy is understudied. One recent systematic review identified one clinical trial and five cohort studies to date (8) but no data on first trimester exposures. prazosin is a well-tolerated generically available medication, but the lack of pregnancy safety data, especially with regards to first trimester exposures, leaves physicians and health care providers with very limited options on how to counsel and monitor pregnant patients taking this medication (1,5).

Objective: The main objective of this study was to evaluate fetal and pregnancy outcomes in a sample of pregnant patients exposed to prazosin during the first trimester of pregnancy.

4.3 Methods

4.3.1 Study Design and Enrollment

This prospective observational study included a sample of patients exposed to prazosin during their pregnancy. This was a prospective cohort with retrospective data collection. The data comes from the FRAME database of patients who were followed at the Fetal Risk Assessment

from Maternal Exposures (FRAME) clinic at London Health Sciences Center, London, Ontario, Canada between January 1, 2000 to December 31, 2021. The FRAME clinic implements a program in which pregnant women exposed to medications are offered counselling on risks associated with those exposures and followed, when required, by clinical pharmacologists. Patients are asked to consent to participate in the FRAME database, which collects information on the medications they are exposed to, the outcomes of their pregnancies, and documents any effects of their medications on their pregnancies or babies.

4.3.2 Data Collection

For this study, the FRAME database was explored to see which patients were taking prazosin during pregnancy and, for these, additional data were collected from retrospective chart review and by telephone interview. For the telephone interview, initial contact was made by a FRAME physician. Subjects were informed that they could end the telephone interview at any time and that the information provided would be included in the FRAME database for use in potential studies in the future. A total of 20 women who were were pregnant or planning pregnancy, and who were taking prazosin at the time they had attended the FRAME clinic were initially identified. Of these, 11 became pregnant while taking the medication, and these formed the final study sample.

4.3.3 Study Variables

Data collected included pregnancy and fetal outcomes, if available, such as: miscarriage, preterm birth, preeclampsia, hemorrhage, NICU admission, cesarean section, obtained through electronic chart records and overall pregnancy satisfaction, obtained through phone-call interviews. To assess fetal growth, birth weight was recorded.

4.3.4 Data Analysis

Data analyses were mainly descriptive (means and frequencies) due to the small sample size. Birthweight corrected for gestational age was assessed and compared to the Canadian normal population distributions, as published by Kramer et al. 2001 for male and female singletons (9). The subject's data was stored as per institutional guidelines. This study was approved by the Western Research Ethics Board (Registration # IRB 00000940).

4.4 Results

The baseline characteristics of the patients, that is, characteristics of the patients before their pregnancies were confirmed, are shown in **Table 4-1.** Baseline characteristics included PTSD history as well as age, BMI and location. All of these women were taking prazosin for PTSD in the beginning of their pregnancy. Six of the 11 patients continued prazosin throughout their entire pregnancy, and the remainder (5/11) discontinued prazosin during the first trimester of their pregnancy after they found out they were pregnant. Dose information on prazosin was not available. Their median age (in years) was 31 years old with an interquartile Range (IQR) of 11.5. Median BMI (kg/ m^2) was 34.34 with an IQR of 35.17. Nine of the 11 patients (81.8%) came from an urban location, and 2/11(18.2%) of the patients came from a rural location.

Previous exposure, prior to pregnancy diagnosis, and continued exposure during pregnancy to alcohol, tobacco, cannabis, and other prescription medication are provided in **Table 4-2.** Eight (72.7%) of these 11 women had a history of being on other prescription drugs, with the most commonly co-prescribed drugs being sertraline and quetiapine. Five of the ll (45.5%) had a history of smoking,1/11 (9.10%) had a history of alcohol consumption, and 2/11(18.2%) had a history of marijuana use. Five out of the 11 patients (45.5%) indicated that they continued to smoke tobacco throughout their pregnancies, and 2/11(18.2%) indicated that they continued to use cannabis. No patient indicated drinking alcohol once they found out about the pregnancy. Six of the 11 subject (54.5%) reported that they had continued to take other prescription drugs after their pregnancy was confirmed, namely escitalopram (1 patient), lisdexamfetamine (1 patient), aripiprazole (1 patient), duloxetine (1 patient) , trazodone (1 patient) , and sertraline (2 patients) during their pregnancies.

It was found that 6 /11 (54.5%) subjects exposed to prazosin during the first trimester of their pregnancy did not report any adverse outcomes and were uneventful pregnancies. Of these six subjects who did not report adverse outcomes, 4/6 (67%) were patients who had continued use of prazosin throughout their pregnancies, and 2/6 (33%) were patients who had discontinued use during the first trimester of their pregnancy. There were 2 miscarriages. Adverse events reported were consistent with background population expectation, including: 1 postpartum haemorrhage, 1 case of preeclampsia, 1 preterm birth,

2 NICU admissions, and 2 caesarean sections. None of the subjects gave birth to low birthweight infants and all subjects in the prazosin cohort exhibited fetal growth within the normal population distribution **(Table 4-3, Appendix F).** Looking at individual patient data as shown in **Table 4-4,** patient 1 experienced hemorrhaging (9.1%) and required NICU (18.2%), patient 3 required a c-section (18.2%), patients 4 and 7 experienced a miscarriage (18.2%), and patient 9 experienced pre-eclampsia (9.1%), required a c-section (18.2%), required NICU (18.2%), and had a preterm baby (9.1%). When the patients were asked about Pregnancy satisfaction, 8/11 (72.7%) reported that they were satisfied and thought their pregnancies had gone as smoothly as possible.

4.5 Discussion

Currently, not enough data exists on the safety of many medications in pregnancy (10). This lack of safety information in practice leads to patients having access to only a limited number of medications when they get pregnant, which are often old, less safe, and less effective (5).

Unfortunately, information on whether a medication is safe to use in pregnancy is difficult to come by and is mostly obtained from following patients who unexpectedly get pregnant while taking a certain medication, thus already exposing the fetus to the medication (11). These cases are not easy to find, which is why the group of patients counselled and followed by our FRAME program provides us with invaluable knowledge on what happens when pregnant patients are exposed to medications.

The US Food and Drug Administration (FDA) and the National Institutes of Health (NIH) released new requirements to encourage inclusion of female participants in clinical research (1,12) Despite these guidelines, the enrollment of pregnant populations and women of reproductive age in clinical trials continues to be poor, leading to a lack of accurate pregnancy-specific prescribing information (1,2,4–6,13–15) . Even if a medication is believed to not represent a risk for the developing fetus, many questions on the pharmacology of drugs in pregnancy remain, which can affect drug response and risk for toxicity. During pregnancy, a variety of physiological changes take place which can impact drug metabolism (16) and can lead to drug serum concentrations outside of their therapeutic windows. In these instances, utilizing standard dosing regimens (which were defined in non-pregnant people) can produce unexpected therapeutic failures or toxicities.

Various studies show that PTSD is prevalent in pregnancy (6) and that maternal PTSD is associated with negative birth or child outcomes, like low birthweight, preterm birth, and less mother-infant bonding (17). Well controlled studies in non-pregnant subjects have reported that prazosin results in significant improvement in the number of PTSD symptoms, including PTSD-associated nightmares (18–20). Despite this finding, there are still very few and adequate studies that exist for the safety of prazosin use in pregnancy, and virtually no data available on safety of exposure to this drug in the first trimester.

A systematic review conducted by Davidson et al. (2021) looked at pregnancy prazosin exposures, but could only locate one randomized-control trial (conducted in the third trimester of pregnancy) and 5 cohort studies studying prazosin use during late pregnancy and lactation (8). As the indication for use of prazosin was mostly for maternal hypertension, the role of the underlying condition should be considered in adverse outcomes. The authors of this review noted that prazosin may have a greater bioavailability and slower elimination in pregnant patients and may possibly lead to hypotension when given to patients who are normotensive and taking prazosin for PTSD, which may cause fetal effects. This systematic review failed to find any reports for the use of prazosin for the indication of PTSD and provided few reports with regards to prazosin's use for other indications in the perinatal time. The authors concluded that it is best to avoid this drug in pregnant patients due to the lack of safety information (8).

One of the studies cited in the Davidson et al. (2021) review was a 1983 study that looked at prazosin use in 8 subjects in the last trimester of pregnancy (8, 21). This study found that prazosin was effective for blood pressure control and outcomes suggested safety when used in the last trimester in these women. These data, although older, has still been used for reference when looking at prazosin safety. The fact that a study with a small sample size conducted in 1983 is still one of the only studies that can be referred to when looking at prazosin exposure during pregnancy illustrates the lack of data that currently exists. However, it is important to highlight that there are no data on the safety (or effectiveness) of prazosin use in the first trimester of pregnancy.

The data presented in our study is the first case series to evaluate this topic. We did not observe any malformations in the newborns, and the babies that required brief NICU admission were reported to be doing well according to mothers who were contacted at follow up, with mothers

reporting normal development of these babies and the NICU admissions being required as a precaution. There was no indication that the neonatal complications were related to prazosin exposure, or that the rate of NICU admissions differed from that of the general population (22). Overall, birthweights in the population studied were within normal ranges for gestational age, and none were classified as low birthweight (i.e. <2500g).

We also note that the proportion of miscarriages (18.2%) did not exceed expected rates based on normal population proportions (23). It should be acknowledged that PTSD itself may lead to an elevated risk of poor outcomes. Ferri at al. (2007) found that PTSD during pregnancy was significantly associated with low birth weight (24). A study conducted by Seng et al (2011) also found that maternal PTSD was significantly associated with obstetrical complications such as shorter gestation and lower birthweight (25). This is something to keep in mind with regards to the adverse outcomes reported in our study, given that there may be reason to expect elevated risk for reasons other than prazosin exposure.

4.6 Limitations

Limitations of the present study include a small sample size, thus limiting the analysis primarily to descriptive findings, and the absence of a comparison group of women not exposed to prazosin during pregnancy (26). Another limitation includes potential bias due to voluntary aspect of recruitment in how data collection was conducted. Although information on socio-economic status or education level was not available for all patients, we acknowledge that there is a risk that women who voluntarily join the program to receive counselling may be from a specific socioeconomic group. However, we believe that given the characteristics of Ontario's health system (i.e. the clinic is free to any Ontario resident), the risk that these women were of disproportionally higher socioeconomic status than the general population seems lower than it would be in places where health care is not unrestricted. An additional limitation is the use of self-reported data, collected via phone call questionnaires, which could be subject to recall and social desirability biases. A further limitation in this study is the lack of drug dosage information. All of the limitations listed above could limit the ability to draw conclusions regarding safety based on this one small case series. Despite these limitations, this study provides preliminary data on the effects of the use of prazosin for the treatment of PTSD during

pregnancy; however, further research is needed. Future studies of the use of this medication for this indication in pregnant women are warranted given the prevalence of this disorder in this population. With larger datasets, accompanied by statistical analyses and replicated studies, it may be possible to make more solid safety conclusions. If possible, this medication should still be avoided during pregnancy, due to its unknown safety profile. However, if a pregnant woman is exposed to this medication, the lack of adverse effects or pregnancy complications in this study is reassuring.

4.7 Conclusion

There is a lack of current research evidence regarding drug safety for pregnant women with PTSD. Our study addresses this lack of information by providing incremental data regarding first trimester exposure in a more recent time to inform the literature and to guide future studies. Although a small sample, this study contributes observational data on the use of prazosin for PTSD during pregnancy and represents an important starting point for amassing more data to improve the care of pregnant women experiencing this condition. Furthermore, our preliminary results also showed that there were no major congenital malformations in the cohort that would have raised concern with regards to this drug's safety

4.8 Tables and Figures

Table 4-1 : Baseline and Exposure Characteristics for Patients pre-confirmed pregnancy (n =11)	
Age (years)	**31[a] (11.5)[b]**
BMI (kg/m^2)	**34.33[a](35.17)[b]**
prazosin for PTSD	**11 (100%)**

Urban Location	**9 (81.8%)**
Rural Location	**2 (18.2%)**
a= median, b =IQR Remaining data is in n (%)	

Table 4-2 Exposures Documented Throughout Pregnancy for the 11 subjects (n(%))

	Past Use	Use Throughout Pregnancy
Smoking	**5 (45.5%)**	**5 (45.5%)**
Alcohol Consumption	**1 (9.10%)**	**0 (0%)**
Recreational Drugs (Marijuana)	**2 (18.2%)**	**2 (18.2%)**
Other Prescription Medications	**8 (72.7%)**	**6 (54.5%)**

Table 4-3 : Pregnancy and Fetal Outcomes for 11 subjects (n (%))

Miscarriage	**2/11 (18.2%)**
Preterm Birth	**1/11(9.1%)**
NICU Admission	**2/11 (18.2%)**
Preeclampsia	**1/11 (9.1%)**
Hemorrhaging	**1/11 (9.1%)**
Caesarean Section	**2/11 (18.2%)**

prazosin Use Continued During Entire Duration of First Trimester	**6/11 (54.5%)**
Pregnancy Satisfaction	**8/11 (72.7%)**
note: there were no fetal malformations reported amongst all patients (n=11) . No infants had a low birthweight (n=11).	

Table 4-4 Pregnancy and Fetal Outcomes for Individual Patients

Patient	Pregnancy / Fetal Outcome
1	NICU, Hemorrhaging[a]
2	No adverse outcome reported[a]
3	C-section[b]
4	Miscarriage[b]
5	No adverse outcome reported[b]
6	No adverse outcome reported[a]
7	Miscarriage[b]
8	No adverse outcome reported[a]
9	Preterm, C-Section, Pre-eclampsia, NICU[a]
10	No adverse outcome reported[a]
11	No adverse outcome reported[b]

Note : a) patients 1,2,6,8, 9 and 10 continued prazosin use through the entirety of their of pregnancy (n=6), and b) Patients 3,4,5,7,10 discontinued use during the first trimester of pregnancy.

4.9 Supplementary Material

Supplementary material for Chapter 4 can be found in **Appendix F**: BWT for GA Curves in Female and Male Singletons in Comparison to Kramer.

4.10 References

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Chapter 5

5 Summary, Conceptualization and Conclusion

This chapter is an integrated discussion of the studies presented in Chapters 3 and 4 of this thesis. Both studies build a greater understanding of PTSD exposure and pharmacological treatment in Pregnancy. The results of both studies infer that interventions, including increased PTSD screening and treatment in pregnancy, as well as further investigation of prazosin safety, are important future considerations. Risk-benefit and safety conclusions can be made by taking the findings of these two studies together when accompanied by larger datasets with statistical analyses and replicated studies. The research contributions, strengths and limitations of these studies will be discussed further in this chapter. As well, the chapter will discuss the directions for future studies in this area.

5.1 Summary

For this thesis and summary, it is acknowledged that the reference to women is in reference to studies that explore biological sex due to the limitations in studies that do not fully embody gender differences and primarily refer to women based on sex and recognize the distinction between sex and gender. Although the higher risk of PTSD in women is well documented, there are significant gaps in research regarding PTSD treatment in pregnant and the association PTSD has with adverse pregnancy, obstetric and fetal outcomes when left untreated (1). The overall aim of the thesis was to address these gaps in one study which explored associations between PTSD exposure and treatment in pregnancy, with adverse pregnancy, obstetric and neonatal outcomes. First, a systematic review, meta-analysis and GRADE assessment was conducted to synthesize existing literature on PTSD in pregnancy with adverse pregnancy, obstetric and neonatal outcomes (**Post-Traumatic Stress** Disorder and Pregnancy Outcomes: A Systematic Review, Meta- Analysis and GRADE Assessment). A subsequent study was then conducted using medical records and telephone interviews of patients in London, Ontario, Canada to explore these outcomes in pregnant women exposed to prazosin treatment for PTSD (**Chapter 4**).

Our systematic review, meta-analysis and GRADE assessment (**Post-Traumatic Stress** Disorder and Pregnancy Outcomes: A Systematic Review, Meta- Analysis and GRADE Assessment) included studies that evaluated associations between PTSD exposure in pregnancy with pregnancy, obstetric and neonatal outcomes. All 40 observational studies included in our systematic review explored the relationship of PTSD exposure with the following outcomes: infant birthweight, preterm birth, gestational age, mother-infant interaction, infant development, infant cognition, obstetric complications, infant negative affectivity, gestational diabetes, preeclampsia, head circumference, infant temperament, breastfeeding duration and sleeping and infant eating patterns. In our systematic review, we found that there appeared to be an association between maternal PTSD exposure with the following birth outcomes: reduced infant head circumference, infant sleeping & eating difficulties, reduced breastfeeding, and lower infant salivary cortisol levels. Our meta-analysis and GRADE assessment were conducted on the following outcomes: low birthweight and preterm birth. In our meta-analysis of studies for which data were available, we found that pregnant women with PTSD had higher odds of delivering a low birthweight baby (OR,2.05; 95%CI: [1.27, 3.33]). We also found that pregnant women with PTSD exposure during pregnancy had higher odds of delivering a preterm infant. (OR: 1.23; 95%CI: [1.11, 1.37]). However, our GRADE assessment revealed that the overall quality of evidence for both low birthweight and preterm birth was low, thus the need for additional research in this area.

Our prospective evaluation of pregnancy outcomes after antenatal exposure to prazosin in the first trimester of pregnancy found that amongst eleven pregnant patients, six (54.5%) did not report any adverse outcomes. Our evaluation also revealed that the infant birthweights of these patients were within the normal range and found that the adverse outcomes we observed for these patients did not extend beyond population norms. These outcomes included one case of postpartum hemorrhage (9.1%), one case of preeclampsia (9.1%), one case of preterm birth (9.1%), two NICU admissions (18.2%), two cesarian sections (18.2%) and two miscarriages (18.2%), we also found that there were no fetal malformations for any of the pregnant patients enrolled in this study.

5.2 Conceptualization

In this section, we will compare findings from our two studies and discuss these findings in the context of existing literature. In our prospective prazosin exposure evaluation (**Chapter 4**), we found that infant birthweights of mothers who had exposure to prazosin in the first trimester of pregnancy for PTSD treatment were within the normal ranges, and none were low birth weight (i.e. <2500g). This contrasts with our expectations based on systematic review and meta-analysis findings (**Post-Traumatic Stress** Disorder and Pregnancy Outcomes: A Systematic Review, Meta- Analysis and GRADE Assessment**),** which suggested that mothers with PTSD during pregnancy may have higher odds of delivering a low birthweight baby (OR, 2.05; 95%CI: [1.27, 3.33]). Our prospective evaluation also found that the proportion of preterm birth (9.1%) did not exceed the global preterm birth rate (2). This also contrasted with our expectations based on our meta-analysis findings, which found that mothers with untreated PTSD exposure during pregnancy had higher odds of having a preterm infant (OR,1.23; 95%CI: [1.11, 1.37]), albeit within a sample of studies which provided conflicting findings. PTSD is well-documented to be more prevalent in women (3–6), and prior research has shown that PTSD in pregnancy can lead to greater odds or risk of delivering a low birthweight or preterm infant (7). Taken together, this can provide preliminary information for future risk-benefit and safety analysis of using prazosin in pregnancy for PTSD treatment and help provide information for future safety conclusions that can be made. Our prazosin study was too small to draw any inferences regarding the impact of PTSD treatment on the odds of LBW or preterm birth and only propensity score matching, or a clinical trial could address this question. Nonetheless, our prazosin study provides some preliminary data to clinicians and patients while awaiting such a trial.

5.3 Strengths

The studies that were reported in this thesis were intended to gather evidence to provide research and clinical and safety data for pregnant women with PTSD with the overall aim of providing healthcare providers with information that is required to help treat PTSD in pregnant women and improve the medical care pregnant women suffering from PTSD receive. To our knowledge, we believe that **Post-Traumatic Stress** Disorder and Pregnancy Outcomes: A Systematic Review, Meta- Analysis and GRADE Assessment is the largest systematic review,

meta-analysis, and GRADE assessment to date of maternal PTSD exposure with adverse pregnancy, obstetric and neonatal outcomes. One strength of this chapter includes the incorporation of a comprehensive and systematic search. A second strength of this chapter includes the synthesis of data in a clear, precise, and thorough means. Additional strengths of this chapter include the use of results from multiple studies, the utilization of varying meta-analytical methods, and the application of sensitivity analyses in exploring sources of heterogeneity, which provided more precise effect estimates with increased power. Furthermore, this study was also strengthened through the conduction of a well-accepted risk of bias assessment and the implementation of a careful GRADE assessment which allowed for careful consideration of the overall quality of evidence (8).

With regards to **Chapter 4**, to our knowledge, this chapter is the first case series that assesses the safety of prazosin use in the first trimester of pregnancy. The strengths of this chapter included the ability to make new observations and accumulate rare data (9). **Chapter 4** was also further strengthened by the utilization of primary data collection, which gave this chapter the advantage of being particularly specific to the study question, diminished potential missingness in information, provided the opportunity for data correction in real-time and provided the opportunity to gather important and relatively unknown information not limited to variables in an established database (10).

Our review and analysis conducted in **Post-Traumatic Stress** Disorder and Pregnancy Outcomes: A Systematic Review, Meta- Analysis and GRADE Assessment is a valuable literature contribution that can further advance our understanding of how maternal PTSD can adversely affect birth outcomes. If born out in additional research, such knowledge provides justification for PTSD screening and treatment during pregnancy. Moreover, our exploratory findings in **Chapter 4** address the lack of information on PTSD treatment in pregnancy by providing findings of prazosin exposure for PTSD treatment in the first trimester that can pilot future studies. As such, **Chapter 4** provides an important starting point for amassing more data to improve the care of pregnant women experiencing PTSD. Taken together, this thesis will help improve the care pregnant women with PTSD currently receive.

5.4 Limitations

The studies each have some important limitations to note. In **Post-Traumatic Stress Disorder and Pregnancy Outcomes: A Systematic Review, Meta- Analysis and GRADE Assessment,** one limitation was the restriction in available study designs that were included in our review and analysis. By the nature of the question, all studies reviewed were observational studies, which have implications for confounding and bias (11–13). Second, we note that there were limitations in both how PTSD exposure and pregnancy outcomes were assessed in the studies that were included as many of these studies varied in which tools they used to measure both PTSD and pregnancy outcomes. Moreover, we acknowledge that the differences in outcome measurement tools may have also biased our findings. Because different outcomes were incorporated in **Post-Traumatic Stress Disorder and Pregnancy Outcomes: A Systematic Review, Meta- Analysis and GRADE Assessment,** studies varied in which tools they used to assess outcomes. For instance, the outcome of mother-infant interaction can usually only be measured through qualitative means as opposed to low birth weight (LBW), which can be clearly defined (<2500 g) and measured precisely. This created limitations in the ability to synthesize and analyze every outcome appropriately, and limited analyses to those that could be pooled and quantified appropriately (LBW and PTB) (14). Third, we note there is a limitation in the scarcity of research that addressed our research question. The sparseness of literature on PTSD exposure in pregnancy and pregnancy outcomes necessitated the inclusion of all studies regardless of their sample size. By including studies with smaller sample sizes in the meta-analyses, and thus imprecise estimates, this may have impacted our meta-analytic estimates, as evidenced by the wide confidence intervals we reported in both meta-analyses. Additionally, the scarcity of literature disallowed us from not including high-quality studies, as reflected in our GRADE assessment, which revealed a low quality of evidence for the studies that assessed low birthweight as well as preterm birth. Because the literature on this topic is so limited creating the necessity of including all studies regardless of quality, it is difficult to draw conclusions with high level of confidence. Future primary research studies addressing this topic should aim for better precision, as well as control or adjust for bias. Increased validity, reliability, and generalizability in future studies will allow for more interpretable conclusions and produce higher-quality evidence.

For our prospective study (**Chapter 4**) limitations include our small sample size, which constrained our analysis primarily to descriptive statistics (15). A further limitation is that our data collection relied on self-report which could have introduced biases including biases such as recall bias, social desirability bias, measurement error bias, and confirmation bias (16). Taken together, this limited us from making conclusions regarding prazosin safety in pregnancy. However, our small amount of data nonetheless provides important data to clinicians who are faced with counselling pregnant women who have had exposure to prazosin in the first trimester. Such data are lacking and, while anecdotal, this data is an important contribution. In the absence of a "gold standard" clinical trial, future studies addressing this topic should aim for optimal sampling approaches, a larger sample size, conduct more statistical analyses, as well and be replicated for more interpretable results.

5.5 Clinical Relevance

Despite the fact that PTSD is two to three times more likely in women (3–6), there is a dearth of information on pregnancy outcomes for women with PTSD. There is also a lack of pregnancy drug safety information for them. prazosin, an older antihypertensive drug, is being prescribed to women who suffer from PTSD (17) but it completely lacks safety data in the first trimester of pregnancy. However, many women with PTSD may experience unexpected pregnancies which they detect only after the embryo would have been exposed to their medications in the first trimester. Healthcare providers currently have very limited data to counsel these patients, or to provide evidence-based follow-up strategies (18,19). Our systematic review and analysis addressed the deficiency of information on how PTSD exposure may affect birth outcomes by providing synthesizing and analyzing the current literature that exists on this topic. The findings from our systematic review and meta-analysis (**Post-Traumatic Stress** Disorder and Pregnancy Outcomes: A Systematic Review, Meta-Analysis and GRADE Assessment) will help to pilot clinical guidelines for pregnant patients who suffer from PTSD as it contributes evidence that untreated PTSD is harmful and thus, raise justification for investigating and implementing PTSD treatment during pregnancy. When further taking practical clinical implications into account, the findings from **Post-Traumatic Stress Disorder and Pregnancy Outcomes: A Systematic Review, Meta- Analysis and GRADE Assessment** also raise justification for implementing counselling programs or

treatments for factors associated with PTSD that are also associated with adverse pregnancy, obstetric and neonatal outcomes. Such factors include poor nutrition, and substance abuse (20–22). The findings from our prospective cohort study (**Chapter 4**) contribute data in an area where there are currently no data. Future studies, with a larger dataset, detailed statistical analyses, and replication studies, can help with the formation of safety recommendations. Although definitive safety conclusions cannot be made from our prospective evaluation alone, the lack of adverse effects or pregnancy complications in this study is reassuring and will likely be a source that physicians use when consulting pregnant women exposed to this medication. Taking all of this together, this thesis provides highly clinically relevant information as well as addresses the gaps that exist for evidence-based medical care in obstetrics. We anticipate that our findings will inspire more research on this topic as well as on other disorders and treatments in which pregnancy outcomes and safety information is still lacking.

5.6 Conclusion

Overall, this thesis contributes evidence for associations between PTSD in pregnancy with adverse birth outcomes and provides incremental data that shows a lack of adverse pregnancy outcomes in a small sample of women with PTSD who had first-trimester prazosin exposure. The findings from this thesis emphasize the importance of understanding how PTSD in pregnancy may negatively affect pregnancy outcomes and highlight the importance of studies regarding PTSD treatment such as prazosin.

5.7 References

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Appendices

Appendix A	PRISMA Checklist
Appendix B	Scoping Search Strategy
Appendix C	Main Findings for Subcategories
Appendix D	Sensitivity Analysis Output
Appendix E	R studio Codes for Meta-Analyses
Appendix F	BWT for GA Curves in Female and Male Singletons in Comparison to Kramer Curves

Appendix A: PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	26
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	26
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	27-28
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	27-28
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	29

Section and Topic	Item #	Checklist item	Location where item is reported
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	28-29
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	28-29
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	28-29
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	28-29
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	28-29
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	28-29

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	29-30
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	30
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	30
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	30
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	30
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	30

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	30
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	29-30
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	30
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	31-34
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	31-34
Study characteristics	17	Cite each included study and present its characteristics.	31-34
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	34-35
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	31-35

Section and Topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	34-35
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	35
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	35
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	35
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	34-35
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	35-56
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	36-41
	23b	Discuss any limitations of the evidence included in the review.	41-42
	23c	Discuss any limitations of the review processes used.	41-42

Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	42-43
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	28
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	28
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA
Competing interests	26	Declare any competing interests of review authors.	NA
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	69

Table A1. PRISMA Checklist

Appendix B: Search Strategy

	Database		
Concept	PubMed	GOOGLE SCHOLAR	EMBASE
Exposure	"stress disorders, post traumatic"[MeSH Terms] OR ("stress"[All Fields] AND "disorders"[All Fields] AND "post traumatic"[All Fields]) OR "post-traumatic stress disorders"[All Fields] OR "ptsd"[All Fields] OR ("stress disorders, post traumatic"[MeSH Terms] OR ("stress"[All Fields] AND "disorders"[All Fields] AND "post traumatic"[All Fields]) OR "post-traumatic stress disorders"[All Fields] OR ("post"[All Fields] AND "traumatic"[All Fields] AND "stress"[All Fields] AND "disorder"[All Fields]) OR "post traumatic stress disorder"[All Fields]) OR ("injuries"[MeSH Subheading] OR "injuries"[All Fields] OR "trauma"[All Fields] OR "wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields] OR "trauma s"[All Fields] OR "traumas"[All Fields])	PTSD, OR trauma, OR posttraumatic stress disorder OR traumatic experience OR traumatic exposure OR trauma victim OR stress disorder OR severe trauma OR trauma disorder	(PTSD or posttraumatic stress disorder or trauma or traumatic exposure or traumatic experience or severe trauma or stress disorder or traumas or severe stressor).af.
Population	"pregnant women"[MeSH Terms] OR ("pregnant"[All Fields] AND "women"[All Fields]) OR "pregnant women"[All Fields] OR ("pregnant"[All Fields] OR "pregnants"[All Fields]) OR ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields]) OR ("gestate"[All Fields] OR "gestated"[All Fields] OR "gestates"[All Fields] OR "gestating"[All Fields] OR "gestational"[All Fields] OR "gestations"[All Fields] OR "pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "gestation"[All Fields]) OR ("maternally"[All Fields] OR "maternities"[All Fields] OR "maternity"[All Fields] OR "mothers"[MeSH Terms] OR "mothers"[All Fields] OR "maternal"[All Fields])	pregnant OR pregnancy, OR gestation, OR maternal, OR pregnant women OR pregnant persons OR expecting mother OR gestation	(Pregnancy or pregnant women or gestation or obstetrics or maternal or expectant mother or pregnant persons or pregnant).af.

Outcome	“pregnancy outcome"[MeSH Terms] OR ("pregnancy"[All Fields] AND "outcome"[All Fields]) OR "pregnancy outcome"[All Fields] OR (("birth s"[All Fields] OR "birthed"[All Fields] OR "birthing"[All Fields] OR "parturition"[MeSH Terms] OR "parturition"[All Fields] OR "birth"[All Fields] OR "births"[All Fields]) AND ("outcome"[All Fields] OR "outcomes"[All Fields])) OR (("fetale"[All Fields] OR "fetally"[All Fields] OR "fetals"[All Fields] OR "fetus"[MeSH Terms] OR "fetus"[All Fields] OR "fetal"[All Fields] OR "foetal"[All Fields]) AND ("outcome"[All Fields] OR "outcomes"[All Fields])) OR (("obstetric"[All Fields] OR "obstetrically"[All Fields] OR "obstetrics"[MeSH Terms] OR "obstetrics"[All Fields] OR "obstetrical"[All Fields]) AND ("outcome"[All Fields] OR "outcomes"[All Fields]))	pregnancy outcome OR birth outcome, OR fetal outcome OR baby outcome OR pregnancy complications OR adverse birth outcome OR obstetric outcomes OR birth complications OR neonatal outcomes	(pregnant outcomes or pregnancy outcome or birth outcomes or neonatal outcomes or obstetric outcome or pregnancy complications or fetal outcomes or adverse birth outcomes or obstetrical complications).af.)
Linking concepts	1 AND 2 AND 3 N=200	1 AND 2 AND 3 N=168	1 AND 2 AND 3 N=42

Table B1: Scoping Search Strategy for Chapter 3

Appendix C : Main Findings for Subcategories

Study	Main Findings
Blackmore et al. (2016)	**Of the 358 deliveries, 29 (8.1%) were considered low birthweight (< 2500g) Univariate analysis showed that birthweight was not significantly associated with either history (r = −.10, p = .850) or frequency of traumatic events (r = .00, p = .936),**
Engel et al. (2005)	**Probable PTSD was not associated with birthweight**
Ferri et al. (2007)*	**PTSD was associated with low birth weight, after adjusting for confounders and mediator PR = 1.91* (95%CI 1.01–3.63)**
Gelaye et al. (2020)	**PTSD was not associated with low birth weight (LBW) at delivery.**
Koen et al. (2016)	**No association was observed between maternal diagnosed life-long PTSD and decreased standard deviation scores of weight-for-age (WAZ score)**
Lipkind et al. (2010)*	**Probable PTSD was significantly associated with a difference in birth weight (unadjusted), but this was not significant when controlling for confounding variables. Low birth weight was two-times more likely in women with high PTSD scores.**

Maslow et al. (2016)*	**Probable 9/11-related posttraumatic stress disorder 2 to 3 years after 9/11 were associated with low birth weight (LBW) during the early study period.**
Morland et al. (2007)	**PTSD was not significantly associated with low birthweight**
Rashind et al. (2020)*	**In univariate analysis model, PTSD was significantly associated with low birthweight (LBW). In logistic regression model, PTSD was independently associated with low birthweight (LBW) in the presence of other factors like maternal / paternal schooling, gravida, history of preterm, BMI of the mother and maternal anemia**
Rogal et al. (2007)	**low birth weight was not significantly associated with antenatal PTSD**
Rosen et al. (2007)*	**Those respondents who were experiencing both a mental health condition (one of which being PTSD) and IPV had the highest odds (2.5 time greater of having a low birth weight infant (p=0.026). The odds of having a low bwt baby was 2.1 timesgreater in those women who had ptsd (p= 0.017)**
Seng et al. (2011)*	**Current PTSD symptom count was significantly associated with lower birth weight, compared to trauma-exposed resilient cohort and non-exposed cohort; negative correlation of current PTSD symptom count with birthweight was significant (P<0.001)**
Weinreb et al. (2018)	**There were no significant differences between low birthtweight oucome for partipants who received**

	the intervention for PTSD compared to those who did not ($\chi 2 = 3.62$, df = 3, p = .306)
Xiong et al. (2008)	**The frequency of low birth weight was higher in women with PTSD (23.1%) and with depression (11.6%) than that in women without PTSD (9.1%) Antenatal PTSD found to be associated with increased risk of low birth weight – low birth weight was three-times more likely in women with antenatal PTSD.**
Feeley et al. (2011)*	**Mothers who reported more PTSD symptoms had infants who weighed less at birth**
* is significant	

Table C1: Main Findings for Low Birthweight (n=15)

Study	Main Findings
Blackmore et al. (2016)	**trauma history (r = .05, p = .336) and frequency of traumatic events (r = .04, p = .430) were not significantly associated with gestational age**
Engel et al. (2005)	**Probable PTSD was not associated with gestational duration**
Gelaye et al. (2020)	**PTSD was not associated with gestational age at delivery.**
Harville et al. (2015)*	**For PTSD, the associations were in the direction of PTSD being associated with reduced gestational age (adjusted beta -2.85 days, p = 0.17)**
Koen et al. (2016)	**No association was observed between maternal diagnosed life-long PTSD and small for gestational age (SGA)**
Lipkind et al. (2010)	**Probable PTSD was not associated with a difference in gestational age of delivery.**
Lutgendorf et al. (2021)	**compared to service members without PTSD.PTSD case status was not associated with size for gestational age (SGA).**
Rogal et al. (2007)	**gestational age was not significantly associated with antenatal PTSD**
Weinreb et al. (2018)	**There were no significant differences in gestational age for partipants who received the intervention for PTSD compared to those who did not**
* is significant	

Table C2. Main Findings for Shorter GA (n=9)

Study	Main Findings
Gelaye et al. (2020)*	**Compared to those without PTSD, women with PTSD (34.5%) had higher odds of delivering preterm (OR = 1.28; 95%CI: 1.00–1.65)**
Harville et al. (2015)*	**For PTSD, the associations were in the direction of PTSD being associated with higher preterm birth rate (adjusted OR 3.61, 0.93–14.03)**
Haviland et al. (2021)	**Compared to participants with less perceived stress, the risk of preterm delivery was no different among participants with a moderate score perceived stress (RR 1.23, 95% CI 0.68, 2.25) and a high score of perceived stress (RR 1.62, 95% CI 0.73, 3.62)**
Koen et al. (2016)*	**No association was observed between maternal diagnosed life-long PTSD and preterm delivery**
Lipkind et al. (2010)*	**Preterm delivery was two-times more likely in women with high PTSD scores.**
Lutgendorf et al. (2021)	**Compared to service members without PTSD. PTSD case status was not associated with preterm birth,**

MacGinty et al. (2020)	**No association was observed between antenatal maternal psychological distress and preterm birth**
Morland et al. (2007)	**PTSD was not significantly associated with preterm birth (pre-term contractions)**
Rogal et al. (2007)	**Preterm delivery was not significantly associated with antenatal PTSD. However, an association was observed in that preterm delivery was nearly three-times more likely in mothers with antenatal PTSD (although not statistically significant)**
Seng et al. (2011)	**Current PTSD was not significantly associated with pre-term birth.**
Weinreb et al. (2018)	**There were no significant differences between preterm delivery outcomes for those who received the intervention for PTSD compared to those who did not ($\chi 2 = 2.203$, df = 3, p = .531)**
Xiong et al. (2008)	**Antenatal PTSD was associated with decreased risk of preterm birth**
Yonkers et al. (2014) *	**Risk of preterm birth was elevated in women with a likely diagnosis of PTSD (Adjusted OR = 1.22, 95% C.I. 0.57–2.61)**

Shaw et al. (2014)*	**Spontaneous preterm delivery was higher in those with active PTSD (9.2%, n=5176) than those with historical (8.0%, n=590) or no PTSD (7.4%, n=5982) before adjustment (P= .02).**
* is significant	

Table C3. Main Findings for Preterm Birth (n=14)

Study	Main Findings
Feeley et al. (2011)*	**Mothers who reported more PTSD symptoms were less sensitive and less effective at structuring interactions with their infant.**
Parfitt et al. (2013)	**Maternal PTSD was not significantly correlated with any maternal sensitivity, control, or unresponsiveness**
Parfitt & Ayers (2009)*	**PTSD was significantly correlated with mother-infant interaction. Mothers with PTSD reported a significantly poorer relationship with their infant.**
Muller-Nix et al. (2004)*	**At 6 months: high-stress post partum PTSD mothers of preterm infants were associated with significantly lower maternal sensitivity and significantly higher maternal control compared with full-term mothers At 18 months: high-stress post partum PTSD mothers of preterm infants were associated with significantly greater infant compliance and passivity**
Ayers et al. (2007)	**Maternal PTSD symptoms were not associated with the mother-baby bond.**
Davies et al. (2008)*	**Mothers with FT or PS PTSD symptoms perceived their attachment to be significantly less to their infants, Mothers with FT or PS PTSD also perceived greater infant-directed hostility and reduced pleasure when interacting with their infants. FT mothers also reported that they had**

	significantly less desire in being within close proximity to their infant
Seng et al. (2013) *	**Pre-existing maternal PTSD was an elevated risk factor for impaired bonding.**
Ionio et al. (2014) *	**Infants whose mothers had higher PTSD symptoms at two months physically distanced themselves from their mother. Data showed that persistence of PTSD symptoms had a different effect on early mother–child interactions than those of mothers who have not had postpartum stress symptoms**
Parfit et al. (2014)	**Maternal PTSD at three months postpartum was not significantly correlated with a poorer baby-bond at 3- months and 15-months postpartum.**
Mcdonald et al. (2011)	**PTSD babies showed greater amounts of hard crying when reuniting with their mothers than during the baseline play episode Infants of mothers without elevated symptoms of PTSD showed higher amounts of fussing in the second reunion with their mothers relative to the first reunion but low levels of hard crying throughout the procedure. Early PTSD symptoms (at either 6 weeks or 3 months postpartum) was not significantly correlated with maternal perception of the child at 2 years postpartum.**
Breastfeeding	

Beck et al. (2011)*	**Women with higher PTSD scores were significantly less likely to have breastfed their infant for as long as they wanted to, and were significantly less likely to be exclusively breast-feeding at 1 month postpartum.**
Halperin et al. (2015)*	**Significantly more women with PTSD symptoms did not breastfeed their infant.**
* is significant	

Table C4.Main Findings for Reduced Mother-Infant Interaction (n=12)

Study	Main Findings
Infant NA	
Campbell et al. (2020)*	**significant positive linear association between the prenatal stress and infant negative affectivity (NA). For each one-unit increase in prenatal stress index, the infant NA score increased by 0.40 (0.16–0.64) (b [95% confidence interval], and PTSD was the strongest contributor to the prenatal stress score in Hispanic women**
Parfitt et al. (2013)	**Maternal PTSD was not significantly correlated with infant cooperation, difficulty, compliance or passivity**
Infant temperament	
Bosquet Enlow et al. (2011)	**Maternal PTSD symptoms were not significantly associated with measures of infant emotional reactivity. Maternal PTSD symptoms were significantly correlated with maternal reports of the infant's ability to recover once distressed. Maternal PTSD showed minimal associations with infant emotional reactivity although infants of mothers with symptoms of PTSD to show a greater increase in hard crying during the second still-face episode relative to the first still-face episode. Maternal PTSD was associated with infant recovery from distress; infants of mothers with symptoms of PTSD showed greater amounts of hard crying during the second reunion than during the baseline play episode, the first reunion, and the second still-face episodes. Infants of mothers without elevated symptoms of PTSD showed higher amounts of fussing in the second reunion relative to the first reunion but low levels of hard crying throughout the procedure.**

Davies et al. (2008)*	**Mothers with FT or PS PTSD symptoms perceived their infants to be more difficult in temperament.**
Cognition	
MacGinty et al. (2020)	**No association was observed between antenatal maternal psychological distress and early developmental outcomes**
Feeley et al. (2011)	**Maternal PTSD symptom score was not related to infant cognitive development at 6-months postpartum.**
Parfitt et al. (2014a)*	**Maternal postpartum PTSD was moderately associated with poorer cognitive outcomes, but was not significantly associated with language or motor scores.**
Sleeping/Eating Behaviour	
Pierrehumbert et al. (2003)*	**There was a statistically significant difference between the aggregated index of problems (sleeping and eating), with significantly more difficulties with premature infants of mothers with PTSD, with sleeping problems being most affected.**
Cortisol	

Yehuda et al. (2005)*	**Infant salivary cortisol was lower in infants of women with PTSD. Lower cortisol levels were most apparent in babies born to mothers with PTSD in their hird trimesters on 9/11**
* is significant	

Table C5. Main Findings for Infant & Neonatal Complications (n=9)

Study	Main Findings
Engel et al. (2005)*	**PTSS (Post Traumatic Stress Symptomology) was inversely associated with infant head circumference at birth, such that a 1-unit increase in PCL score was associated with a 0.07 cm decrement in head circumference (P = 0.01)**
Koen et al. (2016)*	**Maternal trauma was significantly associated with a 0.3 unit reduction in infant HCAZ (head circumference) scores at birth (95% CI: 0.1; 0.5) This association remained significant when adjusted for study site, SES, and recent life stressor**
MacGinty et al. (2020)*	**antenatal maternal psychological distress was associated with a smaller head circumference at birth (coefficient=−0.30, 95% CI: −0.49; −0.10).**
* is significant	

Table C6. Main Findings for Reduced Head Circumference (n=3)

Study	Main Findings
Blackmore et al. (2016)	**Neither trauma history, $\chi 2$ (1, N = 358) = 0.51, p = .473; nor frequency of traumas, $\chi 2$ (3, N = 358) = 3.49, p = .323, was significantly associated with obstetric complication**
Lutgendorf et al. (2021)	**compared to service members without PTSD.** **PTSD case status was not associated** **with major birth defects RR 1.03,(95% CI 0.79–1.34)**
Nillni et al. (2020)*	**PTSD symptoms, aOR = 1.16, 95% CI [1.00, 1.35],** **significantly predicted an increased** **risk of an adverse pregnancy outcome**
Seng et al. (2001)*	**Logistical regression model found five** **obstetric complications to be significantly associated with maternal PTSD, one of which was excessive fetal** **growth**
Shaw et al. (2017)*	**current PTSD diagnosis (reference = no PTSD) was associated with an increased risk of GDM (RR 1.4, 95% confidence interval (CI) 1.2, 1.7) and preeclampsia (RR 1.3, 95% CI 1.1, 1.6). PTSD also predicted prolonged (>4 day) delivery hospitalization (RR 1.2, 95% CI 1.01, 1.4), and repeat hospitalizations (RR 1.4, 95% CI 1.2, 1.6), but not caesarean delivery.**

* is significant	

Table C7.Main Findings for Obstetric Complications (n=5)

Study	Main Findings
Head Circumference	
Engel et al. (2005)*	**PTSS (Post Traumatic Stress Symptomology) was inversely associated with infant head circumference at birth, such that a 1-unit increase in PCL score was associated with a 0.07 cm decrement in head circumference (P = 0.01)**
Koen et al. (2016)*	**Maternal trauma was significantly associated with a 0.3 unit reduction in infant HCAZ (head circumference) scores at birth (95% CI: 0.1; 0.5) This association remained significant when adjusted for study site, SES, and recent life stressor**
MacGinty et al. (2020)*	**Antenatal maternal psychological distress was associated with a smaller head circumference at birth (coefficient=−0.30, 95% CI: −0.49; −0.10).**
Breastfeeding	
Beck et al. (2011)*	**Women with higher PTSD scores were significantly less likely to have breastfed their infant for as long as they wanted to, and were significantly less likely to be**

	exclusively breast-feeding at 1 month postpartum.
Halperin et al. (2015)*	**Significantly more women with PTSD symptoms did not breastfeed their infant.**
Sleeping/Eating Behaviour	
Pierrehumbert et al. (2003)*	**There was no significant difference between preterm infants of mothers with high or low PPQ, and controls, in relation to sleeping or eating difficulties. However, there was a statistically significant difference between the aggregated index of problems (sleeping and eating), with significantly more difficulties with premature infants of mothers with PTSD, with sleeping problems being most affected.**
Cortisol	
Yehuda et al. (2005)*	**Infant salivary cortisol was lower in infants of women with PTSD. Lower cortisol levels were most apparent in babies born to mothers with PTSD in their third trimesters on 9/11**

* is significant	

Table C8.Evidence for Overall Associations

Appendix D: Sensitivity Output

tau^2 (estimated amount of residual heterogeneity): 0 (SE = 0.5190)
tau (square root of estimated tau^2 value): 0
I^2 (residual heterogeneity / unaccounted variability): 0.00%
H^2 (unaccounted variability / sampling variability): 1.00
R^2 (amount of heterogeneity accounted for): 100.00%
Test for Residual Heterogeneity: QE(df = 1) = 0.4065, p-val = 0.5237 Test of Moderators (coefficients 2:9): QM(df = 8) = 28.0447, p-val = 0.0005
estimate se zval pval ci.lb ci.ub
countryPakistan 3.6806 1.1943 3.0817 0.0021 1.3398 6.0214 **
Case-Control 1.5444 0.7181 2.1507 0.0315 0.1369 2.9518 *
Prospective Cohort 1.6547 0.6294 2.6289 0.0086 0.4210 2.8884 **
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Table D1 Sensitivity Analysis for Low BWT

tau^2 (estimated amount of residual heterogeneity): 0 (SE = 0.0108)
tau (square root of estimated tau^2 value): 0
I^2 (residual heterogeneity / unaccounted variability): 0.00%
H^2 (unaccounted variability / sampling variability): 1.00
R^2 (amount of heterogeneity accounted for): 0.00%
Test for Residual Heterogeneity:
QE(df = 3) = 2.4423, p-val = 0.4858
Test of Moderators (coefficients 2:6):
QM(df = 5) = 6.5415, p-val = 0.2570

Table D2: Sensitivity Analysis for Preterm Birth

Appendix E: Codes for Analyses

Section E1: Code for LBW Analysis

```
library(metafor)
# create the dataset
publisher<- c("Blackmore et al. (2016)", " Engel et al. (2005)", " Ferri et al. (2007) ", " Gelaye et al. (2020)" , " Koen et al.
 (2016)", " Maslow et al. (2016)", " Morland et al. (2020)", " Rogal et al. (2007)", " Seng et al. (2011)", " Xiong et al.
 (2008)", " Feeley et al. (2011)", " Rosen et al. (2007)", " Lipkind et al. (2010)", " Rashind et al. (2020)", " Weinreb et al.
 (2018)")
APTSDposbwtpos <- c(NA, NA, 13, 128, NA, NA, NA, 2, 13, 2, 5, NA, NA, 71, 5)
BPTSDposbwtneg <- c(NA, NA, 64, 1433, NA ,NA, NA, 29, 242, 11, 0, NA, NA, 13, 55)
CPTSDngbwtpos<- c(NA, NA, 49, 128, NA, NA, NA, 70, 24, 27, 16, NA , NA, 154, 13)
DPTSDngbwtneg<- c(NA, NA, 669, 2761, NA, NA, NA, 1009, 560, 258, 0, NA, NA, 212 ,76)
country <- c("USA", "USA", "Brazil", "Peru", "South Africa", "USA", "USA", "USA", "USA", "USA", "Canada", "USA",
 "USA", "Pakistan", "USA")
assessmenttool <- c("DSM", "PCL", "CIDI", "PCL", "MINI", "PCL", "PCL", "MINI",
                    "National Women's StudyPTSD Module", "PCL", "PPQ",
                    "University of Michigan Composite International Diagnostic Interview (UM-CIDI)",
                    "PCL", "MINI", "Four-item Primary Care-PTSD Screen")
studydesign <- c("Prospective Cohort", "Prospective Cohort", "Prospective Cohort",
                 "Prospective Cohort", "Prospective Cohort", "Prospective Cohort",
                 "Prospective Cohort", "Prospective Cohort", "Prospective Cohort",
                 "Prospective Cohort", "Cross-Sectional", "Retrospective Cohort",
                 "Case-Control", "Case-control", "Case-control")
OR <- c(NA, NA, NA, NA, NA, 3, NA, NA, NA, NA, NA, NA, 2.49, NA, NA)
CIlower<- c(NA, NA, NA, NA, NA, 1.6, NA, NA, NA, NA, NA, NA, 1.02, NA, NA)
CIupper<-c(NA, NA, NA, NA, NA, 5.6, NA, NA, NA, NA, NA, NA, 6.08, NA, NA)
Pvalue<- c(0.85, 0.69, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA)
 Totalsample <- c(358, 51, 795 ,4450, 366 ,3271, 101 ,1100, 839, 298, 21, 148, 446, 450, 149)
metaptsd <- data.frame(publisher, APTSDposbwtpos, BPTSDposbwtneg, CPTSDngbwtpos, DPTSDngbwtneg,
 Totalsample, OR, Pvalue, CIlower, CIupper, country, assessmenttool, studydesign)


#do analysis
 metaptsd
 bwtmeta1 <- escalc(measure="OR", ai= APTSDposbwtpos, bi=BPTSDposbwtneg, ci=CPTSDngbwtpos,
 di=DPTSDngbwtneg, sei=TransOR, data=metaptsd)
 bwtmeta1
 analysis1 <- rma(yi, vi, data=bwtmeta1)
 analysis1
 predict(analysis1, transf=exp, digits=2)
bwtmeta2 <- data.frame(summary(bwtmeta1))
bwtmeta2 <- escalc(measure="OR", ai= APTSDposbwtpos, bi=BPTSDposbwtneg, ci=CPTSDngbwtpos,
 di=DPTSDngbwtneg, sei=TransOR, data=bwtmeta2)
bwtmeta2  <- conv.wald(out=OR, ci.lb=CIlower, ci.ub=CIupper, pval=Pvalue, n=Totalsample, data=bwtmeta2,
 transf=log)
Bwtmeta2



#create random effect model meta-analysis and forest plot
analysis2 <- rma(yi, vi, data=bwtmeta2)
predict(analysis2, transf=exp, digits=2)
predict(analysis2, transf=exp, digits=2)
forest(analysis2, transf=exp, slab = paste(publisher))


#sensitivity analysis for country, assesment tool and study design
metaptsd <- data.frame(publisher, APTSDposbwtpos, BPTSDposbwtneg, CPTSDngbwtpos, DPTSDngbwtneg,
 Totalsample, OR, Pvalue, CIlower, CIupper, country, assessmenttool, studydesign)
 metaptsd
```

```
bwtmeta1 <- escalc(measure="OR", ai= APTSDposbwtpos, bi=BPTSDposbwtneg, ci=CPTSDngbwtpos,
 di=DPTSDngbwtneg, sei=TransOR, data=metaptsd)
bwtmeta1
metaregmodel <- rma(yi, vi, mods = ~ country + studydesign + assessmenttool, random = ~ 1 | publisher, data =
 bwtmeta1)
metaregmodel
forest(metaregmodel, transf=exp, slab = paste(publisher), xlim = c(-50, 50))

bwtmeta2 <- data.frame(summary(bwtmeta1))
bwtmeta2 <- escalc(measure="OR", ai= APTSDposbwtpos, bi=BPTSDposbwtneg, ci=CPTSDngbwtpos,
 di=DPTSDngbwtneg, sei=TransOR, data=bwtmeta2)
bwtmeta2  <- conv.wald(out=OR, ci.lb=CIlower, ci.ub=CIupper, pval=Pvalue, n=Totalsample, data=bwtmeta2,
 transf=log)
bwtmeta2
 metaregmodel2<- rma(yi, vi, mods = ~ country + studydesign + assessmenttool, random = ~ 1 | publisher, data =
 bwtmeta2)
 metaregmodel2
forest(metaregmodel2, slab = paste(publisher), xlim = c(-50, 50), col = "red", addfit = TRUE, digits = 2, mlab =
 "Sensitivity
```

Section E2: Code for PTB Analysis

```
#forpreterm
remotes::install_github("wviechtb/metafor")
install.packages("remotes")
force=TRUE
library(metafor)
#create dataset
  publisher<- c("Yonkers et al. (2014)",              "Shaw et al. (2014)", "Harville et al. (2015)", "Gelaye et al. (2020)",
 "Koen et al. (2016)",  "Haviland et al. (2021)", "Morland et al. (2020)", "Rogal et al. (2007)",  "Seng et al. (2011)",
 "Xiong et al. (2008)", "Lutgendorf et al. (2021)", "Lipkind et al. (2010)", "MacGinty et al. (2020)", "Weinreb et al.
 (2018)")
 APTSDpospretermpos <- c(13, 175,   4,          112,       NA,        NA,NA, 5, NA, 1, 141, NA, NA, 3)
  BPTSDpospretermneg <- c(3,          1746,     22,         1407,      NA, NA, NA, 26, NA, 12, 1516, NA, NA, 57)
 CPTSDngpretermpos<- c(114, 982, 15, 167, NA, NA, NA, 76, NA, 28, 7817, NA, NA, 8)
  DPTSDngpretermneg<- c(44, 12303, 248, 2722, NA, NA, NA, 1003, NA, 257, 93747, NA, NA, 81)
 Totalsample <- c(174, 15206, 289, 4408          ,NA, NA, 101, 1110, NA, 298, 103221, NA, 961,149)
 OR <- c(1.22,NA, 3.61,1.28,2.3,NA,NA            ,NA        ,NA        ,0.8       ,1.1, 2.67 ,NA,NA)
CIlower<- c(0.57    ,NA,        0.93,1     ,0.82       ,NA,        NA,        NA,        NA,0.1, NA, NA, NA, NA)
Clupper<-c(2.61,    NA,         14.03,     1.65        ,6.38       ,NA,        NA         ,NA, NA, 6.39, NA, 1.23, NA, NA)
study_design <- c("Prospective Cohort", "Retrospective Cohort", "Prospective Cohort", "Prospective Cohort",
 "Prospective Cohort", "Prospective Cohort", "Prospective Cohort", "Prospective Cohort", "Prospective Cohort",
 "Prospective Cohort", "Retrospective Cohort", "Case Control", "Prospective Cohort", "Case Control")
country <- c("USA", "USA", "USA", "Peru", "South Africa", "USA", "USA", "USA", "USA", "USA", "USA", "South
 Africa", "USA")
assessment_tool <- c("Antenatal PTSD MPSS", "Antenatal PTSD MPSS", "PCL", "PCL", "MINI", "Cohen's 4-item
 Perceived Stress Scale", "PCL", "MINI", "National Women's Study PTSD Module", "PCL", "Antenatal PTSD MPSS",
 "PCL", "(SRQ-20)", "Four-item Primary Care-PTSD Screen")
Pvalue<- c(NA,0.2,0.06,NA, NA,NA,NA,NA,0.067, NA, NA ,NA ,NA, NA)
metaptsd <- data.frame(publisher, APTSDpospretermpos,  BPTSDpospretermneg, CPTSDngpretermpos,
 DPTSDngpretermneg, Totalsample, OR, Pvalue, CIlower, Clupper)
#conduct analysis
metaptsd
 pretermmeta1 <- escalc(measure="OR", ai= APTSDpospretermpos, bi=BPTSDpospretermneg,
 ci=CPTSDngpretermpos, di=DPTSDngpretermneg, sei=TransOR, data=metaptsd)
  pretermmeta1
```

```
 analysis1 <- rma(yi, vi, data=pretermmeta1)
analysis1
predict(analysis1, transf=exp, digits=2)
analysis1 <- rma(yi, vi, data=pretermmeta1)
analysis1
predict(analysis1, transf=exp, digits=2)
pretermmeta2 <- data.frame(summary(pretermmeta1))
pretermmeta2<- escalc(measure="OR", ai= APTSDpospretermpos, bi=BPTSDpospretermneg,
 ci=CPTSDngpretermpos, di=DPTSDngpretermneg, data=metaptsd)
pretermmeta2  <- conv.wald(out=OR, ci.lb=CIlower, ci.ub=CIupper, pval=Pvalue, n=Totalsample, data=pretermmeta2,
 transf=log)
pretermmeta2
#random effect and forest plot
analysis2 <- rma(yi, vi, data=pretermmeta2)
predict(analysis2, transf=exp, digits=2)
predict(analysis2, transf=exp, digits=2)
forest(analysis2, transf=exp, slab = paste(publisher))


# conduct sensitivity mods adjustment
metaptsd <- data.frame(publisher, APTSDpospretermpos,  BPTSDpospretermneg, CPTSDngpretermpos,
 DPTSDngpretermneg, Totalsample, OR, Pvalue, CIlower, CIupper, country, assessment_tool, study_design)
 metaptsd
  pretermmeta1 <- escalc(measure="OR", ai= APTSDpospretermpos, bi=BPTSDpospretermneg,
 ci=CPTSDngpretermpos, di=DPTSDngpretermneg, sei=TransOR, data=metaptsd)
  pretermmeta1
 metaregmodel <- rma(yi, vi, mods = ~ country + study_design + assessment_tool, random = ~ 1 | publisher, data
 =  pretermmeta1)
 metaregmodel
 forest(metaregmodel, transf=exp, slab = paste(publisher), xlim = c(-50, 50))

pretermmeta2 <- data.frame(summary(pretermmeta1))
pretermmeta2 <- escalc(measure="OR", ai= APTSDpospretermpos, bi=BPTSDpospretermneg,
 ci=CPTSDngpretermpos, di=DPTSDngpretermneg, sei=TransOR, data=pretermmeta2)
pretermmeta2 <- conv.wald(out=OR, ci.lb=CIlower, ci.ub=CIupper, n=Totalsample, data=pretermmeta2, transf=log)
pretermmeta2
 metaregmodel2<- rma(yi, vi, mods = ~ country + study_design + assessment_tool, random = ~ 1 | publisher, data =
 pretermmeta2)
 metaregmodel2
 forest(metaregmodel2, slab = paste(publisher), xlim = c(-50, 50), col = "red", addfit = TRUE, digits = 2, mlab =
 "Sensitivity analysis")
```

Appendix F: BWT for GA Curves in Female and Male Singletons in Comparison to Kramer

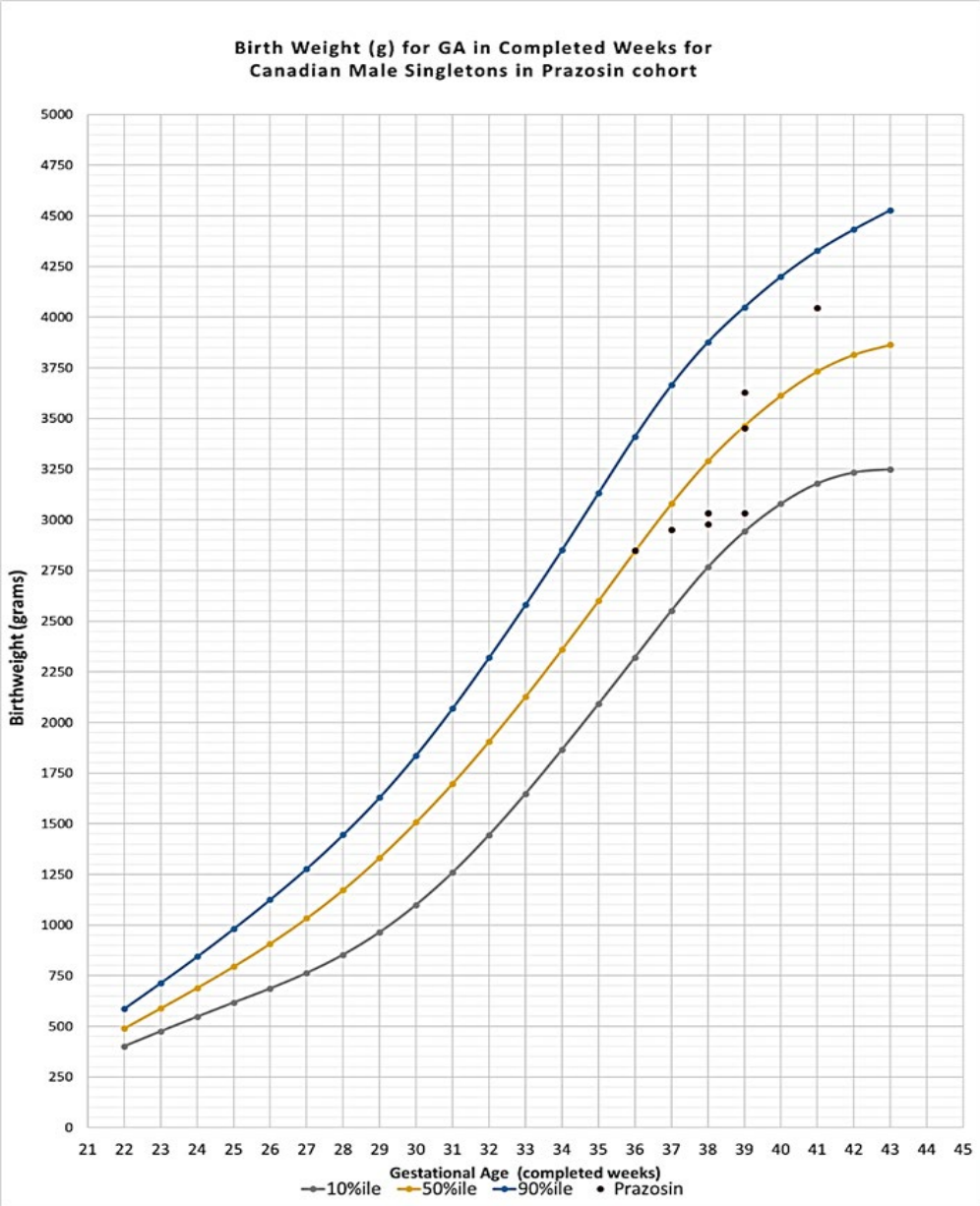

Figure F1- Birthweight for gestational age in male singletons for prazosin given births in comparison to Kramer curve percentiles for the general population (1).

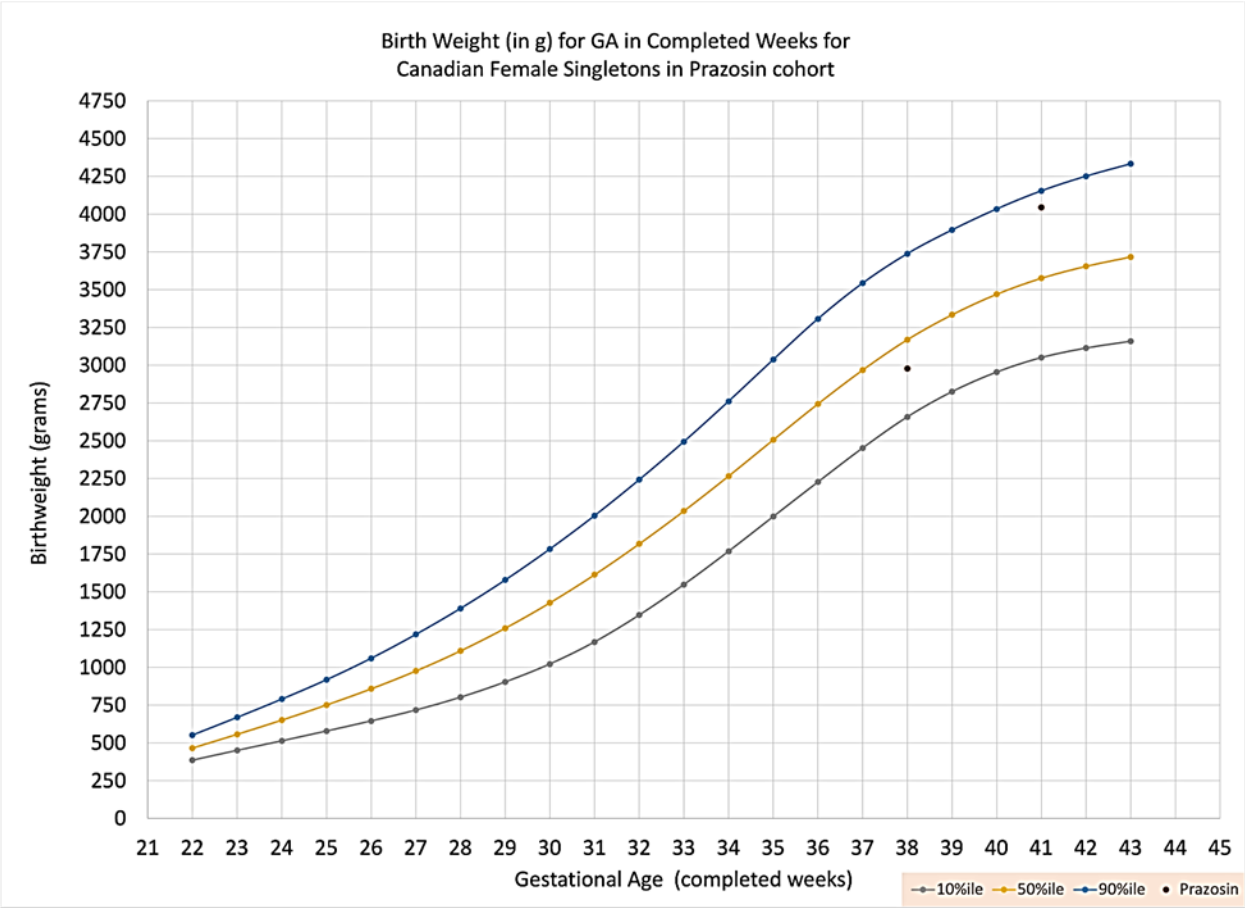

Figure F2- Birthweight for gestational age in female singletons for prazosin given births in comparison to Kramer curve percentiles for the general population (1).

References

1. Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M, et al. A New and Improved Population-Based Canadian Reference for Birth Weight for Gestational Age. Pediatrics.