Prospective Evaluation of Pregnancy Outcomes after Gestational Exposure to Prazosin

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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.

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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 patients [3]. This knowlege 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 [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 [5,9].

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.

Methods :

This prospective observational study included a sample of patients exposed to Prazosin during their pregnancy. 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 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. 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 taking Prazosin and had attended the FRAME clinic were initially identified. Of these, 11 became pregnant while taking the medication, and these formed the final study sample. Data collected included pregnancy and fetal outcomes, if available, such as: miscarriage, preterm birth, preeclampsia, hemorrhage, cesarian section, obtained through electronic chart records and overall pregnancy satisfaction, obtained through phone-call interviews. To assess fetal growth, birth weight was recorded. Data analyses were 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 [10] for male and female singletons. The subject's data was stored as per institutional guidelines. This study was approved by the Western Research Ethics Board (Registration # IRB 00000940).

Results:

The baseline characteristics of the patients, that is, characteristics of the patients before their pregnancies were confirmed, are shown in Table 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, 6/11 of the patients continued Prazosin use during the first trimester of their pregnancy after finding out they were pregnant, and the remainder (5/11) discontinued prazosin during the 1st trimester after they found out they were pregnant. Dose information on Prazosin was not available. Their mean age (in years) was 33.1 with a standard deviation (SD) of 6.62. Mean BMI (kg/ mˆ2) was 32.3 with a SD of 5.44. 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.

Table 1. Baseline and Exposure Characteristics for Patients pre-confirmed pregnancy (n =11)

Age (years)	**33.1[a] (6.62)[b]**
BMI (kg/mˆ2)	**32.3[a](5.44)[b]**
Prazosin for PTSD	**11 (100%)**
Urban Location	**9 (81.8%)**
Rural Location	**2 (18.2%)**
a= average, b =s.d Remaining data is in n (%)	**a= average, b =s.d Remaining data is in n (%)**

Previous exposure, prior to pregnancy diagnosis, and continued exposure during pregancy to alcohol, tobacco, cannabis, and other prescription medication are provided in Table 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 l1 (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. The majority of patients lived in an urban location [9/11(81.8%)] rather than a rural area [2/11 (18.2%)]. 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 pregancy was confirmed, namely Escitalopram (1 patient), Lisdexamfetamine (1 patient), Aripiprazole (1 patient), Duloxetine (1 patient) , Trazadone (1 patient) , and Sertraline (2 patients) during their pregnancies.

Table 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%)**

It was found that 6 /11 (54.5%) subjects did not report any adverse outcomes and were uneventful pregnancies. There were 2 miscarriages. 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. None of the subjects gave birth to low birthweight (bwt) infants (Table 3A). Overall, birthweights for gestational age (GA) fell between the 10^{th} and 90^{th} percentiles (%ile), so all subjects in the Prazosin cohort exhibited fetal growth within the normal population distribution. Looking at individual patient data as shown in Table 3B, 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.

Table 3A. 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 we no fetal malformations, no infants had a low birthweight	**note: there we no fetal malformat**

Table 3B. Pregnancy and Fetal Outcomes for Individual Patients

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

Discussion:

Currently, not enough data exists on the safety of many medications in pregnancy [11]. 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 [12]. These cases are not easy to find, which is why the group of patients counseled 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 [13,14]. 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. [4,5,6,1,2,15,16,17]. 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 [18] 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 [19]. 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 [20,21, 22]. 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) [8] 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. 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 period. 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 review [8] was a 1983 study that looked at Prazosin use in 8 sujects in the last trimester of pregnancy [23]. 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, is 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. Overall, birthweights in the population studied were within normal ranges for gestational age, and none were classified as low birthweight (i.e. <2500g). With regards to additional fetal outcomes, the proportion of miscarriages (18.2%) did not exceed expected rates based on normal population proportions [24].

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 [25]. A study conducted by Seng et al (2011) study also found that maternal PTSD was significantly associated with obstetrical complications such as shorter gestation and lower birthweight [26]. 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.

Limitations of the present study include a small sample size, thus limiting analysis to descriptive findings, and

the absence of a comparison group of women not exposed to Prazosin during pregnancy. Another limitation is the use of self-reported data, collected via phone call questionnaires, which could be subject to recall bias and social desirability bias. The above could limit the ability to make any conclusions regarding safety based on this one small case series. This study provides preliminary data on the effects of use of Prazosin for the treatment of PTSD during pregnancy; however, further research is definitely 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.

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 period 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 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.

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Bullet Points

What is already known:

Prazosin is used to treat PTSD symptoms

PTSD is prevalent in pregnant populations

What this study adds:

The first observational data on the use of Prazosin for PTSD during pregnancy

Clinical significance

Provides clinicians and patients with preliminary data for drug safety for Prazosin in Pregnancy