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Luke E Grzeskowiak, Catherine Leggett, Lynn Costi, Claire T Roberts, Lisa H Amir
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Title: Impact of Serotonin Reuptake Inhibitor Use on Breast Milk Supply in Mothers of Preterm Infants: A Retrospective Cohort Study

Running title: Antidepressant Use and Breast Milk Supply

Author Line:

Luke E Grzeskowiak, Catherine Leggett, Lynn Costi, Claire T Roberts, Lisa H Amir

Author Affiliations:

1. Luke E Grzeskowiak, SA Pharmacy, Flinders Medical Centre, SA Health, Australia & Adelaide Medical School, The Robinson Research Institute, The University of Adelaide, Australia
2. Catherine Leggett, SA Pharmacy, Women's and Children's Hospital, SA Health, Adelaide, South Australia, Australia
3. Lynn Costi, SA Pharmacy, Women's and Children's Hospital, SA Health, Adelaide, South Australia, Australia
4. Claire T Roberts, Adelaide Medical School, The Robinson Research Institute, The University of Adelaide, Australia
5. Lisa H Amir, Judith Lumley Centre, La Trobe University, Melbourne, Victoria, Australia

Corresponding author: Dr Luke Grzeskowiak. Level 6, Adelaide Health and Medical Sciences Building, University of Adelaide, Adelaide 5000, Australia. Ph: +61 8 8313 1687. Email: luke.grzeskowiak@adelaide.edu.au

Abstract

Aims: To examine the association between late pregnancy exposure to serotonin reuptake inhibitor (SRI) antidepressants and difficulties in achieving an adequate breast milk supply in women who gave birth to preterm infants, while accounting for the potential impacts of underlying maternal psychiatric illness.

Methods: Retrospective cohort study of 3,024 women delivering liveborn preterm infants (<37 weeks' gestation) between January 2004 and December 2008. The primary outcome was postnatal domperidone use, considered a valid proxy for presence and pharmacological management of low milk supply. Relative risks adjusted for maternal soiodemographics and comorbidities (aRRs) were calculated for low milk supply, comparing women with late pregnancy exposure to SRI antidepressants (n = 86), women with a psychiatric illness but no antidepressant use (n = 126), and women with neither antenatal exposures (n = 2 812).

Results: Compared to non-exposed women, non-medicated psychiatric illness (aRR 1.64; 95%CI 1.16-2.30) but not late pregnancy SRI use (aRR 1.00; 95%CI 0.59-1.70) was associated with an increased risk of domperidone use, indicative of low milk supply.

Conclusions: These findings do not support the previously observed negative impacts of antidepressant use on breastfeeding, instead suggesting that women with an underlying psychiatric illness appear at greatest risk of experiencing low milk supply and could benefit from additional breastfeeding education and support.

Keywords: serotonin agents, antidepressive agents, breastfeeding, lactation, premature birth

Structured Summary

Statement 1: What is already known about this subject

- Serotonin plays an important role in human breast milk volume homeostasis within the mammary gland during lactation
- Previous research demonstrates women taking antidepressants have lower rates of breastfeeding intention and initiation and are more likely to experience delayed secretory activation
- Whether use of SRIs during lactation is associated with a reduction in breast milk volume or leads to impaired long-term breastfeeding outcomes is unclear

Statement 2: What this study adds

- In a cohort of mothers of preterm infants, use of SRIs in late pregnancy was not associated with an increased risk of experiencing low milk supply
- Women with an underlying psychiatric illness appear at greatest risk of experiencing low milk supply and could therefore benefit from additional breastfeeding education and support.

Main Body of Text

Introduction:

Serotonin has been identified as playing an important role in human breast milk volume homeostasis within the mammary gland during lactation, with increased levels leading to mammary gland involution and reduced milk production.[1] This raises concerns that medications that alter serotonin signaling, such as the serotonin reuptake inhibitor (SRI) antidepressants, may interfere with the normal physiological processes involved in lactation and therefore place women at increased risk of poor breastfeeding outcomes. Previous research has identified that women taking antidepressants have lower rates of breastfeeding intention and initiation,[2, 3] but most recent evidence suggests this is largely due to residual confounding from underlying maternal psychiatric illness.[4] Marshall et al, however, demonstrated an association between maternal Selective Serotonin Reuptake Inhibitor (SSRI) use and delayed secretory activation (defined as onset of copious milk production; also known as stage II lactogenesis) which was independent of underlying maternal depressive illness.[5] While it is well established that delayed secretory activation is associated with a reduced duration of breastfeeding,[6] whether this observed delay associated with SSRI use is also associated with a reduction in breast milk volume or leads to impaired long-term breastfeeding outcomes is unclear. Therefore, the aim of this study was to examine the association between late pregnancy exposure to SRIs and difficulties in achieving an adequate breast milk supply in women who gave birth to preterm infants, while accounting for the potential impacts of underlying maternal psychiatric illness.

Methods:

Ethical Approval

This project was approved by the Women's and Children's Health Network Human Research Ethics Committee (REC2219-10-14).

Study Design and Setting

We conducted a retrospective cohort study of all women delivering liveborn preterm infants (<37 weeks' gestation) at the Women's and Children's Hospital (WCH) in South Australia between January 2004 and December 2008 (n=3 054). We excluded women exposed to antidepressants other than serotonin reuptake inhibitors (n=13) or antipsychotics (n=17), leaving a final cohort of 3 024 women.

The WCH is accredited as part of the Baby Friendly Hospital Initiative (BFHI) and has a dedicated lactation support service. This study utilised linkable electronic health administrative data within the WCH, including the WCH Perinatal Statistics Collection and the WCH Hospital Pharmacy Dispensing Records. The Perinatal Statistics Collection (PSC) includes electronic data on the pregnancy and outcome of every live birth and late fetal death occurring at the hospital.[7] The information in the PSC has been previously validated and is reliable when compared with hospital case records.[8] These data have been previously utilised to investigate outcomes associated with the use of antidepressants during pregnancy and the use of domperidone for the management of low milk supply, the full details of which have been previously published elsewhere.[9, 10]

Measures

Antidepressant use and psychiatric illness

Late pregnancy exposure to serotonin reuptake inhibitors was identified from the WCH Pharmacy Dispensing Records. Women were classified as exposed if they were dispensed a serotonin reuptake inhibitor antidepressant during late pregnancy (second and third trimesters).

Hospital pharmacy dispensing records have previously been validated as an indicator of exposure to antidepressants in late pregnancy, including exposure around the time of delivery.[7]. In an effort to obtain a suitable comparison group consisting of women with similar underlying disease to those exposed to antidepressants during pregnancy, we identified a cohort of women with an identified psychiatric illness during pregnancy but who were not dispensed an antidepressant (disease comparison termed 'nonmedicated psychiatric illness'). The presence of a psychiatric illness during pregnancy was identified from the electronic PSC, with midwives recording the diagnosis if the woman is receiving medication for her psychiatric illness or if it was recorded in the notes that the woman received psychological/psychiatric support during her pregnancy. This has been utilised as a disease comparator group in previous studies.[11] The remaining group of women consisted of those who did not have a psychiatric illness and were not dispensed an antidepressant (termed 'non-exposed').

Breastfeeding Outcomes and Domperidone use

The primary outcome was postnatal domperidone use. Domperidone is a galactagogue which stimulates and promotes milk production and is commonly used as a pharmacological treatment for mothers who are experiencing lactation difficulties.[12, 13] Therefore, domperidone use was considered a proxy for the presence and pharmacological management of low milk supply. Data relating to women dispensed domperidone were obtained from the WCH Pharmacy Dispensing Records in accordance with previously published methods.[14] Domperidone is only able to be prescribed by medical doctors for mothers of preterm infants in the neonatal unit utilising a pre-printed prescribing checklist, with no restrictions according to level of experience (e.g. interns, registrars and consultants all eligible to prescribe). Prescribers in the Neonatal Unit are only allowed to prescribe mother's domperidone for the explicit indication of lactation insufficiency, with mothers referred to other physicians for the

management of conditions not affecting their infant. Further, we have previously undertaken a detailed medication chart review for a random selection of 215 of 1,605 mother-infant dyads where domperidone was prescribed, with 100% of records indicating that domperidone was prescribed for lactation insufficiency.[9] Guidelines regarding the use of domperidone or management of low milk supply during this time period have remained consistent, recommending domperidone as the first-line pharmacological treatment. Domperidone is the most widely prescribed first-line agent for management of maternal low milk supply across Australian neonatal units.[13] Data on any breastfeeding at neonate discharge from hospital are routinely collected and were utilised to determine additional breastfeeding outcomes. Furthermore, in the 2008 calendar year only, additional data were also available pertaining to initiation of breastfeeding and exclusivity of breastfeeding during infant admission to the Neonatal Unit.

Covariates

Data on additional maternal and neonatal characteristics were obtained from the PSC. Maternal age and body mass index (BMI) was determined at the time of first antenatal booking visit. Women were classified as non-smokers or smokers during pregnancy based on maternal self-report at the first antenatal visit. The estimated length of gestational age at delivery is based on the last menstrual period and ultrasound examination. According to parity, women were classified as either primiparous or multiparous. Method of delivery was classified as either vaginal delivery (including instrumental deliveries) or lower segment caesarean section (LSCS; including elective and emergency). Maternal ethnicity was classified as Caucasian or other. Socioeconomic status for each woman was determined using her residential postcode at the time of delivery. Women were then ranked according to their level of advantage or relative disadvantage, based on data from the Socio-Economic Indexes

for Areas (SEIFA), calculated from the Australian Bureau of Statistics' (ABS) five-yearly Census of Population and Housing. SEIFA scores were converted to quintiles, representing widely used measures of relative socio-economic status.

Data Analyses

The association between maternal SRI exposure status and domperidone use was evaluated using a generalised linear model (Poisson distribution) with robust variance estimates (and resulting relative risks (RR) and 95% confidence intervals). Analyses were adjusted for possible confounders including maternal age, parity, smoking status, socioeconomic status, and gestational age at birth. We also conducted a sensitivity analysis restricting the analysis to the 2008 calendar year when data on breastfeeding initiation and EBF at discharge were available. Statistical significance was defined as a two-sided p-value of <0.05. All statistical analyses were undertaken using STATA IC 14 (Stata, College Station, Texas).

Results

Among the cohort of 3024 eligible women, 86 (2.8%) were exposed to a SRI in late pregnancy, 126 (4.2%) were exposed to non-medicated psychiatric illness and the remaining 2812 (93.0%) were non-exposed.

Table 1 describes the demographic and clinical characteristics of women according to exposure status. While women exposed to SRIs in late pregnancy differed from non-exposed women across a number of characteristics, they were largely representative of women with non-medicated psychiatric illness.

The prevalence of domperidone use was highest among women with non-medicated psychiatric illness (23.8%), followed by those with SRI use (16.3%) and those who were non-exposed (14.6%). The unadjusted and adjusted differences in domperidone use between groups are presented in **Table 2**. Compared to non-exposed women, non-medicated psychiatric illness (aRR 1.64; 95%CI 1.16-2.30) but not late pregnancy SRI use (aRR 1.00; 95%CI 0.59-1.70) was associated with an increased use of domperidone use, indicative of low milk supply.

The cumulative percentage of women dispensed domperidone postpartum according to late pregnancy exposure status is presented in **Figure 1**. Across all groups more than 50% of women who received domperidone were dispensed it within the first 3 weeks postpartum. The rate of domperidone use appeared similar among the SRI use and non-medicated psychiatric illness groups within the first 3 weeks postpartum, before tapering off in the SRI use group while continuing to increase in the non-medicated psychiatric illness group. **Figure 2** demonstrates that the prevalence of domperidone use was highest among mother's with a non-medicated psychiatric illness across all gestations.

In a sensitivity analysis involving only those women who delivered in the 2008 calendar year where data were available on breastfeeding initiation and we were able to restrict the cohort to women who initiated breastfeeding, no difference in domperidone use was observed between women with SRI use in late pregnancy and non-medicated psychiatric illness (RR 1.05; 95%CI 0.28-3.94). When further restricted to primiparous women, no difference in domperidone use was observed between women with SRI use in late pregnancy and non-medicated psychiatric illness (RR 1.06; 95%CI 0.49-2.28).

Discussion

Main Findings

We found that use of SRIs in late pregnancy is not associated with an increased risk of domperidone use in mothers of preterm infants. These findings suggest that use of serotonin disrupting antidepressants during lactation do not appear to place women at increased risk of experiencing low milk supply.

Strengths and Limitations

To our knowledge, this is the largest study undertaken to investigate the potential impacts of maternal SRI use and non-medicated psychiatric illness on breast milk supply difficulties. The major strength of this study lies in the identification of a group of women with non-medicated psychiatric illness to provide greater adjustment for potential confounding associated with underlying maternal illness. Further, utilisation of data on domperidone use as a proxy for the presence of low milk supply represents a novel approach towards addressing a topic of particular significant importance, with a previous clinical audit finding 100% agreement between domperidone use and management of lactation insufficiency. In accordance with hospital policy, domperidone is supplied to mothers in the Neonatal Unit utilising a carefully developed prescribing checklist which requires prescriber acknowledgement of persistent low milk supply despite previous utilisation of non-pharmacological interventions. Therefore, domperidone supply is likely to represent those women experiencing the greatest breastfeeding difficulties. Further strengths of this study include undertaking additional sensitivity analyses to determine the potential impact of breastfeeding initiation on observed breastfeeding outcomes.

There are a number of limitations associated with this study. Use of hospital pharmacy dispensing data may not have identified all women who were taking an antidepressant in late pregnancy, meaning some women in the control groups may have been exposed to SRIs unknowingly. Such misclassification, however, is likely to be non-

differential with respect to the outcome under investigation and therefore is unlikely to have impacted greatly on the effect estimate.[15] We are not able to confirm that women exposed to a SRI in late pregnancy continued to take it while breastfeeding and we do not have data on whether women in the non-medicated psychiatric illness or non-exposed group were prescribed an antidepressant in the postpartum period. However, based on previous drug utilisation studies,[16] the number of women in the non-medicated psychiatric illness group who may have been previously on an antidepressant and then restarted it during lactation is likely to be low, as is the relative number of women in the non-exposed group who may have been newly prescribed an antidepressant in the postpartum period. In addition, there was no measure of the type and severity of maternal psychiatric illness, which would have added to understanding the independent effects of psychiatric illness on the risk of low milk supply, and we did not assess the impact of dose or indication of SRI use. A noted limitation is that women identified as having a non-medicated psychiatric illness (which excluded users of non-SSRI antidepressant or antipsychotics) reflect a heterogenous group with a range of likely psychiatric diagnoses and severities reflecting imbalances of other neurotransmitters, besides serotonin. Lastly, given we restricted the study to mothers of preterm infants. It is unclear whether the findings will also be generalizable to mothers of term infants.

Interpretation

The role of serotonin and serotonin transport in the regulation of lactation has been reviewed in detail elsewhere.[17] In brief, numerous animal studies have established serotonergic transmission as a key regulator of lactation homeostasis, with increased levels of serotonergic activity (including through use of SRIs) accelerating the rate of mammary gland involution, leading to a reduction in milk production.[17] Whether similar effects occur in humans is unclear, with it previously noted that the mammary glands of mice, cattle and

humans express unique patterns of 5-HT receptors that vary among the species.[18] The potential impacts of SRI exposure have only been investigated in one human study, where maternal SSRI use was associated with a 2-fold delay in secretory activation.[5]. In comparison to our study, there are a few note-worthy differences that could explain inconsistent study findings. The findings from Marshall *et al.* were based on a total of only 8 mothers of term infants exposed to SSRIs, compared to our sample of 86 women taking SRIs. Furthermore, all women had experienced secretory activation by day 7, with no examination of breast milk volume or longer term breastfeeding outcomes.[5] We focused on mothers of preterm infants as this was envisaged to enable us to obtain more complete data on domperidone use occurring within the hospital and the longer neonatal hospital admission enabled examination of longer term breastfeeding outcomes. Further, mothers of preterm infants are the most vulnerable for experiencing difficulties with milk supply and their infants benefit the most from the available of mother's own milk for feeding. Given the additional breastfeeding supports often available to mothers of preterm infants, it is possible that these may overcome any challenges related to delayed secretory activation and therefore avoid potential negative impacts posed by serotonin disruption during lactation.

Notably, these findings do not provide evidence against a role of serotonin in lactation, rather, they provide evidence that interference of serotonin signalling through antidepressant use is unlikely to directly impact on breast milk production. It is well recognised that successful lactation is moderated by a range of behavioural, social, clinical, and biological factors, with one of the most significant clinical factors being giving birth to a preterm infant.[19] Of note, previous studies have demonstrated that acute and chronic physical and mental stress can impair the milk ejection reflex by attenuating oxytocin release.[19] This could lead to incomplete emptying of the breast and a resultant reduction in overall milk production. This may explain why underlying maternal psychiatric illness appeared to have

the greatest impact on inadequate breast milk supply and point towards the needs for increased awareness of maternal illnesses that can impact on milk supply to identify women that may require additional support and education to attain optimal breastfeeding outcomes. These findings suggest the need to provide additional attention and support to women taking antidepressants during lactation. Although the risks to the breastfed infant associated with antidepressant use in lactation are considered low, the choice to breastfeed when taking an antidepressant may pose a dilemma for some women.[20] Concerns regarding infant "exposure" through human milk may lead to unnecessary anxiety among mothers and in turn negatively impact on the physiological processes involved in lactation or their determination to persist with any breastfeeding difficulties should they arise.

In conclusion, we found no evidence that use of SRIs in late pregnancy was associated with an increased risk of low milk supply in mothers of preterm infants. Women with an underlying psychiatric illness appear at greatest risk of experiencing low milk supply and could therefore benefit from additional breastfeeding education and support.

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Conflict of Interest: All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors Statement: LEG conceptualised and designed the study, carried out the initial analyses, and drafted the initial manuscript. CL, LC, CTR, and LHA helped design the study, assisted in interpretation of results, and reviewed and revised the initial manuscript. All authors approved the final manuscript as submitted.

Details of Ethics Approval: This project was approved by the Women's and Children's Health Network Human Research Ethics Committee (17 July 2013; REC2219-10-14).

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375 **Tables:**

Table 1. Demographic and Clinical Characteristics for Mothers of Preterm Infants Exposed to Serotonin Reuptake Inhibitors, Non-Medicated Psychiatric Illness, or Neither During Late Pregnancy

Characteristic	SRI Use (n=86)	Non-Medicated Psychiatric Illness (n=126)	Non-Exposed (n=2 812)
Age, mean ± SD	30.2 (5.3)	29.0 (6.2)	29.5 (6.2)
Maternal BMI (kg/m^2), mean ± SD	26.9 (6.1)	26.6 (6.8)	26.3 (6.6)
Parity			
Multiparous, n(%)[†]	50 (58.1)	71 (56.4)	1 441 (51.4)
Smoking status, n(%)[†]			
Non-smoker	52 (61.9)	68 (56.7)	1 889 (74.2)
Quit during pregnancy	2 (2.4)	7 (5.8)	95 (3.7)
Smoker	30 (35.7)	45 (37.5)	562 (22.1)
Ethnicity, n (%)[†]			
Caucasian	82 (95.4)	116 (92.1)	2 289 (81.4)
Other	4 (4.7)	10 (7.9)	523 (18.6)
Socioeconomic status, SEIFA, n(%)[†]			
5 (Highest)	11 (12.8)	21 (16.7)	441 (15.8)
4	10 (11.6)	25 (19.8)	483 (17.3)
3	15 (17.4)	19 (15.1)	478 (17.1)

2	16 (18.6)	21 (16.7)	665 (23.8)
1 (Lowest)	34 (39.5)	40 (31.8)	732 (26.2)
Psychotropic medication use, n(%)[†]	6 (7.0)	10 (7.9)	50 (1.8)
Substance abuse, n(%)[†]	6 (7.0)	19 (15.1)	144 (5.1)
Delivery type			
Caesarean section	50 (58.1)	67 (53.2)	1 424 (50.6)
Gestational age (Weeks), median (Range)	35 (25-36)	34 (22-36)	34 (23-36)
Dispensed domperidone, n(%)[†]	14 (16.3)	30 (23.8)	410 (14.6)
Initiated breastfeeding[‡]**, n(%)**[†]	19 (95.0)	12 (85.7)	499 (88.3)
Any breastfeeding at neonatal discharge from hospital, n(%)[†]	74 (86.1)	105 (84.0)	2 379 (84.8)
2008 cohort only (n=305)			
Exclusively breastfeed infant during entire neonatal unit admission [‡]**, n(%)**[†]	4 (20.0)	1 (7.1)	115 (20.4)

[†] Percentages are calculated from non-missing data

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Table 2. Multivariate Analysis of Postnatal Domperidone Use According to Maternal Psychiatric Illness and Prenatal SRI Exposure During Late Pregnancy

SRI Use Vs. Non-Exposed	SRI Use Vs. Non-Medicated Psychiatric Illness	Non-Medicated Psychiatric Illness Vs. Non-Exposed
	Unadjusted RR (95% CI)	
1.12 (0.66, 1.87)	0.68 (0.37, 1.25)	1.63 (1.17, 2.28)
	Adjusted RR (95% CI)[a]	
1.00 (0.59, 1.70)	0.62 (0.33, 1.16)	1.64 (1.16, 2.30)

Abbreviations: SRI, serotonin reuptake inhibitor; aRR, adjusted relative risk; CI, confidence interval

[a] RR adjusted for maternal age, parity, smoking status, socioeconomic status, and gestational age at birth

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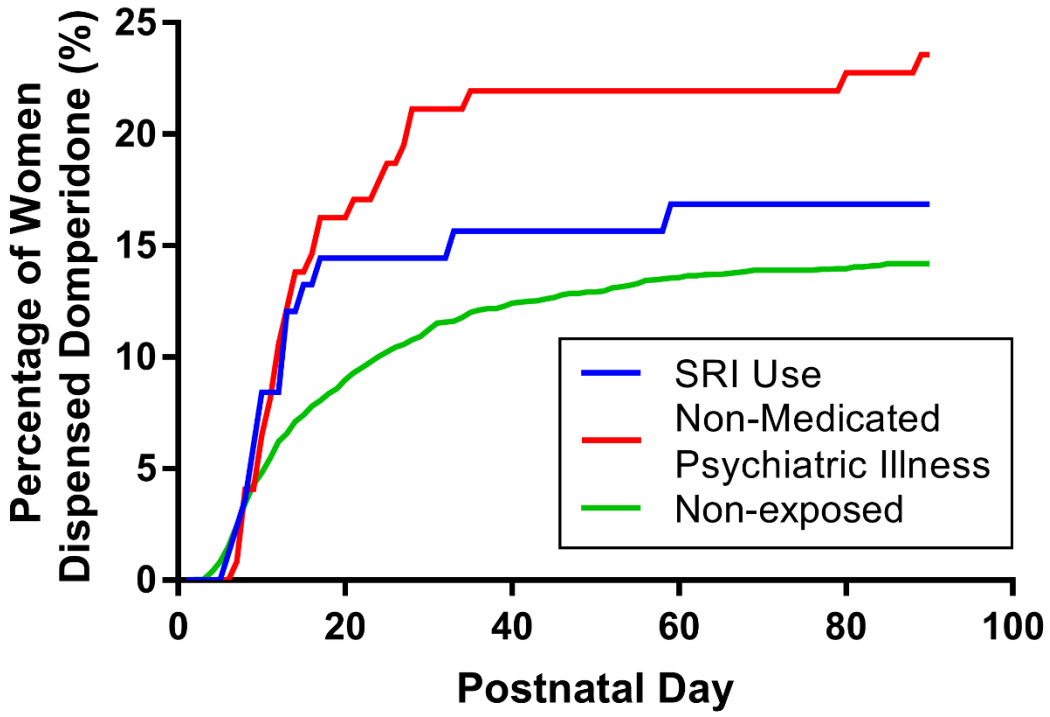
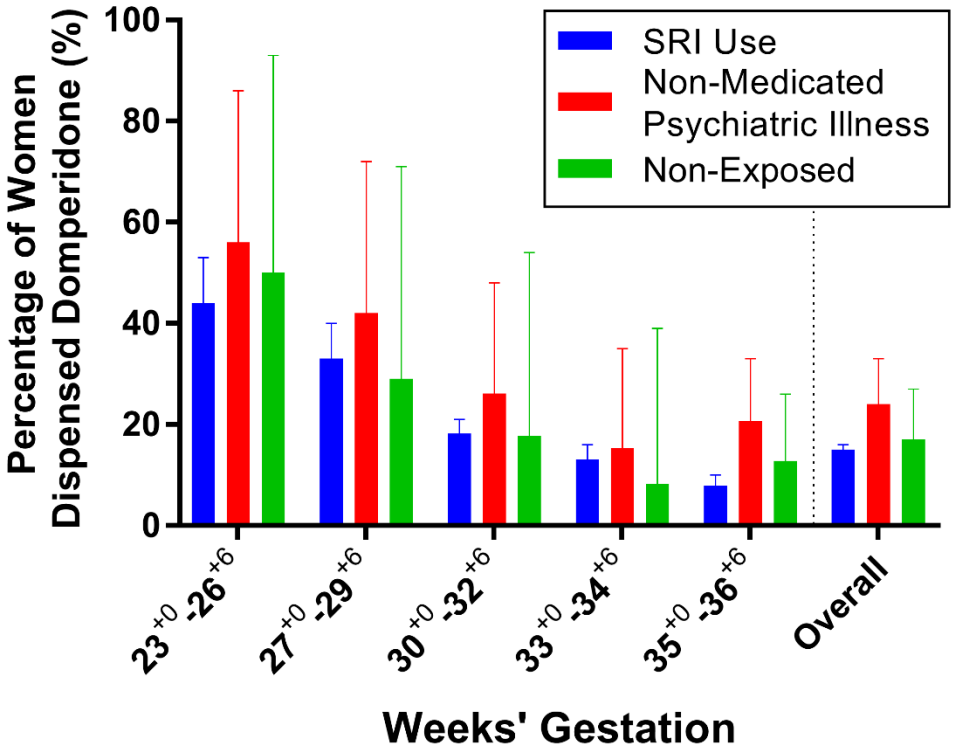
Figure Captions:

Figure 1: Cumulative Percentage of Women Dispensed Domperidone Postpartum According to Late Pregnancy Exposure Status



386 Figure 2: Percentage of Women Prescribed Domperidone According to Exposure Status and

387 Gestational Age at Birth



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