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Research paper

# Dose-effect of maternal serotonin reuptake inhibitor use during pregnancy on birth outcomes: A prospective cohort study

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ABSTRACT

*Background:* While antidepressant use during pregnancy is increasingly common, there is concern about the possible effects of in-utero antidepressant exposure on the child. Our objective was to examine whether there is a dose-effect of maternal serotonin reuptake inhibitors (SRI) during pregnancy on birth outcomes.
*Methods:* Women between 12 and 16 weeks of gestation, who were using an SRI, were eligible for participation in this nation-wide prospective observational cohort study. Recruitment took place between April 2015 and February 2018 ($n$ = 145). SRI exposure and psychopathology symptoms were assessed throughout pregnancy. Exposure was defined as SRI standardized dose at 36 weeks of gestation and mean SRI standardized dose over total pregnancy. Multivariable linear and logistic regression were used to examine the associations with birth weight, gestational age at birth, and being small for gestational age.
*Results:* Maternal SRI dose at 36 weeks of gestation was significantly associated with birth weight (adjusted ß = -180.7, 95%CI -301.1;-60.2, $p$-value < 0.01) as was mean SRI standardized dose during total pregnancy (adjusted ß = -187.3, 95%CI -322.0;-52.6, $p$-value < 0.01). No significant associations between maternal SRI dose and gestational age or being small for gestational age were observed.
*Limitations:* Although prospective, we cannot make full causal inferences given that we did not randomize women to different dosages.
*Conclusion:* These findings suggest that careful dosing of SRI use during pregnancy may prevent a negative impact on birth weight and indicate the need for further investigation of causality.

## 1. Introduction

Antidepressants (ADs) are the first-choice drug treatment for mood and anxiety disorders. The use of ADs during pregnancy has been growing steadily (Molenaar et al., 2019), with prevalence rates ranging between 2 and 13% (Molenaar et al., 2020). As ADs cross the placenta, there is substantial concern about the possible effects of in utero AD exposure on the unborn child (Ewing et al., 2015). Several studies showed associations between in utero AD exposure and unfavorable neonatal outcomes, such as preterm birth, low birth weight, low Apgar score, Persistent Pulmonary Hypertension of the Neonate, and cardiac abnormalities (Bérard et al., 2016; Corti et al., 2019; Eke et al., 2016; Ross et al., 2013; Sujan et al., 2017). Furthermore, other studies have shown that AD use during pregnancy has been associated with increased risks of adverse developmental child outcomes, such as altered brain development, childhood overweight and psychiatric and neurobehavioral outcomes (Grzeskowiak et al., 2013; Liu et al., 2017; Lugo-Candelas et al., 2018; Skurtveit et al., 2014). Fetal programming might account for an impact of ADs on early intra-uterine development, which might result in both unfavorable neonatal outcomes as well as

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unfavorable long-term outcomes (Pluess and Belsky, 2011). Unfortunately, most of these studies are large retrospective register studies. Important confounders, especially the severity of the underlying mood or anxiety disorder (i.e. the indication for AD treatment), are often not controlled for. In addition, these register studies are often based on prescription of ADs rather than actual use and information. Finally, the dose that is actually taken is often lacking, which restricts further understanding of a causal relationship between AD use and child outcomes.

Given the importance of both adequate treatment of maternal mental health as well as the life-long health of the offspring, more clarity on the relationship between AD use during pregnancy and child development is urgently needed (Clark, 2016). This knowledge will support pregnant women's decision-making about whether to continue pre-existing AD use during pregnancy, or to consider guided lowering or discontinuation of their AD use, possibly in combination with other non-pharmacological treatment options, such as cognitive behavioral therapy (Bockting et al., 2018; O'Connor et al., 2019).

The current study aimed to prospectively investigate the effects of maternal serotonin reuptake inhibitors (SRIs) daily dose on birth outcomes. The existence of a dose-response relationship ('biological gradient') is a strong indicator of a causal link between a specific determinant and outcome although its absence should not be regarded as precluding causation (Hill, 1965). Though SRIs have been associated with preterm birth and suboptimal fetal growth (Eke et al., 2016; Zhao et al., 2018), to date, findings on dose-effects of SRIs on birth outcomes are sparse and conflicting (Oberlander et al., 2008; Roca et al., 2011; Suri et al., 2007). We examined whether maternal SRI daily dose is associated with birthweight, gestational age, and whether the child is small for gestational age (SGA) in a graded way. This was studied in a Dutch sample of pregnant women, while controlling for a large set of confounders, including maternal depressive and anxiety symptoms. We examined both the association between birth outcomes and exposure to SRI dose at 36 weeks of pregnancy and the association between birth outcomes and mean dose exposure during total pregnancy.

## 2. Methods

### 2.1. Study design and participants

The present study was an observational cohort study of pregnant women with SRI use during pregnancy. It was part of a larger nationwide research project on antidepressant use during pregnancy, including both a randomized controlled trial (RCT), called 'Stop or Go' (NTR4694), in which women were randomized to continue or discontinue SRIs during pregnancy (Molenaar et al., 2016), and a prospective observational cohort. This study was approved by the Medical Ethical Committee of the Erasmus Medical Center (MEC-2014–505). The current study reports on participants from the observational cohort only.

Women were recruited between April 2015 and February 2018 during their prenatal booking visit in midwifery practices and hospitals, through general practitioners, or through advertisement in (social) media. Women received study information on both the RCT and the observational cohort. When women were not eligible or declined to participate in the RCT, they were asked to participate in the observational cohort. Written informed consent was necessary for participation.

For the present observational study, participants were considered eligible if they were between 12 and 16 weeks pregnant, used an SRI (either a Selective Serotonin Reuptake Inhibitor (SSRI) or Serotonin Noradrenalin Reuptake Inhibitor (SNRI)) in their first trimester, and were proficient in Dutch and/or English. Women with a multiple pregnancy were non-eligible.

### 2.2. SRI dose

SRI type and current daily dose were assessed at baseline (between 12 and 16 weeks of gestation) and at 24 and 36 weeks of gestation. To ensure correct dosing information, medication adherence was assessed, using the medication adherence rating scale (Horne and Weinman, 1999). We standardized the prescribed dose per individual by computing dose equivalent scores, as not all SRI types are equally dosed to reach their therapeutic effect. Dose equivalent scores were computed by dividing the prescribed dose by the standard initial dose for the SRI type prescribed. Standard initial doses according to the American pharmaceutical treatment guidelines (the National Library of Medicine of the National Institutes of Health (https://www.nlm.nih.gov)) are: citalopram 20 mg, escitalopram 10 mg, fluoxetine 20 mg, fluvoxamine 100 mg, paroxetine 20 mg, sertraline 50 mg, and venlafaxine 75 mg.

### 2.3. Birth outcomes

Outcomes were: birth weight (in grams), gestational age at birth (in days), and small for gestational age (SGA). Birth weight was reported by the mothers. In the Netherlands, all mothers receive a medical document stating the birth weight. Gestational age was calculated from the reported due date at baseline, as determined by ultrasound between 8 and 12 weeks of gestation, and the actual date of birth. Infants were classified as SGA when their birth weight was below the tenth percentile for the corresponding gestational age and gender according to the Hoftiezer standards (Hoftiezer et al., 2019). These standards are based on live-born singleton infants born in The Netherlands between 2000 and 2014.

### 2.4. Confounding factors

Potential confounding factors were selected based on literature and included variables that have shown associations with SRI dose and predictive of birth outcomes and were unlikely to be part of the causal chain from SRI exposure to outcome. Maternal age and parity (primiparous/multiparous) were assessed at baseline (Campbell et al., 2012). Socio-economic status was defined by highest level of education (primary/secondary education or higher education) and whether participants had a paid job (y/n) at baseline (Amini et al., 2018; Von Soest et al., 2012). To enable control for symptoms of depression and anxiety during pregnancy in the analysis (Ding et al., 2014; Grote et al., 2010), the Edinburgh Postnatal Depression Scale (EPDS) (Bergink et al., 2011), and the short-form of the state scale of the State-Trait Anxiety Inventory (STAI) (Marteau and Bekker, 1992) were administered at baseline and 24 and 36 weeks of gestation. EPDS scores range between 0 and 30, with a score of 11 or higher indicating a high risk of depressive disorder (Bergink et al., 2011). STAI scores range between 20 and 80, with higher scores indicating greater anxiety. Mean sum scores over the three measurements were calculated to represent symptomatology during total pregnancy. In addition, we accounted for current and lifetime diagnosis of depression and anxiety as measured with the Structured Clinical Interview for DSM-IV-TR Axis I disorders (SCID-I) at baseline (First et al., 2002).

#### 2.4.1. Multiple imputation of missing data

To avoid potential selection bias and a decrease in statistical power associated with complete case analysis, missing values for all outcomes were imputed (White et al., 2011). The percentage of missing data in the present study ranged from 9.0% to 22.8% (mean 15.3%). For 97 participants (66.7%) at least one variable was missing. Birth weight was missing in 14.5% and gestational age in 13.8%. Missing data were imputed using multiple imputation by chained equations under the assumption that missing values were missing at random (MAR) or missing completely at random (MCAR). All missing variables, including

the outcome variables, were imputed (Sterne et al., 2009). Multiple data sets ($N$ = 10) were generated to account for the uncertainty in imputed data. We report on the pooled estimates. To test the robustness of our findings, we performed sensitivity analyses using the non-imputed data set.

### 2.5. Statistical analyses

First, descriptive statistics of the study population were provided. We then used univariable linear and logistic regression to examine the associations of dose-equivalent score at 36 weeks of gestation and mean dose-equivalent score over total pregnancy as continuous variables with continuous birth outcomes (birth weight, gestational age) and the dichotomous variable SGA, respectively. Subsequently, we repeated the analyses, in which we adjusted for confounding factors, following a two-step procedure. In the partially adjusted model we included confounding factors with a solid evidence-based foundation (maternal age, parity, mean EPDS and STAI scores) (Campbell et al., 2012; Ding et al., 2014; Grote et al., 2010). In the fully adjusted model we additionally corrected for education level, having a paid job and a current or lifetime SCID diagnosis of depression and anxiety (Amini et al., 2018; Pluess and Belsky, 2011; Von Soest et al., 2012). Lastly, we performed a sensitivity analysis only including participants with SSRIs and excluding those with SNRIs. The Statistical Package for Social Sciences (SPSS) version 25.0 was used for data analyses and the significance level was set at 0.05, two sided.

## 3. Results

A total of 478 women were referred for counselling and consecutive screening for eligibility. This resulted in a final study sample for the current observational study of 145 women (Fig. 1). Maternal and neonatal characteristics of the sample before multiple imputation are listed in Table 1. Besides a diagnosis (past or present) of depression or anxiety (including panic disorder ($n$ = 38), agoraphobia ($n$ = 34), social phobia ($n$ = 21), specific phobia ($n$ = 19), obsessive-compulsive disorder ($n$ = 22), post-traumatic stress disorder ($n$ = 17), generalized anxiety disorder ($n$ = 4), and anxiety not otherwise specified ($n$ = 7)), we found the following diagnoses (past or present) in our study cohort: alcohol misuse/dependency ($n$ = 6), substance misuse/dependency ($n$ = 4), psychotic disorder ($n$ = 4), anorexia ($n$ = 11), bulimia ($n$ = 6), binge eating disorder ($n$ = 2), somatization disorder ($n$ = 1), and pain disorder ($n$ = 3). Mean EPDS scores throughout pregnancy remained stable and below the cut-off score of 11 (Bergink et al., 2011). At baseline, 17.4% of women scored above the EPDS cut-off score, and 18.5% and 15.2% scored above the cut-off score at 24 and 36 weeks of gestation respectively.

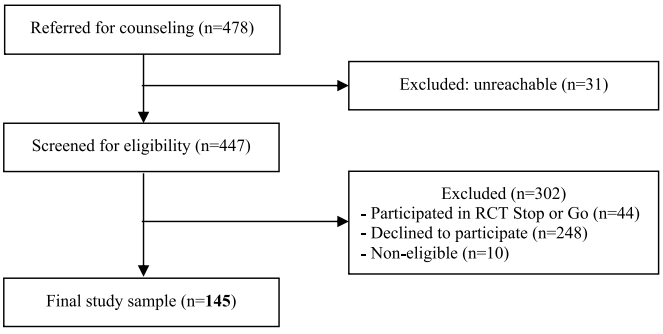


**Fig. 1.** Flow diagram of participant inclusion.

**Table 1**
Maternal and neonatal characteristics (before multiple imputation).

| Maternal demographic characteristics | $N$ = 145[a] | |
|---|---|---|
| | *Mean* | *SD* |
| Age at enrolment in years | 32.2 | 4.7 |
| | *N* | *%* |
| Primiparous, yes | 76 | 57.6 |
| Level of education, high | 77 | 60.6 |
| Paid job, yes | 105 | 79.5 |
| **Maternal mental health characteristics** | | |
| | *N* | *%* |
| Type of SRI | | |
| Citalopram | 43 | 29.7 |
| Escitalopram | 20 | 13.8 |
| Fluoxetine | 12 | 8.3 |
| Fluvoxamine | 1 | 0.7 |
| Paroxetine | 22 | 15.2 |
| Sertraline | 32 | 22.1 |
| Venlafaxine | 15 | 10.3 |
| | *Mean* | *SD* |
| Dosage per SRI type in mg/day | | |
| Citalopram | 19.8 | 10.5 |
| Escitalopram | 13.1 | 6.0 |
| Fluoxetine | 35.1 | 37.8 |
| Fluvoxamine | 100.0 | – |
| Paroxetine | 19.9 | 8.6 |
| Sertraline | 77.2 | 36.0 |
| Venlafaxine | 94.7 | 58.8 |
| Duration of SRI use in months, median (range)[b] | 48 | (1 – 252) |
| Mean dose equivalence during pregnancy | 1.2 | 0.7 |
| Dose equivalence at 36 weeks of pregnancy | 1.1 | 0.8 |
| Mean EPDS score during pregnancy[c] | 6.9 | 4.0 |
| Mean STAI score during pregnancy[d] | 35.9 | 9.3 |
| | *N* | *%* |
| SCID diagnosis of depression[e] | 101 | 70.1 |
| SCID diagnosis of anxiety[f] | 95 | 66.0 |
| **Neonatal characteristics** | | |
| | *Mean* | *SD* |
| Birth weight in grams | 3347.1 | 509.2 |
| Gestational age at birth in days | 275.1 | 10.3 |
| | *N* | *%* |
| Small for gestational age (SGA, < 10th percentile) | 18 | 14.5 |

[a] Numbers may not always sum up due to missing data.
[b] Values for this variable were nonnormally distributed, and therefore, median and range are reported.
[c] Mean EPDS score calculated from sum scores at 16, 24 and 36 weeks of pregnancy.
[d] Mean STAI score calculated from sum scores at 16, 24 and 36 weeks of pregnancy.
[e] Lifetime (previous or current) SCID diagnosis of depression.
[f] Lifetime (previous or current) SCID diagnosis of anxiety disorder.

### 3.1. Effects of maternal SRI dose at 36 weeks of gestation on birth weight, gestational age, and SGA

The analysis of maternal SRI dose at 36 weeks of gestation showed a negative association with birth weight (β = −156.7, 95%CI −280.0;−33.4, df=1, $p$-value = 0.01), which remained present after adjustment for the full set of confounders (adjusted β = −180.7, 95%CI −301.1;−60.2, df=9, $p$-value < 0.01). No significant associations of SRI dose at 36 weeks of gestation with gestational age (β = −1.3, 95%CI −3.7;1.1, df=1, $p$-value = 0.28) or SGA (OR = 1.2, 95%CI 0.7;2.1, df=1, $p$-value = 0.55) were observed (Table 2). Sensitivity analyses both with the non-imputed dataset and with exclusion of participants using SNRIs showed similar results.

**Table 2**
Dose effect of SRI medication on birth outcomes.

| Effects of dose at 36 weeks of gestation | Unadjusted (ß / OR) | 95% CI | *p*-value | Partially adjusted[a] (ß / OR) | 95% CI | *p*-value | Fully adjusted[b] (ß / OR) | 95%CI | *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| Birth weight (grams) | −156.7 | −280.0;−33.4 | 0.01 | −158.2 | −280.2;−36.2 | 0.01 | −180.7 | −301.1;−60.2 | <0.01 |
| Gestational age (days) | −1.3 | −3.7;1.1 | 0.28 | −1.3 | −3.6;1.0 | 0.26 | −1.5 | −3.8;0.9 | 0.23 |
| SGA (<10th percentile) | 1.2 | 0.7;2.1 | 0.55 | 1.2 | 0.7;2.1 | 0.54 | 1.3 | 0.7;2.4 | 0.37 |
| Effects of mean dose over total pregnancy | | | | | | | | | |
| Birth weight (grams) | −166.3 | −299.3;−33.2 | 0.01 | −165.5 | −299.5;−31.6 | 0.02 | −187.3 | −322.0;−52.6 | <0.01 |
| Gestational age (days) | −1.8 | −4.5;0.9 | 0.18 | −1.7 | −4.3;0.9 | 0.20 | −1.9 | −4.5;0.8 | 0.18 |
| SGA (<10th percentile) | 1.2 | 0.6;2.3 | 0.59 | 1.2 | 0.6;2.3 | 0.60 | 1.3 | 0.7;2.5 | 0.47 |

[a] Adjusted for maternal age, parity, mean EPDS score, mean STAI score.
[b] Adjusted for maternal age, parity, mean EPDS score, mean STAI score, education level, paid job, SCID diagnosis of depression and SCID diagnosis of anxiety.

### *3.2. Effects of mean maternal SRI dose on birth weight, gestational age, and SGA*

Similar results were observed for the effects of mean SRI dose during total pregnancy on birth outcomes. An association was found between mean SRI dose and birth weight (β = −166.3, 95%CI −299.3;−33.2, df=1, *p*-value = 0.01), which remained present after adjustment for the full set of confounding factors (adjusted β = −187.3, 95%CI −322.0;−52.6, df=9, *p*-value < 0.01). However, no significant associations were found between mean SRI dose and gestational age (β = −1.8, 95%CI −4.5;0.9, df=1, *p*-value = 0.18) or between mean SRI dose and SGA (OR = 1.2, 95%CI 0.6;2.3, df=1, *p*-value = 0.59). Sensitivity analyses with the non-imputed dataset showed similar results.

## 4. Discussion

In this prospective observational cohort study, we found that, while controlling for maternal depressive and anxiety symptoms, maternal SRI dose during pregnancy, both assessed at 36 weeks of gestation and averaged over total pregnancy, was significantly associated with birth weight of the offspring. Higher daily dose equivalent of maternal SRI during pregnancy was associated with lower birth weight (a 180–190 g birthweight reduction per single dose equivalent increase). Maternal SRI dose at 36 weeks of gestation and mean SRI dose during total pregnancy were not significantly associated with gestational age of the offspring or with being small for gestational age.

Previously, the association between antidepressant use and birth outcomes has mostly been investigated in population-based registers. They often provide large sample sizes and sufficient information on prescribed medication. However, controlling for confounders, especially regarding severity of maternal depressive and anxiety symptoms, can prove to be difficult. Choosing a suitable control population is not straightforward. The effect estimates of children with maternal AD exposure can be compared to those of children born to asymptomatic and unexposed women. Unfortunately, these groups are likely to differ in measurable and unmeasurable factors, more than the groups in our study with varying doses. Examples of these factors include genetics, underlying disease severity and symptomatology, possibly leading to an overestimation of the consequences of AD exposure. A different strategy is therefore to compare children with exposure to maternal ADs with children born to depressed (symptomatic) women without AD exposure (Mitchell and Goodman, 2018). However, many women on ADs will be in remission and will not have symptoms of depression or anxiety during pregnancy, and are thus not comparable to symptomatic women. Such a comparison can result in an underestimation of the consequences of AD exposure, as symptoms of depression and anxiety during pregnancy have also been associated with negative child outcomes, including lower birth weight (Ding et al., 2014; Grote et al., 2010). A recent study in Norway summarized the conflicting study results and attempted to overcome methodologic issues by employing a sibling design, minimizing putative confounding factors related to maternal factors (Nezvalová-Henriksen et al., 2016). They found that SSRI exposure during two or more trimesters was associated with a decrease in birthweight of 205 g.

In the current study, we focused on gaining more insight into causality by evaluating dose-effect within a group of women using antidepressants, while controlling for maternal depressive and anxiety symptoms. Dose-effect or biological gradient is one of the nine Bradford Hill criteria of causality, and although the presence of a dose-effect relationship does not prove causation, it strengthens earlier findings in that direction (Hill, 1965). We observed a dose-effect of maternal SRI use on birth weight, but did not find a significant association between maternal SRI dose and gestational age at birth. These findings are in contrast to earlier dose-effect studies (Oberlander et al., 2008; Roca et al., 2011; Suri et al., 2007). An important difference between our study and two of these previous studies is that they solely included women with a history of major depressive disorder (Roca et al., 2011; Suri et al., 2007), while the current study included women independent of their psychiatric history, correcting for this during analyses. The third previous study was a registry study, facing difficulties with correcting for measures not routinely registered (Oberlander et al., 2008). Another potential explanation is the difference in used SRI exposure. Where the previous studies examined the impact of a high versus low dose, we used a continuous dose measurement, standardizing the different SRI types for initial dosage. Important to note is that the absence of a dose-effect in our study does not translate to an absence of an association between in utero SRI exposure and decreased gestational age at birth, as we did not include a control group without SRI use.

The pathophysiological mechanism underlying the association between prenatal SRI exposure and birth weight remains uncertain, although several pathways have been suggested. Firstly, it has been suggested that high levels of serotonin are associated with lower growth hormone levels in the pituitary gland (Castrogiovanni et al., 2014), which can negatively impact the growth of the fetus both directly and by decreasing the production of insulin-like growth factor, which in turn regulates body weight (Nawathe et al., 2016). Another proposed mechanism is through programming of the fetal hypothalamic-pituitary-adrenal (HPA) axis. An animal study showed that in utero exposure to an SRI increased fetal levels of cortisol and adrenocorticotrophic hormone (Morrison et al., 2004), which can influence fetal development as well as growth hormone and insulin-like growth factor activity (Agha and Monson, 2007). Lastly, SRIs might impact placental function directly. Disrupted placental serotonin synthetic pathways and placental serotonin levels have been associated with fetal growth restrictions (Kliman et al., 2018; Ranzil et al., 2019). Moreover, serotonin acts as a vasoconstrictor (Cruz et al., 1997), potentially influencing fetal growth when present to a greater extent due to maternal SRI use. Jointly, these observations, in combination with our observed dose-effect, make an influence of maternal SRI on fetal growth plausible.

### 4.1. Strengths and limitations

A major strength of this study is the prospective design in which we used longitudinal data for both the measurement of SRI exposure and maternal symptomatology and current and past psychiatric diagnoses. SRI dose was assessed throughout pregnancy and postpartum, allowing us to calculate a mean dose during pregnancy, to account for women fluctuating in their daily dosage. Maternal symptomatology during pregnancy, as measured with the EPDS and STAI, was also questioned during each study assessment, allowing us to correct for mean symptomatology during pregnancy instead of using a single snapshot. Furthermore, we used the standardized SCID-I interview at baseline to determine psychiatric history, which allows for a more reliable classification compared to register-based studies that mostly rely on unstandardized hospital data. Lastly, we included women with SRI use independent of their psychiatric history, which is important for the generalizability, since SRIs are not only prescribed for major depressive disorder. A recent study in Canada investigated treatment indications for ADs in primary care between 2006 and 2015 and found that only 55.2% of these prescriptions were made for major depressive disorder (Wong et al., 2016).

However, our study also has its limitations. Although prospective, we cannot make full causal inferences given that we did not randomize women to different dosages. We corrected for a range of important confounders, including current and lifetime diagnosis of depression and/or anxiety. Other psychiatric diagnoses and other psychotropic medication use during pregnancy were assessed, but due to their limited and variable presence within our population, they were not controlled for. In addition, we used standard initial doses according to the American pharmaceutical treatment guidelines to calculate dose equivalent scores. We did not take into account drug potency, individual metabolization rate, which may be highly variable during pregnancy by factors such as genotype (Avram et al., 2016), and placental transfer per SRI type, which can vary slightly (Frazer, 2001; Rampono et al., 2009). Analysis of SRI serum levels would have been an interesting addition to the current study. Although a dose-effect relationship is an indicator for causality, a more detailed investigation of the biological mechanisms, including placental transfer, is needed to make more definitive conclusions on causality. Out of the 478 women referred for counselling, 248 women declined to participate, without providing a reason or background information, conforming to common and local ethical procedures. These women might have differed in their psychiatric history, current symptomatology and treatment management, possibly limiting the generalizability of our results. However, it seems unlikely in our view that the association between SRI dose and birth weight would materially differ between those women who participated and who did not. Lastly, the non-significant findings on gestational age and SGA could be the result of the small sample size.

## 5. Conclusion

The inverse dose-effect between SRI use during pregnancy and birth weight that was found in this study indicates that management options regarding SRI use during pregnancy should not be limited to continuing or discontinuing. Instead, these findings suggest that careful dosing of serotonin reuptake inhibitor use during pregnancy needs to be considered on an individual level, as this may prevent a negative impact on birth weight. The necessity of SRI use needs to be evaluated, preferably before pregnancy, and other treatment options such as psychological interventions, if available, need to be actively considered. It may be that adding additional psychological interventions may result in a decreased dose needed to be effective (Bockting et al., 2015). Future research should focus on relating birth weight to blood serum levels of SRIs, serum level of SRIs in umbilical cord or meconium, and the replication of our findings in large samples while accounting for relevant confounding factors. Finally, a randomized controlled trial could more definitively establish a causal relationship.

## Contributors

NMM, MEB, HB, CLHB, WJGH and MPLB contributed to study concept and design. NMM, DH, MEB, HB, CLHB, MPLB, AMK and HHB conducted the study and gathered data. NMM, DH and AMK performed the statistical analysis. All authors were involved in the interpretation of the study results, as well as the drafting and revision of the manuscript, and all approved the final version to be published.

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## Declaration of Competing Interest

The authors declare no conflict of interests.

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