Examining differences in placental efficiency following exposure to antidepressants and current depression: findings from an Australian pregnancy cohort study

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Abstract

Introduction: Placental dysfunction and inefficiency, is important in understanding fetal growth restriction and low birth weight. Two recent studies have examined the relationship between antidepressant use in pregnancy and placental weight ratios. These studies had opposite finding with one finding lower placental weight ratio associated with antidepressant use and the other a higher ratio.

Methods: This study examined 342 women recruited in early pregnancy, including 75 taking antidepressants, 29 with current depression and 238 controls. Antidepressant use was measured through self-report in early and late pregnancy, hospital records at delivery and drug concentrations in cord and maternal blood obtained at delivery. Maternal depression was measured using the Structure Clinical Interview for the DSM IV(SCID) at recruitment. Placentas were collected at delivery and weighed, and infant birth weight recorded. Placental efficiency was measured using placental weight residuals.

Results: While placental weight residuals were higher for those on antidepressants, after adjusting for key covariates, the placental weight residuals were not significantly different between antidepressant exposed (expressed by self-report and drug concentrations), depressed and control women. When comparing antidepressant groups separately there was a trend towards higher Selective Serotonergic Reuptake Inhibitors (SSRI) concentrations being associated with higher placental weight residuals, however this did not reach statistical significance.

Conclusion: Antidepressant use in pregnancy was not associated with significant changes in placental efficiency after adjustment for confounding variables. Future research should expand on this to examine other aspects of placental function and include a wide range of potential confounding variables to draw clinically meaningful conclusions.

Introduction

Maternal depression is a high prevalence condition in pregnancy and women with moderate to severe depression may require continuing or commencing antidepressant treatment during pregnancy. There have been consistent concerns about the potential for both exposure to depression- and to antidepressants- to influence placental function. Furthermore, this impact on placental function increases the risk of poorer fetal and neonatal outcomes, such as fetal growth restriction, low birth weight and preterm birth. While there have been investigations of a range of aspects of placental functioning, such as placental enzyme activity, mRNA expression and epigenetic placental changes in relation to maternal mental health, investigations into placental efficiency have been scarcer.

The importance of understanding placental efficiency is the association with a range of important offspring outcomes across pregnancy through to adulthood [1-3]. In particular, this is related to growth restriction and low birth weight where findings have shown that fetal growth restriction (FGR) has been associated with lower cognitive outcomes and higher behavioural problems than control children [4-6]. Furthermore, in a recent systematic review untreated depression has been associated with low birth weight and growth restriction [7]. It has been postulated that placental dysfunction and inefficiency, often measured through the proxy of the ratio of birthweight to placental weight (where an increase or decrease in placental weight in relation to newborn birthweight is considered a measure of placental insufficiency), underlies the association between maternal adversity such as depression and FGR and/or low birth weight{Salavati, 2018 #9154}. A recent review has linked maternal depression, low birth weight and placental endocrine inefficiency terming this 'placental programming' [8]. While there are animal models to suggest there may be a pathway through the regulation of placental function via placental genes resulting in both maternal depression and anxiety and also low offspring birth weight, the evidence in humans at this point is limited [8].

Two recent studies have examined antidepressant use and placental weight [9, 10]. The first study examined 242 women with severe mental disorders and this included 50 on antidepressants, 75 on antipsychotic medication, 59 on both antidepressants and antipsychotics and 58 taking no medication for their severe mental disorder [9]. The antidepressants included selective serotonin reuptake inhibitors (SSRIs), Serotonin and noradrenalin reuptake inhibitors (SNRIs), and noradrenergic and specific serotonergic antidepressants (NaSSAs) and only limited information was presented on diagnosis. The authors found no association with antidepressants and birth weight or gestational age at delivery. However, birthweight to placental weight ratio was significantly higher in those on either antidepressants and also those on both antidepressants and antipsychotics. However, in this first study, smoking was found to be significantly associated with birth weight, but it was not examined as a between group difference or included as a variable in the multivariate regression [9]. While this first study included a screening measure of possible depressive symptoms, the Edinburgh Postnatal Depression Scale (EPDS), it did not have a currently depressed comparison group and the control group included a wide range of potential diagnoses [9, 10].

The second study examined 82 women taking SSRI antidepressants and compared these women to 82 healthy control women [10]. This study did not consider the role of depression in placental efficiency and weight. However, this study found SSRI antidepressant exposure was associated with lower birth weight but with a *lower* birthweight to placental ratio [10]. This second study also identified rates of smoking were significantly different for the women on antidepressants compared to the control group and smoking was also a significant

predictor in a multivariable regression of placental fetal vascular malperfusion but not neonatal outcomes [10]. Given the opposite findings of these two studies for placental weight ratios and antidepressant exposure- and the methodological limitations in measurement and design- it is inconclusive as to whether there is an association between antidepressant treatment and placental efficiency.

A further consideration in examining placental efficiency is the operationalisation of this function, which has been undertaken using several different methods across broader studies [11]. The commonly used method is the birth weight to placental weight ratio (BW:PW), which was used in both previous studies examining antidepressants [9, 10]; however, there are both statistical and conceptual issues associated with the BW:PW ratio. Statistically, researchers across several domains of biology have demonstrated that ratios can lead to spurious results due to no meaningful intercept and variability within the ratio along the regression line [11, 12]. Conceptually, ratios can also lead to misleading conclusions regarding increased efficiency for infants born smaller than expected compared to infants born larger than expected with respect to their placental size. In pursuit of a more reliable measure of efficiency, researchers have assessed the application and stability of a metabolic scaling exponent to define the association between infant and placental weights [13, 14]. Despite some support for the stability of the metabolic scaling exponent for placental efficiency, Christians and colleagues demonstrated that the scaling parameter varied considerably (between ~.76 and ~.86) as the range of gestational age was restricted [11]. Given the variability across placental efficiency measures, Christian and colleagues recommend a residualised approach to operationalising placental efficiency, whereby residuals (i.e., distances from observed data to the least squares regression line) from the regression of placental weight on birth weight are saved and used in analyses.

Current Study

The purpose of this paper is to compare placental efficiency (i.e., placental weight relative to infant weight at birth) between women who were taking antidepressants during pregnancy, women with untreated depression, and a healthy control group. We hypothesise that the heaviest placentas will be observed in the antidepressant group compared to both control and depressed groups, after adjusting for infant birth weight. In addition, we examine the associations between maternal and cord plasma antidepressant concentrations taken at delivery and placental weight adjusted for birth weight. We hypothesise that placental efficiency measured using placental weight residuals and antidepressant concentrations will be positively related, with a stronger association observed for cord compared to maternal plasma.

Method

Measures

Participants

This study draws on data from the Mercy Pregnancy and Emotional Wellbeing Study (MPEWS). This study recruited 342 pregnant women before gestational week 20, which comprised 75 women taking antidepressant medication in pregnancy, 29 women who met criteria for current depressive disorder at recruitment or within 2 years of conception based on the diagnostic measure Structured Clinical Interview for DSM IV (SCID-IV), and 238 control women who were neither on antidepressant treatment or had current depressive

disorder. Further details of the study are described in the published cohort profile [15]. The Mercy Health Human Research Ethics Committee approved this study and a written informed consent statement was obtained from each woman. Inclusion criteria were being less than 20 weeks pregnant and English proficiency. Women who developed pregnancy complications after enrolment were not excluded. Participants were excluded if they had bipolar or psychotic disorders, substance abuse disorder, child protection involvement, intellectual disability, serious pre-existing physical illness and psychiatric illness requiring current acute inpatient admission.

Measures

Demographics and Covariates

A range of demographics and key covariates were collected from surveys in the first and third trimesters and at delivery. These included maternal age, body mass index, educational attainment, ethnicity, marital status, use of alcohol and smoking in pregnancy, pregnancy complications including gestational diabetes mellitus (GDM) and pregnancy induced hypertension (PIH) disorders, gestational week at each assessment, gestational age at delivery, mode of delivery, and infant birth weight and sex. Based on Australian national birth weight percentiles, fetal growth restriction (FGR, $< 10^{th}$ centile) and large for gestational age (LGA, $> 90^{th}$ centile) were calculated using gestational age at delivery, birth weight and sex data. A full description is contained in the cohort profile [15].

Maternal Mental Health

At recruitment, the Structured Clinical Interview for DSM-IV (SCID-IV) Mood disorders schedule was administered to identify current depressive disorders [16].

Antidepressant Use and Plasma Concentrations

Antidepressant type, dosage, and timing of exposure in pregnancy were assessed by a self–report questionnaire at recruitment and in the third trimester; and confirmed in hospital records at delivery. The antidepressant medication class, dose and timing of exposure are reported in Table 3. As previously described [17], maternal and umbilical cord blood were collected at delivery, centrifuged and the plasma stored at -80 °C within one hour of collection. The SSRIs citalopram, escitalopram, fluoxetine, norfluoxetine, paroxetine and sertraline were analyzed with liquid chromatography–mass spectrometry (LC–MS) and the SNRIs duloxetine, venlafaxine and desvenlafaxine were analyzed with ultra-high performance liquid chromatography–tandem mass spectrometry (UHPLC–MS–MS) [17]. In order to compare concentrations across the various antidepressants, a drug level measured within a sample was standardized by relating it to the middle of the therapeutic reference range of that drug [18]. Thus, the degree of fetal exposure could be estimated regardless of the specific antidepressant taken in pregnancy by the mother.

Placental weight

Placenta was collected and processed within 30 minutes of delivery whenever delivery occurred across day or night. Time of delivery was recorded. Placental weight (in grams) was recorded, after the cord was drained of blood and after removal of blood clots. Included in the placental weight was the umbilical cord and the fetal membranes.

Statistical Analyses

To prepare the placental weight data for analyses, we followed methods proposed and used by Christians et al. for a residualised approach for operationalising placental efficiency relative to birth weight [11]. Twenty (5.8%) infants who were preterm (< 37 weeks) were excluded from analyses. Placental weight for the remaining 322 (94.2%) term infants ranged between 276 g and 1,040 g and birth weight ranged between 2,060 g and 5,460 g. To remove variance in both placental weight and birth weight associated with gestational age at birth, sex of the infant and ethnicity, placental weight and birth weight were separately regressed onto these three variables and unstandardized residuals from each model were saved. The placental weight residual variable was then regressed onto the birth weight residual variable and the standardised residuals (i.e., standardised placental weight residuals) from this model were saved for use as the outcome in analyses addressing the hypothesis and exploratory aims.

We began by describing the sociodemographic characteristics of the sample and then compare these characteristics, as well as obstetric, delivery and neonatal outcomes, including raw placental and birth weights, across the three MPEWS groups: antidepressant, depressed, and control. We also provide summary statistics of antidepressant use during pregnancy for women in the antidepressant group (i.e., class, agent, antidepressant concentrations and sertraline-equivalent dose). Then, to address the first hypothesis that the heaviest placentas will be observed in the antidepressant group compared to both control and depressed groups, we first plotted individual standardised placental weight residuals by group using raincloud plots in R and then compared the distributions between the groups using a one-way ANOVA test [19]. We then conducted a series of linear models to estimate adjusted group means when separately controlling for common covariates of placental efficiency: maternal smoking, maternal body mass index (BMI) at recruitment, FGR, PIH and GDM. To address the second hypothesis, zero-order Spearmans's rho correlation coefficients, along with scatterplots, were conducted and presented to examine the associations between antidepressant plasma concentrations and standardised placental weight residuals. Data management and analyses were conducted using SPSS version 26.

Results

Sociodemographic Characteristics

The average age of women at recruitment was 31.92 (SD = 4.71) years and ranged between 19 and 48 years; maternal age at recruitment did not vary significantly by MPEWS group. The sample were predominantly of Oceanic/European ethnic backgrounds (87.9%), and reported being in a married, *de facto*, or otherwise committed relationship (96.1%) and university educated (67.5%) at the time of recruitment. Most women (83.9%) were nulliparous at the time of recruitment into the MPEWS cohort. Sixty-seven women (19.6%) met diagnostic criteria for a major depressive disorder during early pregnancy and up to two years prior to conception. Thirty-one women (9.1%) reported smoking during pregnancy, with 12 (38.7%) reporting having ceased in early pregnancy and 19 (61.3%) who continued throughout pregnancy. Demographic characteristics of the sample (N = 342) by MPEWS groups are presented in Table 1. Fewer women in the antidepressant group, compared to women in the control group only, were nulliparous, and reported a university education and being in a married, *de facto*, or otherwise committed relationship. More women in the antidepressant group, compared to both the depressed and control groups, reported smoking during pregnancy.

Antidepressants used during early pregnancy and the third trimester are presented in Table 2. Of the 75 women taking antidepressants during pregnancy, 71 reported use of antidepressants during early pregnancy and 70 reported use during third trimester. Four women commenced and five women ceased antidepressants between early pregnancy and third trimester. For those who remained on antidepressants during pregnancy (n = 66), four women reported changing agents, however none of these were changes between the classes, SSRI, SNRI and *other*.

Obstetric, Delivery and Neonatal Outcomes by MPEWS Groups

Table 3 displays the obstetric, delivery and neonatal outcomes by the antidepressant, depressed and control groups. Although the raw, unadjusted placental weights in the antidepressant group (*Mean* = 684.29 grams, *SD* = 145.40 grams) were significantly heavier than placental weights in the control group (*Mean* = 631.38 grams, *SD* = 130.93 grams), the raw, unadjusted birth weights did not differ by group. Several other outcomes differed significantly between antidepressant and control groups using pairwise comparison tests ($p < .05$), but not between either antidepressant or control groups and the depressed group ($p > .05$). Specifically, more women taking antidepressants during pregnancy, compared to women in the control group, had a BMI at recruitment in the obese range (37.8% *vs* 17.3%). For infant outcomes, more infants exposed to antidepressants *in utero*, compared to control infants, were large for gestational age (LGA, weighing > 90 percentile for gestational age and sex) (20.3% *c.f.* 9.2%), scored less than 7 on the Apgar test at one-minute following delivery (23.0% *c.f.* 10.5%) and more were admitted to a neonatal intensive care unit (8.1% *c.f.* 1.7%). Significantly more women in both the antidepressant (20.3%) and depressed (24.1%) groups had pregnancy-induced hypertension compared to women in the control group (5.9%). Finally, infants exposed to antidepressants *in utero* were born almost one week earlier (*Mean* = 38.87 weeks, *SD* = 1.26 weeks) than infants in both the depressed (*Mean* = 39.68 weeks , *SD* = 1.28 weeks) and control (*Mean* = 39.56 weeks, *SD* = 1.62 weeks) groups (both p values $< .05$).

Placental Weight Residuals by MPEWS Group

Figure 1 displays the Raincloud plots for standardised placental weight residuals by MPEWS groups. For the control and depressed groups, the mean standardised placental weight residual was below 0, suggesting that, on average, observed placental weight was lighter than predicted by birth weight. Conversely, the mean standardised placental weight residual for the antidepressant group was above 0, suggesting that, on average, observed placental weight was heavier than predicted by the birth weight. Using z scores, the omnibus comparison of group means was significant, $F(2, 319) = 4.00$, $p = .019$, $\eta^2 = .03$; however, standardised placental weight residuals were significantly different between the antidepressant (*Mean* = .30, *SD* = 1.12) and control (*Mean* = -.08, *SD* = .96) groups only. Thus, without adjustment for covariates, placental weight was significantly higher in the antidepressant group compared to the control group, across the range of birth weights.

When adding previously identified covariates of placental weight to separate linear models, smoking during pregnancy, GDM, PIH and FGR were each not significantly associated with standardised placental weight residuals, and the small, significant effect between groups remained the same. A BMI of 30 kg/m^2 at recruitment, however, was associated with significantly higher standardised placental weight residuals ($B = .32$, $p < .024$). In addition, after controlling for BMI > 30, the small effect for group from the unadjusted model was reduced to a negligible partial effect and was no longer significant, $F(2,317) = 2.67$, $p = .071$, partial $\eta^2 = .01$, suggesting that the variance accounted for in

standardised placental weight residuals by antidepressant exposure when compared to the control group, is attributable to the small association observed between maternal BMI at recruitment and standardised placental weight residuals.

Associations Between Placental Weight Residuals and Antidepressants Concentrations in Maternal and Cord Blood

In women taking antidepressants during pregnancy, maternal plasma antidepressant concentrations at delivery were not associated with standardized placental weight residuals (Spearman's *rho* (58) = .21, p = .111). Plasma antidepressant concentrations measured in umbilical cord plasma at delivery were also not associated with standardized placental weight residuals (Spearman's *rho* (57) = .22, p = .093). Although not reaching statistical significance, larger effects were observed for SSRI concentrations, compared to SNRI concentrations, on standardised placental weight residuals (Figures 2 and 3).

Discussion

Our study initially found that unadjusted placental weights were higher in those taking antidepressants and further that the placental residual weights in those taking antidepressants were higher than predicted by their infant's birthweight and higher in comparison to untreated depressed and control women. However, there were several other important differences for those women taking antidepressants when compared to those with untreated depression or control women including a higher body mass index (BMI) with greater likelihood of being in the obese range, increased rate of hypertension in pregnancy, a lower gestational age at birth and lower infant Apgar scores at 1 minute. After adjusting for these covariates, the placental weight residuals were not significantly different between the antidepressant, depressed and control groups. Antidepressant drug concentrations in maternal and cord plasma at delivery were not associated with placental weight residuals. When examining SSRI and SNRI antidepressants separately there was a trend towards SSRI concentrations being associated with higher placental weight residuals than SNRI concentrations, however this difference did not reach statistical significance.

Two recent meta-analyses have found that both antidepressant use and antenatal depression were associated with low birth weight and it was postulated the association was mediated through changes in placental functioning [20, 21]. This has supported examining placental efficiency, such as measured through placental weight residuals, in the context of antenatal depression and antidepressant use. However, while there was an overall significant association between antidepressant use and low birth weight in the first meta-analysis [20], this was found only for retrospective studies whereas there was no such association for prospective studies. Maternal depression, other lifestyle factors, timing of exposure and antidepressant dose could not be included in this meta-analysis. Equally, the most recent meta-analysis [21] examining maternal depression and low birth weight identified 12 studies examining low birth weight and a further 3 studies examining FGR. Among these, only 2 studies for low birth weight and none for FGR utilised a diagnostic measure of depression [21]. The majority of studies relied on Edinburgh Postnatal Depression Scale (EPDS) a screening measure for possible symptoms of depression. It should be noted that the EPDS is not a measure of depression, and the authors of the meta-analysis [21] noted there was a stronger association for low birth weight when the measure of 'depression' was EPDS than a diagnostic measure of depression disorder. The two studies to examine LBW and depression using a diagnostic measure of depression found odds ratios of 0.82 and separately 1.01 respectively in each study [21]. There is considerable evidence to suggest that lifestyle factors

such as smoking are associated with both depression and antidepressant use and equally with low birth weight and placental dysfunction, and yet this was often overlooked as a variable in the studies included in the meta-analyses. Overall, these two meta-analyses suggest much is unknown about the relationship between antidepressant use, antenatal depression and low body weight. Our findings specifically on placental weight residuals support future research which is prospective, has broad, reliable and specific measures of depression, antidepressant use and lifestyle factors such as smoking to progress our understanding of any impact on placental efficiency, intrauterine growth and birth weight.

Overall, this study did not support our hypothesis or the findings of either higher or lower placental efficiency associated with antidepressant use as found in the previous two studies [9, 10]. As neither of the previous two studies controlled for depression as a possible confounder by indication, only one of them examined class of antidepressant and neither included dose or plasma concentrations of antidepressants, our findings make an important contribution to understanding placental weight and efficiency in relation to maternal antidepressant and depression. While we did find a similar trend as Frayne et al. [9] with a higher placental weight for those with antidepressant exposure, this was no longer significant when compared to depressed and control women after the potential key confounding variables were included in the analysis. While our findings do not support antidepressant exposure being an important factor for placental weight and efficiency, they do support the importance of those range of covariates that commonly occur also in women who use antidepressants in pregnancy in research design. When examining antidepressant use in pregnancy it can no longer be ignored the importance of including an untreated depressed control group in addition to a healthy control group, as well as measures of key common covariates in women with depressive disorders in pregnancy when attempting to study pregnancy-related outcomes. Conflicting findings such as the previous two studies on placental weight and antidepressant use – one finding an association with higher placental weight and the other with lower placental weight – are commonplace throughout the research examining the impact of antidepressant exposure on a range of maternal, placental, and offspring outcomes. It is only when there is adequate research design and measurement that includes key potential confounding variables that risks and benefits of antidepressant treatment become clearer. Antidepressants are an effective treatment option for moderate to severe depression and depression is one of the most common co-morbid conditions in pregnancy making accurate research into understanding risks and benefits of critical importance to the clinical care of women.

Even though our study did not find an association between maternal antidepressant use or current depression and changes in placental weight or efficiency as measured by placental weight residuals, placenta functioning continues to be an important focus for perinatal mental health research. The placenta is critical in regulating fetal growth and development and has an important influence on neurodevelopment. Our understanding of how either current depression or antidepressant use might alter placental function will underpin clarity on the programming pathways for intergenerational risk and protective factors for mental health. Previous research, including in humans, has suggested that maternal mental health may influence aspects of placental function, such as the placental enzyme 11β-hydroxysteroid dehydrogenase isozyme 2 and from this increased fetal exposure to cortisol and then through this increased cortisol exposure in utero a subsequent influence on later child outcomes [22-24]. However, it has also been postulated, with support from animal models, that placental function and in particular the production of placental lactogens might also act directly to prime maternal behaviours and mood during pregnancy [8]. Furthermore, what our study would support is that women with depression and also those taking

antidepressants do have a number of risk factors for placental dysfunction and therefore FGR and low birth weight and as such these are a higher risk group for this outcome.

The limitations of our study include the relatively low numbers of women with untreated depression, the low numbers of women taking the specific classes of antidepressants and lack of an analysis of the placenta itself, such as histopathological investigations. A further limitation is that the placentas in our sample were weighed prior to removal of membranes and the umbilical cord, which limits comparison of the raw placental weights in our sample to normative samples.

In conclusion, antidepressant use in pregnancy and current depression were not associated with significant changes in placental weight residuals. Future research requires studies designed with currently depressed as well as antidepressant exposed groups and should include a broad range of variables relevant for placental function. Undertaking research with any less than that risks spurious results influencing clinical care.

Conflict of Interest

The authors declare that they have no competing interests.

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References

[1] J.A. Hutcheon, H. McNamara, R.W. Platt, A. Benjamin, M.S. Kramer, Placental weight for gestational age and adverse perinatal outcomes, Obstet Gynecol 119(6) (2012) 1251-8.
[2] K.R. Risnes, P.R. Romundstad, T.I. Nilsen, A. Eskild, L.J. Vatten, Placental weight relative to birth weight and long-term cardiovascular mortality: findings from a cohort of 31,307 men and women, Am J Epidemiol 170(5) (2009) 622-31.
[3] L.A. Williams, S.F. Evans, J.P. Newnham, Prospective cohort study of factors influencing the relative weights of the placenta and the newborn infant, Bmj 314(7098) (1997) 1864-8.
[4] J. Chen, P. Chen, T. Bo, K. Luo, Cognitive and behavioral outcomes of intrauterine growth restriction school-age children, Pediatrics 137(4) (2016).
[5] R. Geva, R. Eshel, Y. Leitner, A.F. Valevski, S. Harel, Neuropsychological outcome of children with intrauterine growth restriction: a 9-year prospective study, Pediatrics 118(1) (2006) 91-100.
[6] C. Sacchi, C. Marino, C. Nosarti, A. Vieno, S. Visentin, A. Simonelli, Association of Intrauterine Growth Restriction and Small for Gestational Age Status with Childhood Cognitive Outcomes: A Systematic Review and Meta-analysis, JAMA pediatrics 174(8) (2020) 772-781.
[7] U. Ghimire, S.S. Papabathini, J. Kawuki, N. Obore, T.H. Musa, Depression during pregnancy and the risk of low birth weight, preterm birth and intrauterine growth restriction-an updated meta-analysis, Early Human Development 152 (2021) 105243.
[8] H. Creeth, R. John, The placental programming hypothesis: placental endocrine insufficiency and the co-occurrence of low birth weight and maternal mood disorders, Placenta (2020).
[9] J. Frayne, T. Nguyen, Y. Hauck, H. Liira, J.A. Keelan, The Relationship Between Pregnancy Exposure to Antidepressant and Atypical Antipsychotic Medications and Placental Weight and Birth Weight Ratio: A Retrospective Cohort Study, Journal of clinical psychopharmacology 38(6) (2018) 563-569.
[10] M. Levy, M. Kovo, H. Miremberg, N. Anchel, H.G. Herman, J. Bar, L. Schreiber, E. Weiner, Maternal use of selective serotonin reuptake inhibitors (SSRI) during pregnancy—neonatal outcomes in correlation with placental histopathology, Journal of Perinatology 40(7) (2020) 1017-1024.
[11] J.K. Christians, D. Grynspan, S.L. Greenwood, M.R. Dilworth, The problem with using the birthweight:placental weight ratio as a measure of placental efficiency, Placenta 68 (2018) 52-58.
[12] E.T. Poehlman, M.J. Toth, Mathematical ratios lead to spurious conclusions regarding age- and sex-related differences in resting metabolic rate, Am J Clin Nutr 61(3) (1995) 482-5.
[13] P. Gruenwald, The placenta and its maternal supply line: effects of insufficiency on the fetus, University Park Press1975.
[14] M. Gasperowicz, M. Yampolsky, C.M. Salafia, Metabolic scaling law for mouse fetal and placental weight, Placenta 34(11) (2013) 1099-101.
[15] M. Galbally, I.M. van, M. Permezel, R. Saffery, M. Lappas, J. Ryan, E. van Rossum, A.R. Johnson, D. Teti, A.J. Lewis, Mercy Pregnancy and Emotional Well-being Study (MPEWS): Understanding maternal mental health, fetal programming and child development. Study design and cohort profile, Int J Methods Psychiatr Res 26(4) (2017).
[16] M. First, R. Spitzer, M. Gibbon, J. Williams, Stuructured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinical Version. Washington DC and London, American Psychiatric Press, Inc, 1997.

[17] M. Galbally, O. Spigset, A.R. Johnson, R. Kohan, M. Lappas, A.J. Lewis, Neonatal adaptation following intrauterine antidepressant exposure: assessment, drug assay levels, and infant development outcomes, Pediatr Res 82(5) (2017) 806-813.
[18] C. Hiemke, S. Hartter, Pharmacokinetics of selective serotonin reuptake inhibitors, Pharmacol Ther 85(1) (2000) 11-28.
[19] M. Allen, D. Poggiali, K. Whitaker, T.R. Marshall, R.A. Kievit, Raincloud plots: a multi-platform tool for robust data visualization, Wellcome Open Res 4 (2019) 63.
[20] X. Zhao, Q. Liu, S. Cao, J. Pang, H. Zhang, T. Feng, Y. Deng, J. Yao, H. Li, A meta-analysis of selective serotonin reuptake inhibitors (SSRIs) use during prenatal depression and risk of low birth weight and small for gestational age, Journal of affective disorders 241 (2018) 563-570.
[21] U. Ghimire, S.S. Papabathini, J. Kawuki, N. Obore, T.H. Musa, Depression during pregnancy and the risk of low birth weight, preterm birth and intrauterine growth restriction-an updated meta-analysis, Early human development 152 (2021) 105243.
[22] M. Galbally, S.J. Watson, M. Lappas, E.R. de Kloet, E. van Rossum, C. Wyrwoll, P. Mark, A.J. Lewis, Fetal programming pathway from maternal mental health to infant cortisol functioning: The role of placental 11beta-HSD2 mRNA expression, Psychoneuroendocrinology 127 (2021) 105197.
[23] S. Seth, A.J. Lewis, R. Saffery, M. Lappas, M. Galbally, Maternal Prenatal Mental Health and Placental 11beta-HSD2 Gene Expression: Initial Findings from the Mercy Pregnancy and Emotional Wellbeing Study, Int J Mol Sci 16(11) (2015) 27482-96.
[24] K. O'Donnell, J.A. Bugge, L. Freeman, N. Khalife, T. O'Connor, V. Glover, Maternal prenatal anxiety and downregulation of placental 11B-HSD2, Psychoneuroendocrinology (2011).

Table 1. Sociodemographic characteristics by MPEWS group (*N* = 342).

	Antidepressants (*n* = 75)	Depressed (*n* = 29)	Control (*n* = 238)	χ^2
	n (%[a])	n (%[a])	n (%[a])	*p*-value
Ethnicity (missing = 2)				.273^
Oceania/European	68 (91.9)	25 (86.2)	206 (89.9)	
Aboriginal and Torres Strait Islander Australians	1 (1.4)	1 (3.4)	2 (.80)	
Asian	3 (4.1)	3 (10.3)	26 (11.0)	
Middle Eastern	2 (2.7)	0 (0.0)	3 (1.3)	
University Education (missing = 3)	41_a (55.4)	$18_{a,b}$ (62.1)	172_b (72.9)	.015
Full-time Part-time and casual employment	65 (86.7)	26 (89.7)	224 (94.1)	.099
Married, de facto, or otherwise stable relationship (missing = 10)	62_a (88.6)	$29_{a,b}$ (100.0)	228_b (97.9)	.003^
Nulliparous	52_a (69.3)	$26_{a,b}$ (89.7)	209_b (87.8)	.001^
Smoking during pregnancy	14_a (18.7)	0_b (0.0)	17_b (7.1)	.003^
Alcohol during pregnancy	30 (40.0)	8 (27.6)	93 (39.1)	.458

^Fisher's exact test due to expected cell counts less than 5.

$_{a,b}$Cells with differing subscripts denote significantly difference pairwise comparisons at $p < .05$.

[a]Valid percentage due to missing.

Table 2. Antidepressant Summary Statistics in the MPEWS Cohort for Early Pregnancy and Third Trimester, and Maternal and Cord Concentrations at Delivery (n = 75).

	Early Pregnancy (n = 71)		Third Trimester (n = 70)		Maternal AD Concentration (n = 65)		Cord AD Concentration (n = 64)	
Antidepressant class and agent	n (%)	Dose (mg/d) Median (Min - Max)	n (%)	Dose (mg/d) Median (Min - Max)	n (%)	(nmol/l) Median (Min - Max)	n (%)	(nmol/l) Median (Min - Max)
SSRI								
Fluoxetine	5 (7.0)	40 (40 - 50)	6 (8.6)	20 (5 - 40)	5 (7.7)	0 (0 - 863)	4 (6.3)	0 (0 - 735)
Sertraline	22 (31.0)	100 (50 - 200)	26 (37.1)	100 (50 - 150)	23 (35.4)	62.7 (10.6 - 342)	23 (35.9)	36 (2.5 - 127)
Escitalopram	13 (18.3)	10 (5 - 20)	13 (18.6)	10 (5 - 40)	12 (18.5)	43.25 (0 - 97.4)	12 (18.8)	28 (0 - 83)
Citalopram	7 (9.9)	20 (10 - 20)	7 (10.0)	20 (10 - 20)	7 (10.8)	28 (0 - 104)	6 (9.4)	33 (0 - 78)
Paroxetine	2 (2.8)	13.75 (7.5 - 20)	1 (1.4)	20	1 (1.5)	30	1 (1.6)	16
SNRI								
Venlafaxine	6 (8.5)	150 (75 - 225)	4 (5.7)	131.25 (75 - 225)	4 (6.2)	557.8 (57 - 663)	4 (6.3)	624.7 (238 - 769)
Desvenlafaxine	9 (12.7)	100 (50 - 100)	9 (12.9)	100 (50 - 100)	9 (13.8)	324 (0 - 938.5)	9 (14.1)	236 (0 - 595.3)
Duloxetine	3 (4.2)	120 (30 - 120)	3 (4.3)	120 (30 - 120)	3 (4.6)	55 (18.8 - 357.9)	3 (4.7)	26.1 (14 - 146.4)
Other								
Mirtazapine	2 (2.8)	27.5 (10 - 45)	1 (1.4)	45	1 (1.5)	16.2	1 (1.6)	15.5
Agomelatine	2 (2.8)	25	0 (0.0)	-	-	-	-	-

Note. mg/d, milligrams per day; nmol/l, nanomoles per litre; Min, Minimum; Max, Maximum; SSRI, Selective Serotonin Reuptake Inhibitor; SNRI, Serotonin and Noradrenergic Reuptake Inhibitor.

Table 3. Obstetric, delivery and neonatal outcomes by MPEWS group (*N* = 342).

	Antidepressants (*n* = 75)	Depressed (*n* = 29)	Control (*n* = 238)	*p*-value
Obstetric outcomes				
BMI > 30 kg/m^2 at recruitment, n (%)	28_a (37.8)	$5_{a,b}$ (17.2)	41_b (17.3)	.001
Body mass gain during pregnancy (kg/m^2), Mean (SD)	3.83 (2.06)	4.45 (2.32)	4.27 (2.03)	.216
GDM, n (%)	13 (17.6)	2 (6.9)	26 (10.9)	.226^
PIH, n (%)	15_a (20.3)	7_a (24.1)	14_b (5.9)	<.001^
Delivery and Neonatal Outcomes				
Gestational age at delivery (weeks), Mean (SD)	38.87_a (1.26)	39.68_b (1.28)	39.56_b (1.62)	.002
Preterm, n (%)	6 (8.1)	1 (3.4)	13 (5.4)	.637^
Birth weight (g), Mean (SD)	3404.70 (479.29)	3459.93 (482.06)	3403.26 (500.19)	.842
Infant Ponderal Index (g/cm^3), Mean (SD)	2.64 (.29)	2.70 (.27)	2.62 (.29)	.361
FGR, n (%)	4 (5.4)	1 (3.4)	19 (7.9)	.732^
LGA, n (%)	15_a (20.3)	$3_{a,b}$ (10.3)	22_b (9.2)	.042^
Placental Weight (g), Mean (SD)	684.29_a (145.40)	$638.79_{a,b}$ (115.85)	631.38_b (130.93)	.011
Male infant, n (%)	42 (56.8)	18 (62.1)	126 (52.7)	.570
Spontaneous vaginal delivery, n (%)	51 (68.9)	17 (58.6)	167 (69.9)	.466
Apgar < 7 at 1 minute, n (%)	17_a (23.0)	$4_{a,b}$ (13.8)	25_b (10.5)	.027^
Apgar < 7 at 5 minutes, n (%)	3 (4.1)	0 (0.0)	5 (2.1)	.470^
SCN admission, n (%)	10 (13.5)	0 (0.0)	21 (8.8)	.080^
NICU admission, n (%)	6_a (8.1)	$0_{a,b}$ (0.0)	4_b (1.7)	.020^

Note. SD, standard deviation; kg/m^2, kilogram per square metre; g, grams; BMI, body mass index; GDM, gestational diabetes mellitus; FGR, fetal growth restriction; LGA, large for gestational age; SCN, special care nursery; NICU, neonatal intensive case unit.
^Fisher's exact test due to expected cell counts less than 5.
$_{a,b}$ Cells with differing subscripts denote significantly different pairwise comparisons at $p < .05$.

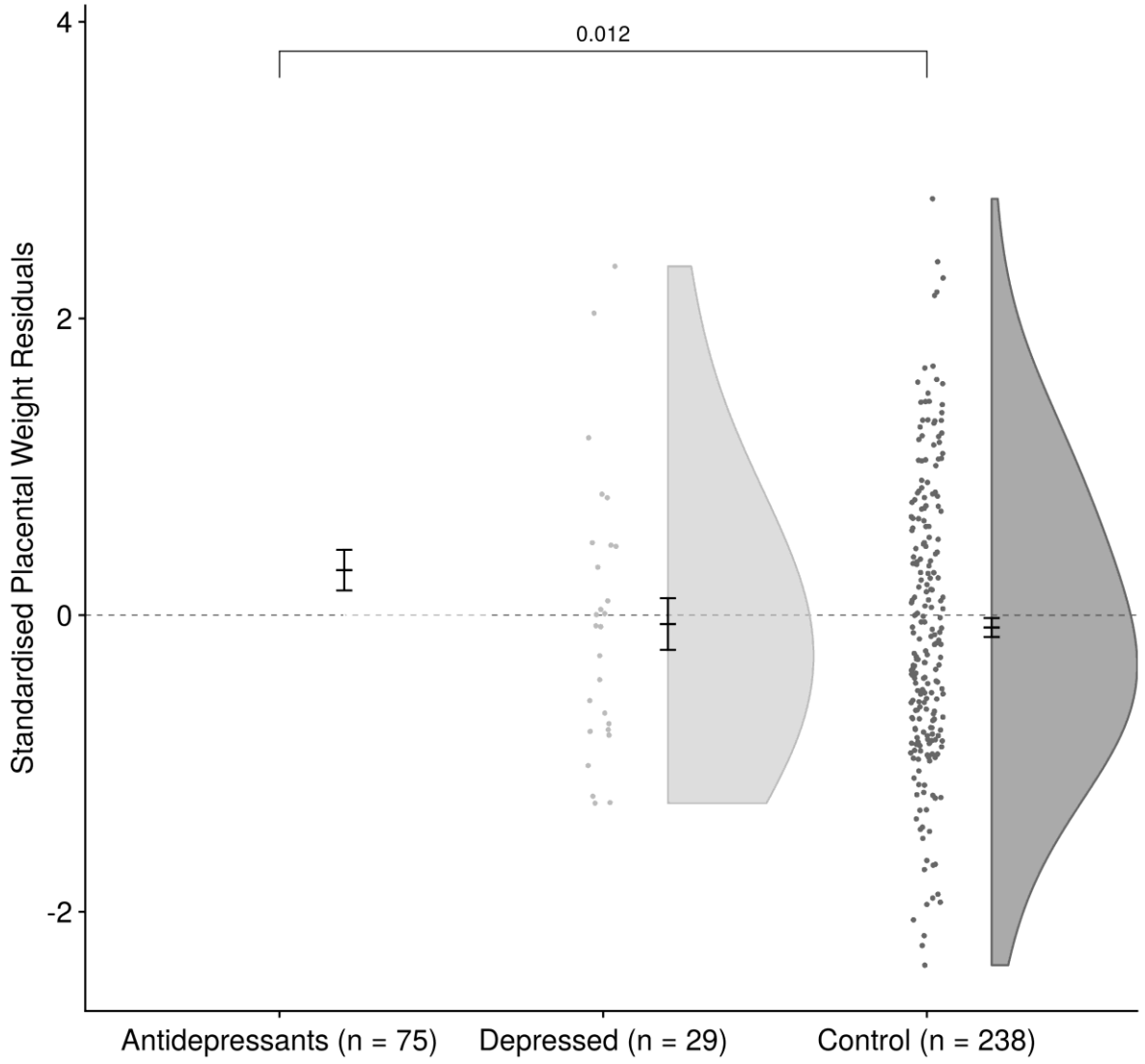

Figure 1. Raincloud plot displaying individual standardised placental weight residuals (z-scores) and distribution by antidepressant, depressed and control groups. Group means with standard error as error bars and p-value for significant pairwise comparisons are displayed. Horizontal dashed line represents value of adjusted placental weight predicted by adjusted birth weight in linear regression model (i.e., z = 0).

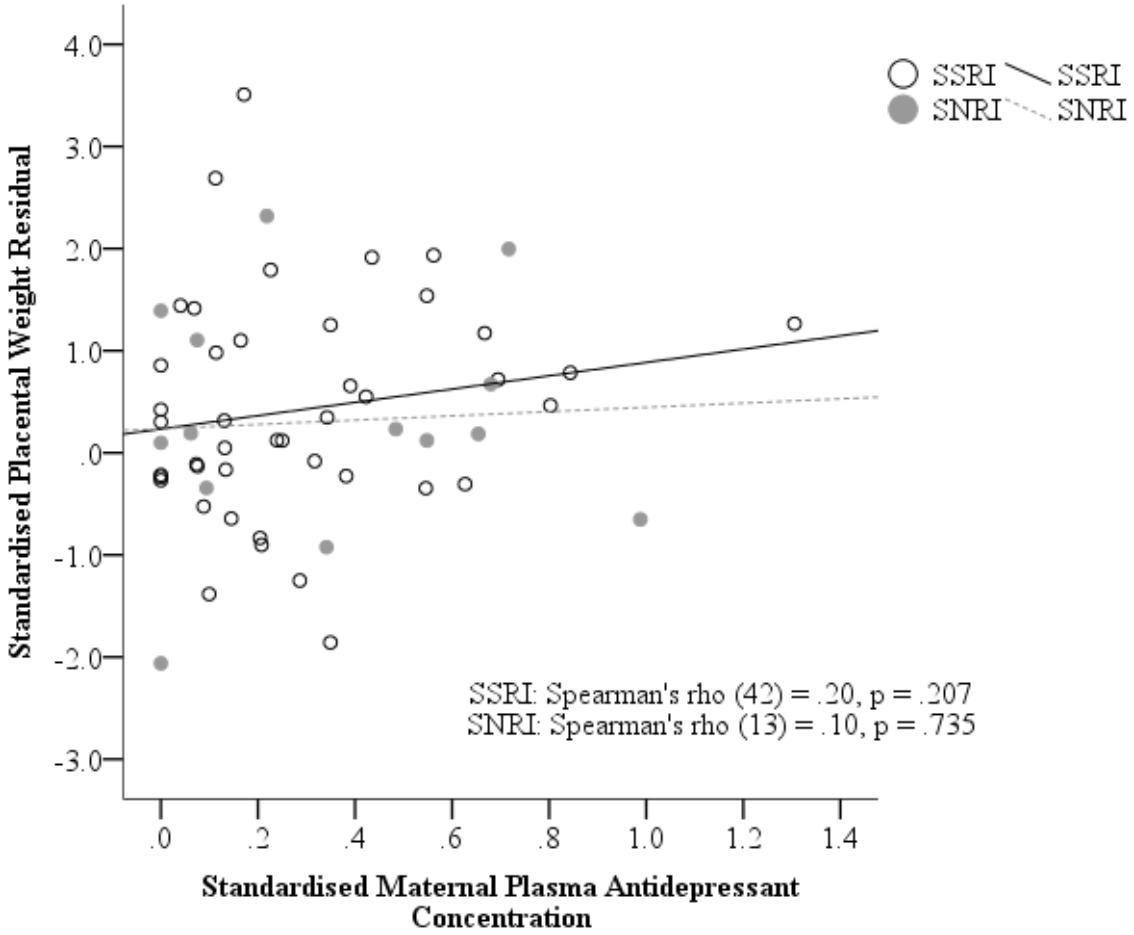

Figure 2. Scatterplots displaying the bivariate associations between the antidepressant concentration in maternal plasma (standardised relative to the middle of the therapeutic reference range for each agent) at delivery and standardized placental weight residuals by antidepressant class exposure during pregnancy. Zero-order Spearman rho correlation coefficients are reported separately for SSRI and SNRI classes.

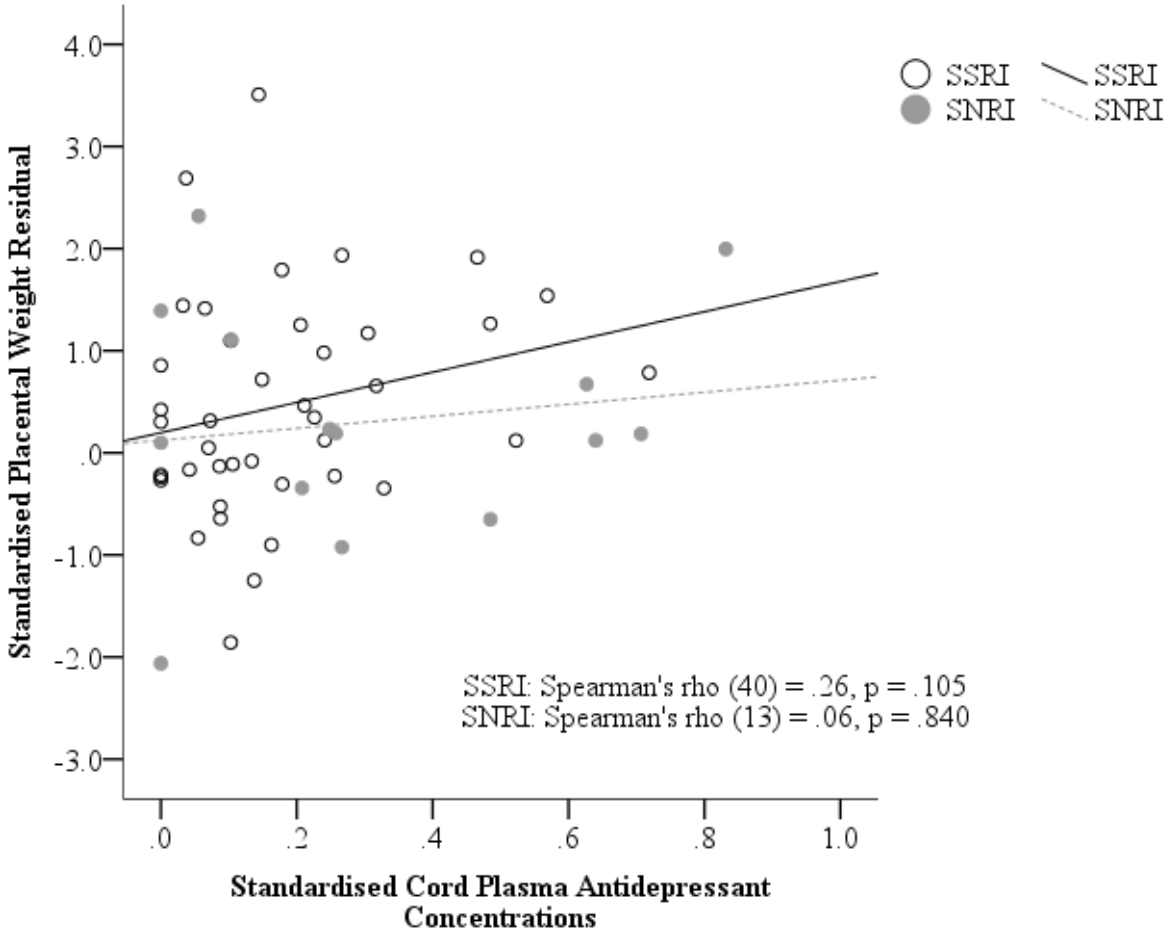

Figure 3. Scatterplots displaying the bivariate associations between the antidepressant concentration in cord plasma (standardised relative to the middle of the therapeutic reference range for each agent) at delivery and standardized placental weight residuals by antidepressant class exposure during pregnancy. Zero-order Spearman rho correlation coefficients are reported separately for SSRI and SNRI classes.