Maternal and Infant outcomes following antidepressant exposure in pregnancy

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MAIN MESSAGES

• Depression in pregnancy is associated with poorer outcomes for women, the developing mother-infant relationship and for infant development

• Evidence for treatments in pregnancy that prevent postnatal depression and improve infant outcomes are limited

• While women in this study on antidepressants had lower levels of depressive symptoms than untreated women they were still higher than control women

• Psychological treatments for depression in pregnancy and the postpartum have been shown to have little effect on improving the mother-infant relationship or child developmental outcomes

• This study gives preliminary evidence to suggest that pharmacological treatment of depression in pregnancy with antidepressants also does not improve mother-infant bonding in the postpartum

• This study has identified predictors such as depressive symptoms and avoidant attachment for mother-infant bonding and these may be good targets for the development of future interventions
EXECUTIVE SUMMARY

Key messages

- Depression in pregnancy is increasingly understood to have an impact on the developing fetus and also appears to predict maternal postnatal depression.
- The efficacy of antidepressants in terms of preventing postnatal depression remains unclear.
- There are clear antenatal predictors of the quality of maternal bonding such as depression and avoidant attachment.
- These predictors show promise as targets for psychosocial interventions.

Background

Depression in pregnancy is associated with poorer outcomes for women and children. The evidence for risks and benefits for treatment for depression in pregnancy is limited including for pharmacological treatment with antidepressant medication. This is despite evidence from a number of countries, which suggest the rate of use of antidepressants in pregnancy is rising. In particular, there is limited evidence as to whether antidepressant treatment in pregnancy, for women who have known risk factors, prevents the development of Postnatal Depression. A Cochrane review which examined the prevention of PND with the use of antidepressants and was inconclusive due to a paucity of studies included. This current study aimed to examine antenatal predictors of postnatal depression and whether antidepressant medication in pregnancy reduces the risk of developing PND.

Perinatal depression is equally relevant for both women’s health and mental health as well as in terms of the optimal social and family environment for early child development, including fetal development. Perinatal depression has been associated with poorer fetal, neonatal and infant developmental outcomes and impaired mother-infant relationship.
Psychological interventions in pregnancy and the postpartum for depression have also examined whether such interventions improve child outcomes as well as reduce maternal symptoms of depression. However to date these interventions have mostly not shown significant effects on either the mother-infant relationship or child development and this was also confirmed in a recent Cochrane review of psychological interventions for the treatment of postnatal depression. This study will examine if treatment of depression in pregnancy with antidepressant medication improves mother-infant relationship in the postpartum.

This study uses a prospective, longitudinal design following 3 groups of pregnant women: women on antidepressants, women who are depressed and not on antidepressant medication and a control group to examine 5 hypotheses. These include, whether women taking antidepressant medication in pregnancy have lower postnatal depressive symptoms and improved bonding with their babies. This study also examined whether antidepressants had an effect on oxytocin and cortisol levels over the perinatal period. Finally, this study examined if attachment assessed in pregnancy was associated with the quality of the mother-infant relationship at 6 months.
THE REPORT

Context

The prevalence of depressive symptoms across the perinatal period has been found to be between 12-20% with up to 40% of women presenting in the postpartum initially becoming symptomatic in pregnancy (1, 2). Perinatal depression is unique in that the morbidity associated with this depressive disorder directly affects not just the individual but also has clear and demonstrable effects on the outcomes for the child and family unit. Therefore, treatment guidelines and models developed for adult depression are not sufficient for managing perinatal depression if the significant impact on children is to be mitigated. The risks that have been associated with untreated perinatal depression include increased pregnancy morbidity and mortality, impaired mother-infant interactions and poorer child developmental outcomes (3, 4). Accordingly, effectively treating depression is critical in terms of early intervention for women and prevention for poorer outcomes for children.

While treatment options for depression include psychological interventions as well as pharmacotherapy, for a variety of clinical reasons, pharmacotherapy may be the most effective treatment for a woman or may be required in conjunction with psychological intervention (5). Our previous research suggests around 2.1% of women take antidepressant medications for depression in pregnancy (6). However, studies from Denmark, USA and Canada all suggest the rate of antidepressant use in pregnancy is rising (7-9). In addition, women who are already being treated with antidepressant medication who discontinue their medication in pregnancy have been shown to have a 68% increased risk of relapse, compared to 26% who remained on their pre-conception dose of antidepressant medication throughout pregnancy (10).

Yet for women the main reason why they cease treatment is concerns about potential effects on their unborn child (11). Despite these concerns there is still limited
evidence for many potential risks and benefits of antidepressants in pregnancy. There is conflicting evidence on malformation risk, pregnancy complications, neonatal risks such as Persistent Pulmonary Hypertension and very limited published data on long term implications for children exposed to antidepressants in pregnancy (12-15). Two recent Cochrane reviews were unable to conclude if antidepressants prevented the development of postnatal depression or were an effective treatment due to the limitation of the available evidence (16, 17).

In addition to a focus on risks of specific treatments in pregnancy, understanding benefits, particularly for protection of child outcomes, have been a focus of recent research for both pharmacological and psychological interventions for depression in pregnancy. A Cochrane review of psychological interventions for prevention of Postnatal Depression found little evidence that any identified intervention improved mother-infant relationship or child developmental outcomes (18). There are no studies examining antidepressants in pregnancy and mother-infant relationship outcomes. There are limited studies, which have suggested possible benefits from antidepressant exposure in pregnancy on specific areas of child development (19, 20).

Given the suggestion of increasing trends in antidepressant treatment of depression in pregnancy, the concerns that women and clinicians have about the limited evidence for risk and benefit from exposure of unborn children to this treatment there is a clear need to increase the evidence base for antidepressant treatment across the perinatal period.

This study contributes to both understanding of early intervention and prevention of depression in the perinatal period and also makes a significant contribution to collaboration and capacity building in research in perinatal mental health. Early intervention capacity is examined through research into one of the earliest periods of intervention possible, in pregnancy, in the most cost effective way through examining antidepressant treatment. This has the potential for prevention of lifelong disability for both the mother and their child.
This study has built a strong team through wide multi-disciplinary collaborations and hence in addition to the specific outcomes from these initial waves of data this study has also built research capacity within perinatal mental health. These unique collaborations across different research and service delivery sectors such as, mental health, pharmacology, attachment research, child development, genetics and epigenetics and hormones have resulted in a sophisticated approach to studying perinatal depression, early childhood and mother-child relationships. The establishment of a perinatal mental health specific biobank is an ongoing resource for Australia in perinatal mental health.

**Implications**

This study is about improving outcomes for women with Perinatal Depression and the outcomes for the children and families of women with depression. Our research team has brought together a team of researchers in the fields of perinatal mental health, obstetrics, child development and attachment, placental pathology and developmental epigenetics. Perinatal depression is an area that requires significant improvement in mental health practice and service delivery and requires substantive research investment to generate effective treatment models and build research capacity.

This is a high quality and innovative research study, which will make an ongoing contribution to knowledge about depression and antidepressants in pregnancy as the further data follow up waves progress into the future. While the study is based in Melbourne with recruitment from a single site given the gold standard measures used throughout the study all of which have established reliability and validity both within Australian populations and overseas the generalisability of the current and future findings is high.
**Message for clinicians**

Our work on the role of antidepressants has not shown effects of enhancing postnatal maternal bonding in women presenting with antenatal depression. This suggests that effective pharmacological management of depressive symptoms is insufficient in itself to address mother-infant interaction. Instead, targeted psycho-social interventions need to be developed and evaluated for such women. Our team intends to pursue this line of research in the future.

**Message for researchers**

The study design implemented in the MPEWS study seeks to examine pregnancy mental health from both fetal and maternal perspectives, and to use both psychological, behavioural and biological data to understand this unique moment in the life cycle. The aims of the study have grown beyond those originally proposed within beyondblue funding as the study has attracted a broader range of cross disciplinary collaborations. The preliminary findings from MPEWS have been presented at an international conference at Durham University, UK and at Colloquiums at Erasmus Medical Centre and Leiden University both in Rotterdam in April 2014. It is planned to present additional findings as the study matures at other national and international conferences and local professional development forums over 2014 and 2015. A number of papers are currently being prepared for submission for publication in peer reviewed scientific journals. This data has also been used as a basis for an NHMRC Project Grant in the 2014 round that is currently under review. A recent review published in BMC Medicine (Lewis, Galbally et al, BMC Med, 2014) summarised the relevant literature and practice implications of the MPEWS study in terms of promoting optimal maternal health and mental health as a key prevention strategy for child development.
**Message for women with perinatal depression**

We know that pregnant women are a vulnerable group for the development or recurrence of pre-existing depressive disorders. Our initial analyses of hormonal predictors of postnatal depression have not been promising, suggesting that biological processes beyond simple levels may be better candidates to understand. Instead, we observed strong psychosocial and symptoms based antenatal predictors of postnatal depression. We found that high depressive symptoms particularly after birth are associated with maternally reported difficulties in bonding with the infant. It remains to be seen whether we could develop interventions for women delivered prior to or after birth, which would both reduce levels of depression and enhance the mother’s bonding process with her infant. However, that is a worthy goal to aim for in future work.

**Approach**

Upon funding the study design was finalised and the study named the Mercy Pregnancy and Emotional Well Being Study (MPEWS). This research project has recruited three groups of women across pregnancy: (1) women with depression who are taking antidepressant treatment in pregnancy; (2) depressed women choosing not to be treated with antidepressants; (3) a control group who have no current or prior history of depression. Women were recruited through antenatal clinics at Mercy Hospital for Women in Heidelberg, Victoria. MPEWS obtained Mercy Health Human Research Ethics Committee Approval and all women provided written informed consent to participate in the study. All women were recruited into the first wave of the study prior to 18 weeks of pregnancy.

At recruitment women underwent the Structured Clinical Interview for the DSM (SCID), mood module. They also completed a survey and had blood collected and stored, to be used for later analysis of oxytocin and cortisol levels. The survey contained a battery of questionnaires including demographics, details of any pharmacological treatments, medical
illnesses and specific measures including the Edinburgh Postnatal Depression Scale (EPDS), State and Trait Anxiety Scale (STAI), Stressful Life Events Inventory, Maternal Antenatal Attachment Scale (MAAS), Experiences in Close Relationships (ECR) and Parental Bonding Instrument (PBI).

The second wave of data collection occurred in 3rd trimester and consisted of a repeat of the survey measure described above and blood collected.

The third wave of data collection occurred at delivery and includes placental samples, cord blood, maternal hair and infant buccal cells. In addition, details of delivery including gestation, birth weight/length/head circumference, method of delivery and complications are obtained from the hospital birth summary.

The fourth wave occurs when the infants are 6 months of age and includes a repeat survey, which in addition to antenatal measures included items on sleep and infant feeding and the Postpartum Bonding Questionnaire (PBQ). At this wave there was also an interaction task and maternal blood and maternal and infant buccal cells collected. Diagnostic interviewing is also repeated for mothers at this time point. The table below summarises these waves of data of collection.

**TABLE 1: DATA COLLECTION IN MPEWS**

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Study Hypotheses

The specific hypotheses originally proposed within the application for the National Priority Research Grant from beyondblue were:

When compared to those with depression not treated with antidepressants, those treated with antidepressants in pregnancy will show:

(H1) A reduction in depressive symptoms in the postpartum (postnatal depression)
(H2) Improved mother-infant interactions at 3 months of age
(H3) A pattern of increasing OT levels across pregnancy and the postpartum
(H4) A pattern of reduced CORT levels across pregnancy and the postpartum
(H5) More secure attachment related emotions and cognitions antenatally and greater sensitivity to their infant at 3 month post partum

Recruitment procedure

Recruitment for MPEWS commenced in October 2012 and, as of May 2014 there have been 267 women recruited into the study. Of those women recruited 166 have delivered and 139 of those who have delivered have had both placenta and cord blood successfully collected. This collection has required a 24/7 roster to ensure processing of samples within 30 minutes of delivery. There have been 65 women and infants that have reached 6 months postpartum and undertaken data collection for Wave 4. The biological samples of placenta, cord blood together with maternal blood in first and third trimester, maternal hair after delivery, infant buccal cells and maternal and infant saliva at 6 months have been collected to form samples for and MPEWS study biobank held at the Mercy Hospital. This biobank forms a resource of international importance for future research examining biomarkers of maternal perinatal depression and discussions are currently underway to establish collaborations and source funding to develop this aspect of the MPEWS study.
Results

Hypothesis 1

Data analysis was possible on 81, 76 and 62 women for whom EPDS data was available for both antenatal points and 6 months postpartum time point respectively. The three groups were examined using mixed modeling in SPSS where the repeated nature of the data could be accounted for and patterns of change over time could be examined for each group. These patterns are displayed in Figure 1 below.

Figure 1: Depression symptoms (EPDS) across study time points (Trimester One, Trimester Three and 6 months post partum) by study group.

As expected, the control group showed a low and stable pattern of depressive symptoms across pregnancy and the 6 month time point. For the depressed without medication group, there was a high initial level of depressive symptoms which steadily reduced over time. For the antidepressant group the levels of symptoms commenced midway between the other groups and showed a U-shaped trajectory, initially reducing and then rising again over the post partum period. As measured by the EPDS at 6 months postpartum in those on antidepressant medication in pregnancy, with a mean EPDS score of 7.33 (Standard Deviation 7.81), compared to women with depression not on antidepressant treatment in
pregnancy who had a mean EPDS score of 8.66 (SD 4.45). However, both groups had higher scores on the EPDS than the control women who had a mean score of 4.78 (SD 3.77). Within the mixed model analysis, differences in the levels of each group averaged across all time points were significantly different (F (75.6)=4.7, p=.01). The groups did not show a significant change in levels over time (F(68.01)=2.06, p=.13). There was not a significant interaction of group by time (F(68.07)=1.5, p=.19). However, it should be noted that these are preliminary analyses and the sample size is relatively small. We would expect if these relations presented in the figure above hold true for the larger sample, then it will show that medication may have an initial effect of keeping depressive levels lower than those who are not treated (we assume this is why the medicated group starts lower). However, medication seems to have limited capacity to continue to reduce depressive symptoms levels over time. Contrary to our prediction, our data support the view that it is the women in the ‘depressed without medication’ group who show the greater reduction in depressive symptoms over time (but this effect is not statistically significant in the current small sample).

**Hypothesis 2**

There was no statistically significant difference between the 3 groups on mother-infant bonding as measured by the PBQ at 6 months of age. The mean score for control group was 67.29 (SD 2.76), for women on antidepressants was 67.33 (SD 6.21) and for depressed women who did not take antidepressants in pregnancy was 67.8 (SD 4.15). In another analysis using a multivariate regression model, we found that the strongest predictor of variation in postpartum mother-infant bonding, measured by the PBQ, was postpartum levels of maternal postpartum depression symptoms, as measured by the EPDS. In the regression model, the first step including postpartum EPDS and postpartum trait anxiety on STAI and significantly accounted for 26% of the variance in bonding. In a second step EPDS scores in 1st and 3rd trimester of pregnancy and trait anxiety in 1st and 3rd
trimester of pregnancy were added and this final model explained 42% of the variance, a significant increase in the predictive power of the model. Further analysis suggested that, even after accounting for the effects of anxiety, high depression remained the strongest and unique predictor of poor bonding. These findings suggest that high depressive symptoms particularly after birth are associated with maternally reported difficulties in bonding with the infant and are clearly important factors in predicting mother-infant bonding and in understanding the risk to child development posed by maternal depression. Once the sample size of those coming through wave 4 is increased, further analysis of variables that are possible predictors of bonding will be undertaken.

**Hypothesis 3 & 4**

The cortisol and oxytocin data for hypothesis 3 and 4 is derived from a pilot sample of n=37 women with control n=19, antidepressant n=9 and depressed n=9. The data reported is based on this selected number of depression and antidepressant exposed cases, matched to control cases on BMI, gestation and excluding preeclampsia and Gestational Diabetes Mellitus (GDM), and who had complete biosamples in November 2013. In this sample of the study blood samples were taken to the Mercy lab and assayed for hormone levels, namely oxytocin and cortisol. Following the final report further assays will be undertaken with the full sample.

This data required a particular treatment given it was repeated and the hypothesis is concerned with predicting changes over time for distinct groups, that is, as explained below, the groups show distinct slopes. Curve estimation regression analysis was used for each individual case to generate a unique intercept (ie the average level over time) and a unique slope (ie the gradient of change of time for that individual). Once generated, both the slope and intercept were far from normally distributed and therefore non-parametric testing was required. The Kruskal-Wallis test was performed to see if the groups differ by intercept or
slope and both tests were non significant (intercept p = .27; slope, p = .35). These tests suggest that, at this stage of analysis, there is no discernible pattern of OT or cortisol across pregnancy, which is distinctive for each group. However, the numbers in these analyses are very small and the pilot work is predominately concerned with testing the capacity to run accurate assays and to examine possible effect sizes and models of data analysis. We anticipate more informative analyses once data is available on a larger number of participants.

**Hypothesis 5**

A range of measure were taken during pregnancy to examine the mother’s attachment related cognitions and emotions. These included the Experiences in Close Relationships questionnaire (ECR) and the Parental Bonding Instrument (PBI). We have also interviewed all participants using the Adult Attachment Interview (AAI) but this is yet to be fully transcribed and coded. At this stage, regression analysis showed that attachment related avoidance in pregnancy quite strongly predicted poor bonding with the infant at 6 months of age (Standardized Beta = -.38, p = .07). While not quite reaching significance, this finding is in line with our predictions.

Additional work on this hypothesis is on going. Infants will be required to be 12 months of age before testing for their attachment security can commence. In preparation for this work, A/Prof Lewis has recruited two Doctoral students (Rebecca Knapp & Alexandra Flowers) to focus on this outcome. All have undertaken training in the Strange Situations Procedure (SSP) with Dr Judith Solomon and testing will commence in the next few months.
Additional Resources

Within Australia additional useful resources on perinatal depression and the use of antidepressant medications in pregnancy include beyondblue’s written booklets available at:


There are also resources available at Black Dog Institute on both depression in pregnancy and antidepressants in pregnancy available at:

www.blackdoginstitute.org.au

Specifically on antidepressants in pregnancy is available at the Royal Women’s Hospital in Victoria through the Pregnancy Psychotropic Information Service at:

www.ppmis.org.au

Internationally there is further information on these topics through Motherisk in Canada at:

www.motherrisk.org

And through the MGH Center for Women’s Mental Health at Harvard University

www.womensmentalhealth.org

The research team has also published a book called: Psychopharmacology and Pregnancy: Treatment Efficacy, Risks, and Guidelines [Hardcover] by Megan Galbally, Martien Snellen, Andrew Lewis This is now available at Amazon:

www.amazon.com/Psychopharmacology-Pregnancy-Treatment-Efficacy-Guidelines/dp/3642545610
Further Research

MPEWS holds great promise for further research. It is the only cohort study designed specifically to focus on maternal depression, antidepressant medication and to also include comprehensive biosampling. Other comparable pregnancy cohort studies have excluded women on psychotropic medication (eg the Singapore GUSTO study) or have examined depression using only a screening tool (eg Barwon Infant Study, ALSPAC, MUSP, RAINΕ, Generation R) reflecting their design to address other endpoints or exposures. Internationally comparable studies typically consider maternal depression only as a covariate. By contrast, it is now emerging that maternal depression is a major driver of fetal and infant development and therefore warrants a pregnancy cohort study designed specifically around this exposure. A broad team of researchers is now collaborating on MPEWS and or recruitment within the unique service setting of a Perinatal Mental Health unit, embedded within one of Melbourne’s largest birthing hospitals with a placental biology lab run by Dr Martha Lappas onsite, is a very unique circumstance for data collection and biosample collection requiring immediate sample processing.

Understanding the critical influence of maternal perinatal depression has significant clinical implications and also in terms of the significance of the scientific questions addressed. Maternal depression across pregnancy is highly prevalent with a significant public health and economic impact. The recent Deloitte Access Economics report shows that perinatal depression affected nearly 100,000 new parents in 2012 with costs of $433 million to the Australian economy. Currently, the optimal treatment for depression in pregnancy is obscured because of our limited understanding of the impact of depression on both mother and fetus and concerns about deleterious effects of antidepressants on fetal development. There are currently lines of development in pharmacotherapy, which this work will directly inform. Intranasal administration of OXT is now actively explored for a number of disorders but its application in pregnancy or in relation to maternal post natal
sensitivity is virtually untouched. Epigenetic markers have been shown to be modifiable by pharmaceuticals, making their identification significant as possible new drug targets for intervention (21). Our study lays the groundwork for further developments since we have gathered high quality data on antidepressant treatment in pregnancy.

**Scientifically, the outcomes of this study will indicate whether glucocorticoid and oxytocinergic factors are major contributors to human development - as they have proven to be in animal studies – with major implications for psychosocial interventions. This project is at the forefront of efforts to determine how the social environment in early life is mediated by long-term programming to produce trajectories of behavior, response to challenge and mental health status later in life (Szyf et al, 2008).**

Psychosocial interventions hold great promise to address adversity in early child development. The outcomes of MPEWS will allow this team and others to design effective psychosocial interventions based on the optimal targets, and delivered to the right patients at the right time. By identifying key biological mechanisms this study will assist in the development of effective interventions with the aim of reducing the number of women who develop perinatal depression and thus aid in preventing poor child developmental outcomes.
References

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