

BMJ Open Lifetime prevalence and correlates of perinatal depression in a case-cohort study of depression

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ABSTRACT

Objectives This study sought to evaluate the prevalence, timing of onset and duration of symptoms of depression in the perinatal period (PND) in women with depression, according to whether they had a history of depression prior to their first perinatal period. We further sought to identify biopsychosocial correlates of perinatal symptoms in women with depression.

Design and setting The Australian Genetics of Depression Study is an online case cohort study of the aetiology of depression. For a range of variables, women with depression who report significant perinatal depressive symptoms were compared with women with lifetime depression who did not experience perinatal symptoms.

Participants In a large sample of parous women with major depressive disorder (n=7182), we identified two subgroups of PND cases with and without prior depression history (n=2261; n=878, respectively).

Primary and secondary outcome measures The primary outcome measure was a positive screen for PND on the lifetime version of the Edinburgh Postnatal Depression Scale. Descriptive measures reported lifetime prevalence, timing of onset and duration of PND symptoms. There were no secondary outcome measures.

Results The prevalence of PND among parous women was 70%. The majority of women reported at least one perinatal episode with symptoms both antenatally and postnatally. Of women who experienced depression prior to first pregnancy, PND cases were significantly more likely to report more episodes of depression (OR=1.15 per additional depression episode, 95% CI 1.13 to 1.17, p<0.001), non-European ancestry (OR 1.5, 95% CI 1.0 to 2.1, p=0.03), severe nausea during pregnancy (OR 1.3, 95% CI 1.1 to 1.6, p=0.006) and emotional abuse (OR 1.4, 95% CI 1.1 to 1.7, p=0.005).

Conclusions The majority of parous women with lifetime depression in this study experienced PND, associated with more complex, severe depression. Results highlight the importance of perinatal assessments of depressive symptoms, particularly for women with a history of depression or childhood adverse experiences.

INTRODUCTION

Background

Perinatal depression (PND), including both antenatal and postpartum depression, carries

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Largest study of its kind, comparing characteristics of women with perinatal depression (PND) to those of women with non-perinatal depression.
- ⇒ Reports detailed characteristics of women with PND but with different psychiatric histories.
- ⇒ An online questionnaire, with no personalised interviews or clinical reports to provide supporting evidence for self-reported data.
- ⇒ Reliance on self-report information years after experiencing PND could lead to recall bias.
- ⇒ The Australian Genetics of Depression Study cohort is mostly young and well-educated and may not generalise to the entire population.

serious risk for both mother and infant. An estimated 53% of women with postpartum depression have ‘high suicidality’,¹ while the rate of self-harming thoughts is three times that of the postpartum community population.² Estimated economic costs of PND in the UK, of which 72% are for ongoing care of the child³ reflect findings that children of women with persistent and severe PND are at increased risk of adverse outcomes.^{4,5}

Peripartum depression is classified diagnostically in the Diagnostic and Statistical Manual of mental disorders fifth Edition (DSM 5)⁶ as a subtype of major depressive disorder (MDD). The classification of the disorder as peripartum is a change from the fourth edition of the manual where the disorder was called postpartum depression. The change in nomenclature reflects the increased recognition that symptoms can begin during pregnancy.

There is ongoing debate as to whether PND is a depressive episode that happens to coincide with the perinatal period⁷; or a distinct disorder with a partially overlapping set of risk factors, stimulated by changes

occurring during pregnancy and confined to the perinatal period.⁸

The strongest known risk factor for PND is a previous diagnosis of a psychiatric disorder.^{5 9–12} Women with a history of depression are at greatly increased risk of experiencing depressive symptoms during and after pregnancy. However, many women with a prior history of depression do not report symptoms in the perinatal period and for others, PND is the first reported episode. This suggests the possibility that the profile of risk factors associated with PND period is at least partially distinct from depression outside of the perinatal period. One suggestion is that PND is itself heterogeneous,^{12 13} with clinical subtypes differentiated by timing and severity of symptoms, perinatal complications and history of psychiatric disorders. A number of studies have found evidence for heterogeneity in symptom profiles across the perinatal period.^{14–16} Most studies have found evidence for groups of women with persistent high or low levels of depression symptoms through the perinatal period, and some have found evidence of transient symptom profiles with changes from the antenatal to postnatal period.¹⁷ Differences in symptom trajectories have been linked to risk factors including a previous history of depression,¹⁸ history of abuse,¹⁹ low social support,¹⁹ low income,¹⁸ lower levels of education^{20 21} and ethnicity.²¹

Objectives

Using the Australian Genetics of Depression Study (AGDS), a large cohort study established in 2016 to investigate genetic risk factors and heterogeneity in depression with over 20 000 participants self-reporting a depression diagnosis,²² we first sought to evaluate the prevalence, timing and duration of symptoms of PND symptoms in women, stratified by whether they had a history of depression prior to their pregnancy. We then sought to evaluate differences in psychosocial characteristics of women with MDD who report symptoms in the perinatal period and those who do not. Online supplemental table 1 summarises the selection process of cases according to their history of depression, as well as their comparison groups.

METHOD

Setting: the AGDS

The AGDS is a large ongoing case cohort study of the aetiology of depression that recruited 20 689 participants (aged between 28 and 58 years; 75% female) during 2016–2018. The analyses conducted here include participants enrolled prior to the initial data freeze in September 2018. Recruitment was primarily through a media campaign (86%) which requested participation from anyone with a depression diagnosis from a health professional, as well as specific invitations to women who had responded to a mobile phone app focused on PND, originally developed in the USA,²³ and also ascertainment through the Pharmaceutical Benefits Scheme prescription records for

antidepressants. For further details of the recruitment strategy, see Byrne *et al.*²²

Study design

Within the cross-sectional case cohort, we investigated the prevalence of PND, and the timing of onset and duration of PND symptoms in two groups of PND cases who were identified according to whether or not they reported having experienced an episode of depression prior to becoming pregnant for the first time. Women with a prior history of depression who met the study criteria for PND were compared with a corresponding control group of women who met criteria for lifetime depression but did not report significant depressive symptoms during the perinatal period—non-perinatal depression cases (NPD) (online supplemental table 1).

Variables

AGDS participants were invited to complete an online questionnaire. A compulsory core module assessed self-reported psychiatric history, the Composite Interview Diagnostic Interview Short Form which assesses the DSM 5 criteria for MDD,²⁴ and experiences of using commonly prescribed antidepressants. Women reporting symptoms of depression during pregnancy or up to 6 months following childbirth were asked to complete the lifetime Edinburgh Postnatal Depression Scale (EPDS),²⁵ an adaptation of the standard EPDS²⁶ that assesses lifetime PND episodes. They were also asked whether symptoms of depression occurred during pregnancy, after giving birth, or both, the age at which they experienced their worst episode of PND, its severity and duration. Furthermore, participants were asked if they had ever been diagnosed with any of 18 psychiatric disorders. For all AGDS participants, further voluntary modules assessed history of psychiatric health conditions and stressful life events.

The outcome of interest was a positive screen for PND for women with either a history of previous depressive episode(s), or no previous depression history. An exposure to a PND episode is defined as the period of time from conception up to 6 months post partum, so that the number of reported live births represents the number of exposures. PND cases were defined as women reporting at least one live birth who had been previously diagnosed with PND by a health professional, or who scored ≥ 13 on the lifetime EPDS, or who met criteria for major depression and reported at least one perinatal episode. The length and timing of onset of the worst PND episode were evaluated for PND cases both with and without a prior history of depression. Length of the worst PND episode was assessed using a 5-point scale: ‘Up to 2 weeks’, ‘2–4 weeks’, ‘1–3 months’, ‘3–6 months’, ‘More than 6 months’. Timing of onset was assessed by participants reporting which trimester of pregnancy or how long after delivery their symptoms began.

The cross-sectional nature of our study meant that no direction of causality could be assessed, but we investigated differences between PND cases with a prior

history of depression (PND_priordep) and NPD (NPD_priordep) cases across a range of clinical and psychosocial variables that have previously been identified to be associated with PND.^{5 27 28} Demographic measures included current age, marital status, education and ancestry. A list of geographical regions from which ancestry is identified is provided in online supplemental table 2. More details are provided in online supplemental methods. Other measures included the self-reported age at onset of depression, number of episodes of depression, history of childhood trauma and sexual or other physical assault, and self-reported previous diagnoses of psychiatric disorders. Eighteen psychiatric disorders were listed, of which twelve, identified by more than 3% of participants, were evaluated in this study (online supplemental table 3). Reproductive measures included age at menarche, parity, age at first birth, presence and severity of nausea and vomiting during pregnancy (NVP) and previous diagnosis of gestational diabetes, endometriosis or polycystic ovarian syndrome. Antidepressant measures included the number of antidepressants that had been tried and their efficacy. More details of these measures are provided in online supplemental methods, which also lists the questions used to assess each characteristic.

Participants: PND cases and non-perinatal comparison group

Participants with major depression either met DSM-5 criteria for MDD, or reported having been previously diagnosed with depression by a health professional.

We identified two groups of PND cases, based on whether they had a history of MDD prior to their first PND episode – PND_priorDep and PND_firstDep, respectively. Parous participants who reported an episode of depression before their first pregnancy and met PND criteria (PND_priorDep) were compared with parous participants who reported an episode of depression before their first pregnancy, but did not experience any depression associated with childbirth (NPD_priorDep). **Figure 1** and online supplemental table 1 illustrate sample selection. Further details are provided in online supplemental methods.

Statistical analysis

Associations between variables and PND were assessed using logistic regression, with PND the dependent variable, including age at survey time and number of births as covariates.

All modules apart from the first were optional, and some categories applied only to a limited number of participants (eg, those who had used at least one antidepressant). For these reasons, the number of participants who completed each category or variable varied. For each variable, the number of respondents is reported. Within each category, analysis employed Bonferroni correction for multiple testing (N=number of tests within each category).

All analyses were conducted using R (V.3.6.0). Figures were generated using ggplot2²⁹ and Glify software.³⁰

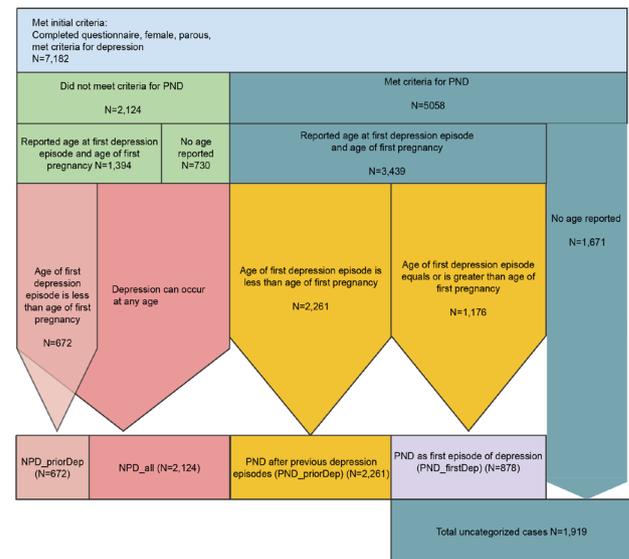


Figure 1 Flow chart: Selection of cases and associated comparative group for first analysis (prior history of major depression) and second analysis (PND is first experience of major depression). Cases met criteria for major depression and had at least one live birth, plus any of: EPDS score ≥ 13 ; a previous diagnosis of PND; or major depression during the perinatal period. EPDS, Edinburgh Postnatal Depression Scale; NPD, non-perinatal depression; PND, perinatal depression.

Public and patient involvement

There was no public or patient involvement in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Lifetime prevalence of depression during the peripartum period

A total of 15 198 female participants (median age of 39) in the AGDS, met DSM 5 criteria for MDD. Of these, 7182 (47%) reported at least one live birth. The prevalence of PND among parous women was 70.4%. A total of 2933 women reported at least one depressive episode prior to their first pregnancy. Of these, 2261 (77%) screened positive for PND, while the remaining 672 women with no PND episodes (23%) formed their comparison group (NPD_priorDep). A total of 878 out of 5058 women reported that their first episode of depression occurred during pregnancy or within the first 6 months after delivery (PND_firstDep), of women who met criteria for PND, 1919 were unable to be categorised as PND_priorDep or PND_firstDep and were lost to further analysis. **Figure 1** and online supplemental table 1 provide details of the sample selection process.

Table 1 shows the reported time of onset of symptoms (for any PND episode) for both case groups (only during pregnancy, only after delivery or both before and after delivery). The majority of women with PND reported

Table 1 Reported timing of symptoms of perinatal depression among women with PND

	During pregnancy only	After delivery only	Both during pregnancy and after delivery	Missing
All PND cases (N=5058)	295 (6%)	1627 (32%)	3073 (61%)	63 (1%)
PND_priorDep (N=2261)	144 (6%)	592 (26%)	1507 (67%)	18 (1%)
PND_firstDep (N=878)	28 (3%)	325 (37%)	510 (58%)	15 (2%)

Results are shown for all those meeting PND criteria and separately for those with a prior history of major depression (PND_priorDep) and those whose first onset of major depression was perinatal (PND_firstDep). PND, perinatal depression.

experiencing symptoms both ante- and postnatally. Onset of symptoms in the postnatal period was more commonly reported by women without a prior history of MDD.

The reported length of the worst episode of PND is shown in table 2. Full details are provided in online supplemental table 4. For both groups of cases, PND was most commonly reported to have lasted for more than 6 months.

The most reported time of symptom onset during the worst episode of PND is shown in table 3. Regardless of whether women had a prior history of depression, the most commonly reported time of onset for the worst episode was 0–4 weeks post partum. However, women with a prior history of depression were more likely to report that the worst episode began during pregnancy than women with no reported prior history, specifically during the first trimester.

Clinical and psychosocial risk factors for PND in parous women

Online supplemental table 5 provides the number and percentage of participants that completed each of the risk factor variables

Clinical and psychosocial risk factors for PND in parous women with a history of depression.

We investigated which risk factors are associated with PND in women with a previous history of depression. Age (OR (PND case status)=0.97 per additional year of age, 95% CI (0.96 to 0.98), $p<0.001$) and number of births (OR (PND case status)=1.3 per additional birth, 95% CI (1.2 to 1.4), $p<0.001$) were significantly associated with PND. Both age and number of births were included

Table 2 Length of worst reported episode of PND stratified by prior history of depression

Length of worst episode	PND_priorDep	PND_firstDep
	Total (%)	Total (%)
Up to 2 weeks	171 (7.7)	37 (4.3)
2–4 weeks	243 (11.0)	76 (8.8)
1–3 months	409 (18.5)	137 (15.9)
3–6 months	448 (20.3)	202 (23.5)
More than 6 months	935 (42.3)	407 (47.3)

PND, perinatal depression.

as covariates in subsequent analyses, which were also adjusted for multiple testing.

Key risk factors for PND among parous women with a prior history of depression were age at onset of depression (OR=0.99 per year later of onset, $p<0.001$), non-European ancestry (OR=1.5, $p=0.03$), specifically Australian Indigenous ancestry (OR 2.5, 95% CI 1.1 to 4.5, $p=0.02$), emotional abuse in childhood (OR 1.4, 95% CI 1.1 to 1.7), $p=0.006$) and severe nausea during pregnancy (OR 1.3, 95% CI 1.1 to 1.6, $p=0.007$). Being diagnosed with any psychiatric comorbidity was also associated with risk of PND (OR 1.2, 95% CI 1.0 to 1.5), $p=0.02$). The most significant individual comorbidity was Attention Deficit Hyperactive Disorder (ADHD) (OR 2.3, 95% CI 1.3 to 4.4, $p=0.009$). This association did not pass the Bonferroni corrected significance threshold; however, this is a conservative correction given the correlation between tests. Full details of all results are provided in online supplemental table 6.

Screening positive for PND among parous women with a history of depression was associated with an overall increased number of reported episodes (OR per episode=1.15 (95% CI 1.13 to 1.17), $p<0.001$) and decreased likelihood of reporting high efficacy of any antidepressant (OR=0.7 (95% CI 0.5 to 0.8), $p<0.001$).

DISCUSSION

We investigated lifetime prevalence and correlates of PND among women in a large cross-sectional study of depression. This is to date one of the largest studies of PND among women with major depression. We found a very high prevalence of perinatal depressive symptoms in women with lifetime depression, with higher likelihood of onset of symptoms during pregnancy in women with a prior history, supporting the need for screening and close monitoring of symptoms in women with a history of depression. Furthermore, our results highlight that PND is associated with a more chronic course of depression, with earlier onset, more episodes and poorer reported efficacy of antidepressants. The finding of a high prevalence of PND in women agrees with previous findings from a study in the Netherlands that found a prevalence of 40% in women with a prior history of MDD.²⁵ The prevalence in our study is higher and this likely reflects that this is a sample enriched for participants with severe

Table 3 Time of onset of the worst episode of perinatal depression

	First trimester	Second trimester	Third trimester	0–4 weeks after delivery	1–3 months after delivery	More than 3 months after delivery
PND_priorDep (%)	400 (18.1)	214 (9.6)	120 (5.4)	724 (32.6)	462 (20.8)	296 (13.3)
PND_firstDep (%)	73 (8.4)	55 (6.3)	42 (4.8)	291 (33.7)	225 (26.1)	176 (20.4)

PND, perinatal depression.

depression.²² While assessment of severity relies on the individual's self-report, previous analyses in the AGDS have shown that those reporting more severe depression have higher genetic risk to depression,³¹ and the association between PND and more chronic course is also supported by genetic data.³²

Another key finding was that women without a prior history were more likely to report symptom onset in the postnatal period and were more likely to report longer duration of symptoms. This may reflect that women with a prior history may have had an ongoing episode of depression when they became pregnant, and we were unable to distinguish whether symptoms had started prior to the first trimester. Furthermore, women with a prior history may have been more likely to be monitored by clinicians and have a treatment plan in place, leading to reduced length of symptoms.

Participants with a prior history of depression who report having at least one ancestor of Aboriginal or Torres Strait Islander (ATSI) descent were more likely to report significant perinatal depressive symptoms. There have been few studies conducted on perinatal mental health among ATSI.³³ One study conducted on a representative population sample in New South Wales did not find an increased prevalence of postnatal depressive symptoms among women of ATSI descent. However, the study did identify several associated risk factors that commonly affect people of ATSI descent such as placement in public housing, financial hardship and poor self-rated health. Many other risk factors such as smoking and obstetric complications are higher in the ATSI population than in non-Indigenous Australians and depression and anxiety are twice as common.³⁴ Results from the Australian Postnatal Screening Programme found that the rate of PND in ATSI women was 18.9% compared with 8.9% in non-Indigenous Australians and 6.3% had PND compared with 2.7% in non-Indigenous women.^{35 36} The findings of our study further highlight the increased risk of PND in ATSI women and the need for better screening and treatment in the Indigenous population.

Another key finding was the association between severe nausea during pregnancy and PND. NVP of varying severity affects approximately 69% of pregnant women. A meta-analysis evaluating the association between the severe form of morning sickness—hyperemesis gravidarum (HG)—and depression and anxiety found significant increased depression and anxiety scores in women with HG.³⁷ A recent longitudinal study in the UK found

that 49% of women with HG had probable depression antenatally and 29% had probable PND. In conjunction with our findings, these results suggest that women with severe nausea during pregnancy are at high risk of depression and may need to be referred for treatment of PND.³⁸

Lastly, we identified psychiatric comorbidities, particularly premenstrual dysphoric disorder and ADHD, and emotional abuse in childhood as being associated with perinatal depressive symptoms. There is an extensive literature on the association between trauma and PND^{39–42} and our study shows that even among those with a prior history of MDD, trauma is a risk factor for PND, consistent with previous reports.²⁵ Several studies have evaluated the association between ADHD in children and perinatal risk factors including PND in mothers.^{43–45} However, a few studies have considered that mothers with PND may also have ADHD symptoms and our results suggest that this is an important consideration. Recent studies that have attempted to account for genetic transmission from mother to child have found that much of the association between PND and ADHD in the offspring is accounted for by shared genetic risk factors between PND and ADHD.^{46 47}

The results of this study should be considered in the light of several limitations. The main limitation of this study is that it is based on an online questionnaire, with no personalised interviews or clinical reports to provide supporting evidence for self-reported data. Answers were based on total life experience, including, but not exclusive to, the perinatal period. Furthermore, the AGDS is a cross-sectional study. Its strength lies in its sample size, but, unlike a longitudinal study, it provides no information with respect to timing of variables significantly associated with PND (with the exception of childhood adverse experiences), so no inference can be made pertaining to cause and effect. In addition, because information only about the worst episode was ascertained, it was not possible to identify all cases where the perinatal episode was the first episode of depression, which may have biased the results. No information on the use of mood stabilisers which would be indicative of mixed episodes was collected.

Furthermore, the lifetime EPDS used to assess PND is a screening, rather than diagnostic tool and may result in overestimation of PND case status,⁴⁸ although O'Connor *et al*⁴⁹ reported a sensitivity of 0.8 for the EPDS in identifying MDD with a cut-off score ≥ 13 , and a specificity of 0.9. The lifetime EPDS is a modification of this scale which has demonstrated internal consistency.²⁵

Missing data are a further limitation. Because not all women completed all parts of the questionnaire, the sample sizes were different for each variable analysed. The results of the study should also be considered in the context that the AGDS cohort is mostly young and well educated and may not generalise to the entire population. The primary aim of the study was to identify genetic risk factors for depression and investigate heterogeneity in depression. Analyses conducted to date suggest that the sample is enriched for severe depression and the finding of a high prevalence of PND symptoms supports this. However, this may limit the generalisability of the findings.

Finally, complications of pregnancy and birth were not assessed in this study apart from NVP and gestational diabetes, so it was not possible to fully assess whether perinatal complications may contribute to PND vulnerability.⁹

CONCLUSIONS

PND is a leading cause of disease for women who give birth, adding to the overall family disease burden and potential cognitive and emotional problems for affected children. This sample of parous women with lifetime major depression found a high rate of perinatal depressive symptoms, particularly for women who experienced an episode of depression before their first pregnancy. There is a compelling literature demonstrating that screening for PND should begin during pregnancy,^{49 50} particularly for women with prior history of depression, which is supported by the finding that the majority of cases in this study experienced PND both before and after delivery. Although women who have been previously diagnosed with major depression are, presumably, under clinical care, it is possible that women may have withdrawn from care if treatment has been ineffective. Standard prenatal care that adopts frequent assessment of depression status provides an opportunity to identify women who might otherwise 'slip through the cracks' and ensure that they continue to receive support in finding a successful treatment or in the prevention of relapse.⁴⁹ Cases were also more likely to have treatment resistant depression, supporting further clinical investigation of antidepressant efficacy in PND.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval All study protocols were approved by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee (Ref 2118). The protocol for approaching participants through the DHS, enrolling them in the study, and consenting for all phases of the study (including invitation to future related studies) and accessing MBS and PBS records was approved by the Ethics Department of the Department of Human Services. Patient consent for participation in the study was obtained. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data used in this analysis and described in this article are available to all interested researchers through collaboration. Please contact NM (Nick.Martin@qimrberghofer.edu.au).

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