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A Systematic Review Investigating if Genetic or Epigenetic Markers are Associated with Postnatal Depression

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J.E. performed the literature search, J.E., E.M., and M.S. were involved in the quality appraisal of the included studies. J.E, E.M, A.B., M.S., W.G.K and J.S. were involved in the writing and editing of the article.

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Abstract

Background

Postnatal depression (PND) is common, affects the health of the mother, the development of the infant and places a large financial burden on services. Genetic and epigenetic biomarkers for PND could potentially improve the accuracy of current antenatal screening approaches. The aim of this systematic review is to report on the evidence for an association between genetic or epigenetic factors and postnatal depression.

Method

A systematic search of five databases (Medline, EMBASE, PILOT, PsychINFO and SCOPUS) was carried out using the following (MeSh) terms and keywords: postpartum, depression, postnatal depression, genetics, genetic polymorphisms and epigenetics. Inclusion criteria were applied and quality of studies was assessed using guidelines from the HuGE Review Handbook (Little & Higgins 2006).

Results

Following removal of duplicate articles, 543 remained; of these 37 met the inclusion criteria. Positive associations have been reported between PND and polymorphisms in the HMNC1, COMT, MAOT, PRKCB, ESR1, SLC6A4 genes in the presence of stressful life events, the BDNF gene when the postnatal period occurs during autumn and winter months and the OXT and OXTR genes in the presence of childhood adversity experienced by the mother.

Epigenetic interactions with genotype, estrogen, and childhood adversity were identified that are predictive of PND.

Limitations

The number of studies investigating some of the markers was small and grey literature was not included.

Conclusion

This review highlights the importance of examining the interaction between epigenetic, genetic, hormonal and environmental factors in order to fully understand the risk factors for PND and to improve the accuracy of current antenatal and early postnatal screening procedures. Women susceptible to PND appear to have heightened epigenetic sensitivity to the physiological changes of childbirth or to environmental factors conferred by genotype.

Key Words: genetic polymorphism, epigenetic, depression, postpartum depression

1. Introduction

The World Health Organisation estimates that 10-15% of women in industrialised countries and 20-40% of women in developing countries experience depression during pregnancy or postnatally (WHO 2009). Outcomes for mothers and infants can be grave with poor mental health consistently identified as a major causal factor in maternal morbidities during the perinatal period (CEMACH 2007, MBRACE 2014). The symptoms that mothers' experience can impact upon the quality of the care they provide to their babies. Critically, the synchrony of maternal-infant interaction is interrupted affecting infant development, with consequences that can be life-long (Apter-Levy et al, 2013).

Women can become depressed at any time during pregnancy or motherhood, however in this review, we focus on depression that is of a postnatal onset and use the term postnatal depression (PND) to refer to depression that has a postnatal onset. An estimated 50% of women with PND go undiagnosed (Beck 2006). If detection rates are to be improved valid and reliable methods of identifying women during pregnancy who have an elevated risk of PND are extremely important.

Depression is a chronic disorder of low mood that is understood to result from an interaction between environmental and hereditary factors (Uher 2008) and research has begun to focus on identifying the genetic factors that contribute to such a common mental illness. Genetic polymorphisms, variants of a particular DNA sequence, and epigenetic modifications which make genes available or unavailable for transcription **(**Syzf et al, 2000) can alter gene expression, and may be a source of differences in physical and psychological processes (El-Ilbiary et al, 2010). If biomarkers, detectable in antenatal blood, could be used to predict PND, this could enhance current approaches to identifying women at risk including psychosocial history and screening for antenatal depression (NICE 2014).

Three literature reviews have previously reported on associations between genetic variants and childbirth related depression. Figueiredo et al (2015) reported on perinatal depression rather than PND. In 2015, Couto et al, summarised the results from studies published prior to April 2014, linking genetic susceptibility to PND. The most recent review, by McEvoy et al (2017), was a qualitative review summarising the evidence for genetic associations with premenstrual dysphoric disorder and postnatal depression. Advancements in genetic research in PND have been rapid over the last few years and there has been no systematic review of the literature on epigenetic biomarkers that may confer increased risk of developing PND. The overall aim of this systematic review, therefore, was to examine the current evidence for an association between genetic or epigenetic markers and postnatal depression.

2. Methods

Data sources and search strategy

The widely-accepted 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) (Moher 2009) guidelines were used to perform a systematic search of the literature. In order to address the question 'Is there an association between genetic or epigenetic markers and postnatal depression?' Medical Subject Headings (MeSH) and text words (postpartum, postnatal, depression, postnatal depression, genetics, genetic polymorphisms and epigenetics) were used to search five online databases (EMBASE, Medline, SCOPUS, PILOT and PsychInfo) to identify primary research studies. Dates were not restricted to make the search as comprehensive as possible. The keywords and MeSH terms were tested in Medline and then refined for the other databases. The reference lists of identified studies were also searched by hand for any further relevant papers.

Inclusion Criteria

To be included in the review the papers had to meet the following criteria: 1. Reporting original research; 2. genetic polymorphisms or epigenetic markers were investigated; 3. either depression or elevated symptoms of depression were measured; 4. human participants were studied. Language was not restricted.

Quality appraisal of studies

To reduce bias in conducting this review and to assist in the interpretation of findings, each study went through a process of quality assessment. A checklist was drawn up using the guidelines laid out in the HuGE Review Handbook, a document developed to assist the integration of evidence from human genomic epidemiological studies (Little & Higgins 2006). In each study we assessed selection bias, bias or error in outcome ascertainment, information bias (analytical validity of genotyping and, in studies of gene- environment interaction, the validity of exposure assessment) and confounding.

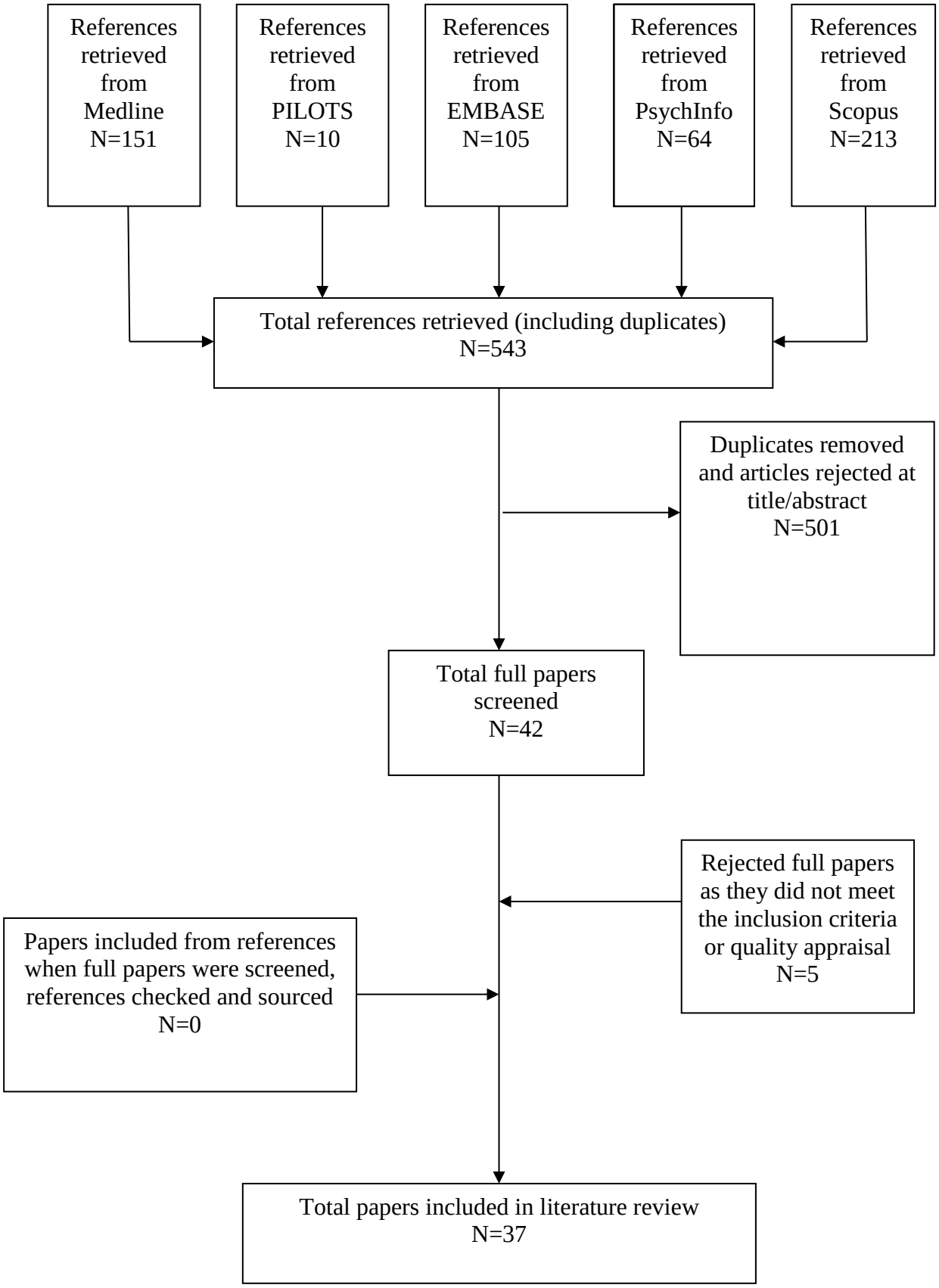
Searching the databases resulted in 543 hits. Duplicates were removed and abstracts and titles were reviewed with reference to the inclusion criteria. Overall, 506 papers were rejected for one or more of the following reasons: they were duplicates; they did not use human participants, they focused on hereditary of genetic markers and the mental health of the infant at some stage in his/her life rather than the mother's mental health; they did not investigate genetic or epigenetic markers; or they did not investigate the mother's postnatal mental health. The results can be viewed in Table 1.

Study	Objectives and Hypothesis clearly stated	Clear eligibility criteria for participants	Information Bias - Genotyping	Selection Bias	Information Bias - Assessment of environmental factors	Information Bias - Assessment of Depression	Ethnicity for participation restricted	Statistical. methods replicable	HWE Assessed	Sufficient descriptive data	Genotype frequencies stated
Bell et al. 2015	Yes	Yes	QC	Sample over weighted for teenage and depressed mothers	n/a	No	No	Yes	Yes	Yes	Yes
Osborne et al. 2015	Yes	Yes	n/a	4 cohorts	n/a	4 cohorts	n/a	Yes	n/a	Yes	n/a
Tan et al. 2015	Yes	Yes	QC	Matched cases from obstetric and psychiatric clinic	n/a	No	Chinese ancestry	Yes	Yes	Yes	Yes
Alvim-Soares et al. 2014	Yes	No	QC	No	n/a	30.9% depressed	Brazilian women of ED	Yes	Yes	Yes	Yes
Frank et al. 2014*	Yes	Yes	NDG	No	n/a	E2PN	NDG	Yes	unknown	available	No
Guintivano et al. 2014	Yes	Yes	n/a	Women with psychopathology	n/a	No	n/a	Yes	n/a	Yes	n/a
Mehta et al. 2014	Yes	Yes	n/a	Women with psychopathology	n/a	No	No	Yes	n/a	Yes	n/a
Schneider et al. 2014	Yes	No	QC	No (excluded women with psychiatric illness history	n/a	E2-3 dpn	No	Yes	Yes	Yes	Yes
Stergiakoue et al. 2014	Yes	Yes	QC	No	n/a	No	No	Yes	Yes	available	Yes
Zhang et al. 2014	Yes	Yes	QC	Depressed postnatal. Women	No	No	Chinese population	Yes	unknown	Yes	Yes
Alvim-Soares et al. 2013	Yes	No	NDG	No	n/a	No	Brazilian women of CD	Yes	Yes	Yes	Yes
El-Ibiary et al. 2013	Yes	Yes	QC	No	No	No	No	Yes	unknown	Yes	Yes
Engineer et al. 2013	Yes	Yes	QC	No	n/a	E2PN	Caucasian	Yes	Yes	No	Yes
Jonas et al. 2013	Yes	No	NDG	No	No	No	No	Yes	Yes	Yes	Yes
Khabour et al. 2013	Yes	Yes	QC	No	n/a	No	No	Yes	Yes	Yes	Yes
Mileva-Seitz et al. 2013	Yes	Yes	NDG	No	No	No	Caucasian	Yes	Yes	Yes	Yes

Pinsonneal.t et al. 2013	Yes	Yes	QC	Women recruited with mood/anxiety/stress disorders	n/a	No	No	Yes	Yes	Yes	Yes
Tavares Pinheiro 2013	Yes	Yes	NDG	No	No	No	No	Yes	Yes	Yes	Yes
Fasching et al. 2012	Yes	Yes	QC	No (excluded women with psychiatric illness history	n/a	E2-3dpn	No	Yes	Yes	Yes	Yes
Gelabert et al. 2012	Yes	Yes	NDG	Psychiatric Caucasian postnatal. women	No	No	Caucasian	Yes	Yes	Yes	Yes
Lewis et al. 2012	Yes	Yes	NDG	Sample over weighted for teenage and depressed mothers	No	No	Caucasian	Yes	No	Yes	Yes
Mehta et al. 2012	Yes	Yes	NDG	mean maternal. age older than original. Sample	No	No	German Women	Yes	Yes	Yes	Yes
Comasco et al. 2011	Yes	Yes	QC	Case control, PND over represented in comparison to population	NDRV	No	No details	Yes	Yes	Yes	Yes
Comasco et al. 2011	Yes	Yes	QC	Case control, PND over represented in comparison to population	NDRV	No	No details	Yes	Yes	Yes	Yes
Binder et al. 2010	Yes	Yes	QC	No	n/a	No	No	Yes	Yes	Yes	Yes
Costas 2010	Yes	Yes	QC	No	n/a	No	No	Yes	Yes	Yes	Yes
El-Ibiary et al. 2010*	Yes	No	NDG	No	No	No	No	Yes	unknown	Yes	Yes
Figueira et al. 2010	Yes	Yes	NDG	No	No	No	No	Yes	Yes	Yes	Yes
Mitchell et al. 2010	Yes	Yes	NDG	Sample over weighted towards unwed mothers 75%	No	CIDI-SF	No	Yes	unknown	Yes	Yes
Doornbos et al. 2009	Yes	Yes	NDG	No (women with diabetes and vegan diet excluded)	n/a	No	Caucasian	Yes	Yes	Yes	Yes
Lin et al. 2009	Yes	Yes	NDG	No	n/a	No	No	Yes	Yes	Yes	Yes
Mahon et al. 2009	Yes	Yes	QC	Women with postnatal bipolar or PND symptoms	n/a	No	No	Yes	Yes	Yes	n/a
Xie L & Innis 2009	Yes	Yes	QC	No	n/a	No	No	Yes	Yes	Yes	Yes
Sanjuan et al. 2008	Yes	Yes	NDG	No	n/a	No	No	Yes	Yes	Yes	Yes
Josefsson et al. 2004	Yes	Yes	NDG	Depressed women	n/a	No	Caucasian	Yes	n/a	Yes	Yes

Sun et al. 2004	Yes	Yes	QC	No inclusion/exclusion criteria	n/a	No	No	Yes	Yes	Yes	Yes

QC - details given of quality control procedures; **NDG -** details given of quality control procedures **E2PN -** EPDS 2-8 week postnatal.ly; **E2/3dpn -** EPDS 2-3 days postnatal. measures end of pregnancy; **30.9% depressed -** EPDS>=13 & Assessed byes psychiatrist at 8 weeks postpartum (30.9% depressed); **Available** – reported elsewhere; **NDRV -**No details given re reliability or validity of measures; **Brazilian women of ED -**Brazilian women of European descent; **Brazilian women of CD -**Brazilian women of Caucasian descent; **4 cohorts -**4 cohorts some psychiatric interview while others had a range of self-report measures *Conference abstrac


References retrieved from Medline N=151
References retrieved from PILOTS N=10
References retrieved from EMBASE N=105
References retrieved from PsychInfo N=64
References retrieved from Scopus N=213
Total references retrieved (including duplicates) N=543
Duplicates removed and articles rejected at title/abstract N=501
Total full papers screened N=42
Rejected full papers as they did not meet the inclusion criteria or quality appraisal N=5
Papers included from references when full papers were screened, references checked and sourced N=0
Total papers included in literature review N=37

2. Results

37 studies were identified that reported on associations between PND and single nucleotide polymorphisms (SNPs), deletion/insertion polymorphisms or epigenetic modifications. As not all studies used a clinical diagnosis of depression (21 studies measured elevated symptoms of depression), the term postnatal depression (PND) has been used throughout to refer to both a formal diagnosis of depression or elevated symptoms of depression. Two studies assessed levels of anxiety in addition to PND (Lin et al, 2009; Sun et al, 2004.) The majority of the studies were carried out with European, Caucasian women.

The literature search identified three genome-wide studies (GWAS) (Byrne et al, 2014; Mahon et al, 2009; Mehta et al, 2014) and two studies that investigated multiple polymorphisms in a large number of genes (Coastas et al, 2010; El-Ibiary et al, 2013). The majority of studies focus on polymorphisms within one or two candidate genes, chosen because they are linked to the aetiology of other mental illnesses such as depression and anxiety, or to biological changes brought about by pregnancy or childbirth. These polymorphisms impact the function of monoamines (Alvim-Soares et al, 2013; Binder et al, 2010; Comasco et al, 2011; Doornbos et al, 2009; Fasching et al, 2012; Gelabert et al, 2012; Khabour et al, 2013; Lin et al, 2009; Mehta et al, 2012; Mitchell et al, 2011; Pinheiro et al, 2013; Pinsonneault et al, 2013; Sanjuan et al, 2008; Sun et al, 2004), Brain Derived Neurotrophic Factor (BDNF) (Comasco et al, 2011; Figueira et al, 2010), the Hypothalamic-Pituitary-Adrenal (HPA) Axis (Engineer et al, 2014; Frank et al, 2014; Schneider et al, 2014; Stergiakoule et al, 2014) or reproductive hormones (Alvim-Soares et al, 2014; Jonas et al, 2013; Mileva-Seitz et al, 2013.) The FADS1/FADS2 gene cluster (Xie & Innis 2009), the MTHFR gene (Lewis et al, 2012) and the cytochrome P450 2D6 genotype (Josefsson et al, 2004) have also been investigated in association with PND.

Polymorphism or Epigenetic Modification	Study	Sample	Environmental Stressor	Assessment of Depression	Main Association reported between variant and PND
Genome wide	Bryne et al, 2014	(N=10893)	n/a	SCI	No associations reported
16,916 SNPs in the regions of the best linkage peaks	Mahon et al, 2009	(N=1210,759)	n/a	SCI	Genetic variations on chromosomes 1q21.3-q32.1 and 9p24.3 may increase susceptibility to PND. Strongest implicated gene was HMCN1.
5-HTTLPR	Zhang et al, 2014	Hans Chinese women with a history of PND (N=220) and healthy controls (N=193)	Socio-demographics Alcohol consumption, Smoking, CA&P SLEDP	SCI within 12 months PN	LL carrier status in the presence of maternal pregnancy complications, prenatal maternal infection, prenatal maternal folate deficiency, SLEDP or age over 32.8 years is associated with higher prevalence rates for PND.
5-HTTLPR	Pinheiro et al, 2013	Postpartum women (N=276)	socio-demographic variables, alcohol consumption, tobacco smoking and SLEDP	EPDS &SCI 45-90 days PN	L carrier status in the presence of stressful life events (SLEs) is associated with PND.
5-HTTLPR polymorphism	Pinsonneault et al, 2013	Brazilian women (N=276)	SLE	EPDS & SCI PN	L allele carrier status in presence of SLE is association with PND.
5-HTTLPR polymorphism	Mehta et al, 2012	Caucasian German women (N=419)	satisfaction with partner and negative life events	EPDS during 3rd trimester, 2-3 days and 6-8 months PN	S allele carrier status predicted PND in presence of SLEs.
5-HTTLPR polymorphism	Binder et al, 2010	(N=274)	n/a	Baseline – SCI <=8 weeks and 9-24 weeks PN Hamilton Rating scale for Depression and SCID Mood Module	S carrier status in the presence of a maternal history of depression was associated with PND in early postpartum period.
5-HTTLPR and STin2	Gelabert et al, 2012	Spanish (N=237)	n/a	EPDS 1 and 24 weeks PN	5-HTT low-expressing genotypes at one loci was associated with PND.
5-HTTLPR and STin2 VNTR	Mitchell et al, 2011	(N=1206)	socioeconomic status measured by education	SCI	S and 12 carrier status associated with a bi-directional outcome making women more sensitive to their environment.

5-HTTLPR and STin2 VNTR polymorphisms	Sanjuan et al, 2008	Spanish women (N=1804)	n/a	EPDS & SCI at 2-3 days, 8 and 32 weeks PN	High expression genotype associated with PND.
81 SNPs in 12 genes	El-Ibiary et al, 2010 & 2013	Postnatal women (N=48)	Dyadic Adjustment Scale, MOS Social Support Survey, Life Threatening Events Survey, and QIDS-SR16 scale	SCI PN	3 SNPs in HTR2A associated with PND.
SNPs in TPH2 and SNPs that are known to be of functional relevance were genotyped	Fasching et al, 2012	Caucasian women (N=361)	n/a	EPDS 3rd Trimester, 2-3 days & 6 months PN	A haplotype block in promoter region of TPH2 was associated with depression pregnancy and postnatally.
TPH2 gene 2755C>A	Lin et al, 2009	Chinese women (N=200)	n/a	36 weeks AN & 8 and 18weeks PN - SCI	TPH2 275A allele was reported only in women with co morbid PND and anxiety - estimated disease risk was 1.73
5 SNPs from TPH1	Sun et al, 2004	Pregnant Taiwanese women (N=206)	n/a	SCI	T27224C was associated with co morbid PND and anxiety
TPH1 (218A>C) TPH2 (1463G>A) and SLC6A4 (L/S)	Khabour et al, 2013	(N=370)	marital status, depression history, living status (with immediate or extended family)	EPDS PN	No association
Val158Met COMT	Alvim-Soares et al, 2013	Brazilian/Caucasian women (N=116)	n/a	EPDS>= 13 at 8 weeks PN	Association reported between Met carrier status and PND
5HTT (l/S) COMT, MAOA	Comasco et al, 2011	Swedish women(N=275)	SLE, History of depression, maternity stressors	EPDS at 6 weeks and 6 months PN	Association between COMT at 6 weeks but not 6 months
MAOA, 5-HTT and COMT	Doornbos et al, 2009	Dutch women (N=89)	n/a	EPDS at 16 and 36 weeks AN, 6 & 12 weeks PN	Associations reported during late pregnancy and early postnatal period
BNDF Val66Met, 5HTT (L/S), PER2	Comasco et al, 2011	Swedish (N=275)	Season of delivery, SLEs, maternity stressors	EPDS at 6 weeks and 6 months PN	MET carrier status associated with PND only when mothers delivered in winter or autumnal months.

BNDF Val66Met	Figueira et al, 2010	(n=227)	n/a	EPDS and SCI	No association
SNPs from CRHR1 and GR	Tan et al, 2015	Women of Chinese descent (N=725)	n/a	SCI PN	No association
FKBP5, NR3C1 and CRHR1 - 9 SNPs from these genes were grouped into haplotypes	Schneider et al, 2014	German (N=431)	n/a	EPDS 3rd Trimester, shortly after birth and 6-8 months PN	No association
Bcll (GR) (rs853180) and ER22/23EK (rs10482704) and CRHR1 (rs1876828, rs242939 and rs242941)	Stergiakoule et al, 2014	Pregnant women from the UK (N=8340)	n/a	EPDS 18 weeks AN and 8 week PN	Weak associations reported between SNPs of CRHR1 and prenatal depression and PND.
Bcll (GR) (rs41423247) and ER22/23EK (rs6190) and haplotype of the CRHR1	Engineer et al, 2013	English Caucasian pregnant women (N=200)	n/a	EPDS during pregnancy and 2-8 weeks PN	rs242939 was associated with PND. rs242939 is associated with depression only during pregnancy.
CRHR1 gene (rs7209436/rs242924/rs242940/rs173365/rs110402) and CRHR2 (rs3779250)	Frank et al, 2014	Pregnant women from the UK (N=250)	n/a	EPDS 24-26 weeks AN and PN	2 SNPs individually (rs242924, rs173365) showed a sig protective effect (OR 0.41(0.19-0.90) p=0.024 and OR 0.37 (0.16-0.87) p=0.024 respectively.) The TATGG haplotype was also protective.
508 SNPs in 44 genes	Costas et al, 2010	Spanish postnatal women (N=1804)	n/a	EPDSand STAI 2-3 days, 8and 32 weeks PN. If EPDS>=9 SCI	3 SNPs at protein kinase C beta (PRKCB) significantly associated with PND.
HMNC1 rs2891230	Alvim-Soares et al, 2014	Brazilian/European (N=110)	n/a	EPDS>= 13 at 8 weeks postnatal	Heterozygosity associated with PND.
OXT peptide rs2740210 rs4813627 and OXT receptor rs237885	Jonas et al, 2013	MAVAN* (N= 431)	early life adversity	CES-D 6 months PN	rs2740210 interacted with early life adversity to predict PND

OXT peptide rs2740210 rs4813627	Mileva-Seitz et al, 2013	Caucasian mothers from MAVAN* (N=187)	quality of care mothers experienced in early life	CES-D 12-24 weeks AN & 6 months PN	Both SNPs interacted with environmental factor to predict PND
FADS1/FADS2	Xie L & Innis SM 2009	Canadian Caucasian (N=69)	n/a	EPDS 36weeks AN and 8 & 24 weeks PN	Associations reported in both antenatal and postnatal period
CYP2D6 genotypes	Josefsson et al, 2004	Caucasian (N=145)	n/a	EPDS 35-36 weeks AN, 6-8 weeks and 6 months PN	No association
Methylenetetrahydrofolate reductase (MTHFR) C677T	Lewis et al, 2012	Pregnant women (N=6809)	Folic acid supplementation	EPDS 18 & 32 weeks AN and 8 and 2 & 8 months PN	No association
Serum hormone and PPD specific DNA methylation in the OXTR	Kimmel et al, 2016	Subjects derived from the JHPC & data collected by Mehta et al (2014) & FRAMES (N=240)	n/a	Various approaches including SCI, EPDS, BDI & HDRS, AN and PN	Moderate evidence for an interaction of CpGs in the OXTR with childhood abuse status to mediate PND
Replication study testing model formulated by Guintivano et al 2014	Osborne et al, 2015	Women without a history of psychiatric illness (N=240)	n/a	Various approaches including SCI, EPDS, BDI & HDRS, AN and PN, self report.	Good accuracy of predictive model reported (AUC of 0.81(95% CI: 0.68-0.93, p=0.01)
DNA methylation of HP1BP3 AND TTC9B genes after administration of E2	Guintivano et al, 2014	Women with a history of major depression or bipolar disorder (JHPC) (N=93)	n/a	SCI	Two biomarkers loci at HP1BP3 and TTC9B found to be predictive of PND when combined with blood count data
OXTR DNA methylation levels OXTR rs53576 and rs2254298	Bell et al, 2015	Pregnant women (N=500)	psychosocial factors	EPDS AN & PN	Interaction between increased methylation and rs53576 GG carrier status associated with PND

Genome wide. Gene expression and hormones levels	Mehta et al, 2014	Women with psychopathology (N=62) replication cohort (n=24)	n/a	EPDS, HDRS & BDI - 1st trimester, 3rd Trimester and 3 months PN	116 transcripts were identified that allowed prediction of PND status with 88% accuracy

Environmental factors were measured in combination with genetic polymorphisms in 11 of the studies and included stressful/negative life events, satisfaction with partner, season of delivery, maternity stressors, history of depression or other psychiatric illness, social support, folic acid supplementation, socioeconomic group and early life adversity.

In this review, studies have been classified as genome-wide association studies, targeted SNP genetic studies or epigenetic studies.

Table 2 Summary of the included studies detailing the author, sample, genetic/epigenetic markers, environmental factors and main findings of the studies.

MANVA - Maternal adversity, Vulnerability and Neurodevelopment study over 75% Caucasian primary sample n=201 (Hamilton, replication sample Montreal n=151) **FRAMES –** Franconian Maternal Health Evaluation studies; **JHPC** – John Hopkins Prospective PPD sample **SLE** –stressful life events **SLEDP** – stressful life events that occur during pregnancy **CA&P** Prenatal exposure to chemical agents or pollutants **EPDS**- Edinburgh Postnatal Depression Scale **SCI** – Structured clinical interview/clinical diagnosis **STAI** - Spielberger State-Trait Anxiety Inventory **HDRS** - Hamilton Depression Rating Scale **BDI** - Beck Depression Inventory

2.1 Genome-wide association studies

Byrne et al (2014) (N=10 893) did not detect any genome wide associations specifically for PND. However, a larger genome wide association alongside linkage studies conducted by Mahon et al (2009) (N=1210759) identified genetic variability on chromosomes 1q21.3-q32.1 and 9p24.3, that may increase susceptibility to PND. The hemicentin-1 gene was the most strongly implicated gene when fine mapping was carried out (nominal p=0.00017). This gene encodes an extracellular protein that contains four estrogen receptor-binding sites.

2.2 Targeted Genetic Studies

Monoamines

Polymorphisms that affect monoamine signaling have been a natural focus for genetic studies of PND because of the well-characterized involvement of monoamines, particularly serotonin, in depression at other life stages. The most frequently studied polymorphism within the serotonin system is a 44-base insertion/deletion in the the serotonin transporter (5HTT) gene that encodes the serotonin transporter (5-HTTLPR). Both the S allele and the L allele have been linked to PND (Gelabert et al 2012; Pinheiro et al 2013; Zhang et al 2014; Mehta et al 2012: Gelabert 2012; Binder 2010; Zhang 2014; Sanjuan et al 2008.) Inconsistencies in determining the risk allele are likely due some studies examining environmental factors alongside genotype and others examining the two in isolation.

Polymorphisms in the tryptophan hydroxylase-2 (TPH2) gene, three SNPS in the serotonin receptor 5-HTR2A gene (rs6311, rs2070040, and rs6314), a polymorphism in the mono-amine-oxidase type A gene (MAOA-uVNTR) and a functional SNP at position 158 the catechol-O-methyl transferase (COMT) gene are all linked to increased risk for PND (Fasching 2012; El-Ibiary et al. 2013 Doornbos et al 2009; Comasco et al 2011; Alvim-Soares 2013), However, no associations are found between the TPH1 gene and PND (Sun 2004; Khabour et al 2013).

Brain Derived Neurotrophic Factor

Alterations in expression levels of brain derived neurotrophic factor (BDNF), a growth factor with important functions in neuronal development and neuroplasticity, have been associated with variety of psychiatric disorders (Martinowich and Lu 2008). Studies suggest that the BDNF Val66Met polymorphism alters both the rate of protein secretion with the methionine (Met) variant causing insufficient secretion in comparison to the Valine (Val) variant (Groves

2007) and Met carrier status is associated with reduced hippocampal volume (Frodl et al, 2007). Carrier status was not in itself found to be associated with PND by either a case-control study (N= 275) from a population-based Swedish cohort (Comasco et al., 2011) or in a random sample (N=227) of women (Figueira et al 2010). However, a significant association between BDNF Met66 carrier status and PND symptoms was detected at six weeks postpartum in mothers who delivered during autumn and winter months, even when controlling for pre-partum and postpartum environmental risk factors in the case control study (Comasco et al., 2011).

Hypothalamic-Pituitary-Adrenal (HPA) Axis

Six studies examined the genetic variability in genes linked to stress reactivity (Engineer et al 2013; Stergiakouli 2014; Frank et al 2014; Schneider et al 2014; Tan et al 2015; Costas et al 2010). Genetic variability in the corticotrophin releasing hormone receptor 1 gene (CRHR1) which binds corticotrophin releasing hormone, a potent mediator of physiological responses to stress, FK506 binding protein 5 gene (FKBP5), a member of the immunophilin family which plays an important role in glucocorticoid receptor signaling and the glucocorticoid receptor gene itself (GR and NR3C1) were investigated in association with PND. Initially, SNPs in the CRHR1 and the GR appeared to be candidate predictive biomarkers for PND (Frank et al 2014; Engineer et al 2013). However, a fully powered replication study (N=8340) did not confirm these findings (Stergiakouli 2014) and reported only a weak association, between the SNPs in the CRHR1 gene and both antenatal depression and PND. Further to this, no associations with PND were reported by either Schneider et al (2014) or Tan et al (2015) between haplotypes or SNPs occurring in the FKBP5, NR3C1 and CRHR1 genes. Both of these case-control studies had good sample sizes (N=431 and N=725 respectively). This suggests that the associations

between CRHR1 gene polymorphisms and PND are not strong enough to act as predictive markers at a population level.

Costas et al (2010) carried out a large multi-centre cohort study (N=1804) of Spanish women which included 508 SNPs in 44 genes and reported a potential role for a haplotype (GG-TT-CC at three individual SNPs rs2051684, rs381901 and rs198183) in the protein kinase C beta gene (PRKCB) in conferring risk of PND. PRKCB is involved in the signal transduction pathways that regulate the HPA axis (Shelton 2007.) No other studies have investigated this haplotype in association with PND to date and further study in other sample populations are required to determine its utility as a predictive marker.

Hormones of the Reproductive System

Estrogen has long been thought to play a role in the aetiology of PND and associations between genetic polymorphisms that affect estrogenic function and PND have been reported (Mahon et al 2009; Alvim-Soares et al 2014). Following the earlier reported genome wide linkage study by Mahon et al (2009), a smaller targeted study by Alvim-Soares et al (2014) also reported an association between SNPs in the hemicentin-1 gene and PND. Specifically, they identified the GA genotype of an intronic SNP rs2891230 within the gene as being associated with PND (chi-square = 15.64; $p<0.01$; df=2). A polymorphism in the estrogen receptor gene, ESR1 (the upstream TA microsatellite repeat), has also been associated with PND (Pinsonneault et al 2013); the long allele of this polymorphism associated with increased EPDS scores. A potential interaction between the serotonin transporter (S allele of the 5HTTLPR) and ESR1 (L allele) was detected. Although Costas et al (2010) included genes involved in the regulation of sex hormones in their study of 44 candidate genes and PND, they reported no associations.

However, neither the rs2891230 nor the rs2077647 SNPs were included in their analysis and the positive associations reported indicate these SNPs merit further detailed investigation.

SNPs related to oxytocin function have also been investigated. Oxytocin (OXT) is a nine-amino acid peptide which functions both as a hormone during labour and lactation, and as a neurotransmitter that is released when a mother interacts with her infant (Magon & Kalra 2011). The role that oxytocin has in mediating social behaviours are central to forming healthy relationships and has led to a growing interest in the contribution oxytocin may have in the pathophysiology of neuropsychiatric disorders such as depression (Cochrane et al 2013). Oxytocin is associated with decreased cortisol levels and lower anxiety in stressful social situations and reduced amygdala activity in threatening situations (Olff et al, 2013). Jonas et al (2013) and Mileva-Seitz et al (2013) reported associations between SNPs of the oxytocin gene (rs2740210, rs4813627) and PND when the mother had experienced negative childhood experiences, such as early childhood adversity or a lack of quality of care from her own mother. Childhood trauma scores were moderated by OXT rs2740210 genotype; women who had the CC genotype experienced higher level of depression than women with at least one A allele (Jonas et al 2013). Mileva-Seitz et al (2013) concurred that early life experiences had a stronger moderating effect for this genotype (CC) and also for the GG genotype in the rs4813627 SNP. While SNP rs237885, which occurs in the oxytocin receptor gene, was associated with antenatal depression scores it was not associated with PND scores (Mileva-Seitz et al 2013). When considering the strength of the evidence from these two studies it should be noted that both of these studies drew their sample from the same source – the Maternal Adversity, Vulnerability and Neurodevelopment Study so they are not independent cohorts, and replication of these findings in additional populations would add strength to their use as markers of PND.

Additional genetic markers

Quantitative trait analysis showed that genetic variability in the FADS1/FADS2 gene cluster that contributes to variability in blood lipid fatty acids is associated with perinatal depression; rs174575 carrier status was associated with increased risk of depressive symptoms at both 36 weeks gestation and at six months postpartum (Xie & Innis 2009), suggesting that this may be a useful marker of depression but it is not specific to postnatal onset. The haplotype GTCT in rs174553, rs99780, rs174575, rs174583 respectively was also associated with PND risk at 36 weeks gestation (p=0.028). Additionally, studies have examined the interaction between MTHFR C677T genotype and folic acid supplementation during pregnancy (Lewis et al 2012) and the cytochrome P450 2D6 (CYP2D6) genotype (Josefsson et al 2004) and risk of PND but no associations were identified.

2.3 Epigenetic Studies

DNA methylation is the most extensively studied epigenetic mechanism to date and involves the addition of a methyl group to the 5' carbon of a cytosine molecule (Moore 2013). The presence of this methyl group physically blocks transcription factors from binding to DNA, and in general methylation of the promoter region of a gene decreases expression. Methylation levels can be impacted by genetic differences and can be altered as a a result of environment exposures. Changes in DNA methylation can be heritable and have been shown to contribute to the psychopathology of mental health disorders (Bale et al. 2010). Four studies that investigated DNA methylation in association with PND were identified, all of which reported positive associations.

Oxytocin is a key regulator of stress and anxiety and interacts with psychosocial risk factors and gonadal hormones (Olff et al, 2013). Genetic and epigenetic variability in the oxytocin

receptor (OXTR) gene are linked to PND. Bell et al. (2015) identified an interaction between rs53576 and methylation in the OXTR gene amongst women who did not have depression prenatally but developed PND. Women with the GG genotype showed 2.63 greater odds of PND for every 10% increase in methylation level, whereas methylation was unrelated to PND amongst "A" carriers. However, no association was found for women who had symptoms of antenatal depression, suggesting that this interaction may be specific for postnatal onset.

Guintivano et al. (2014), identified estrogen-induced changes in DNA methylation in two genes, HP1BP3 and TTC9B, that were common to both mouse hippocampus samples following long-term treatment with estradiol, and in blood samples from pregnant women with pre-existing mood disorders. DNA methylation status, and corresponding gene expression levels of HP1BP3 and TTC9B were highly predictive of PND with an area under the receiver operator characteristic curve (AUC) of 0.96 in women with antenatal depression and euthymic women. Further evidence supporting the use of DNA methylation levels in HP1BP3 and TTC9B as predicative biomarker loci for PND was demonstrated in a follow up study by Osborne at al. in 2015. Employing a statistical model including the methylation status of HP1BP3 and TTC9B, PND status was correctly predicted in a cohort of high-risk women, as well as in an independent cohort of women without a previous diagnosis of a psychiatric disorder with an AUC of 0.81.

OXTR expression is influenced by exposure to gonadal hormones including estrogens. DNA methylation levels in an intronic region of the OXTR gene proximal to an estrogen binding site were found to be predictive of PND in both a cohort of women drawn from the general population and a cohort of women with a history of psychiatric illness (Kimmel et al 2016). The investigators also reported a significant interaction between methylation at two OXTR CpG sites (chr3, positions 8810078 and 8810069) and childhood abuse in determining risk

for PND. Additionally, they reported that DNA methylation status negatively correlated to serum estradiol levels, suggesting that the patterns indicative of PND are mediated by hormone exposure.

2.4 Gene Expression Studies

Only one study to date has examined the utility of gene expression patterns as predictors of PND. Using a genome wide approach Mehta et al. (2014) identified a group of 116 transcripts that predicted PND in a high-risk cohort who were euthymic in the third trimester of pregnancy with 88% accuracy. Network analysis of the candidate transcripts indicate that 39 of the 116 genes identified are involved in estrogen signaling. These results suggest that PND risk can be predicted prenatally in those who are already experiencing mood problems; however, this approach has not yet been tested for women who have no symptoms prenatally.

Gene	Polymorphism / modification	Suggested Mechanism	Results	Papers
5-HTT	5-HTTLPR	5-HTTLPR status interacts with environmental factors to increase risk of PND	'S' allele status in the presence of SLEs or a history of depression is associated with PND 'L' allele status in the presence of SLEs is associated with PND	Binder 2010; Mehta et al 2012; Gelabert et al 2012; Pinheiro et al 2013; Zhang et al 2014
5-HTT	5-HTTLPR & STin2 VNTR	Genotype makes women more reactive to the environment. Tryptophan depletion during the third trimester of pregnancy and the early postnatal period makes women with high expressing genotypes vulnerable to PND at these times.	'S' allele combined with 10' allele carrier status is protective in a positive environment and confers risk in a negative environment Genotype LL of 5-HTTPLR and STin2.12 was associated with depressive symptoms in a dose-response fashion at 8 weeks postpartum but not at 32 weeks.	Mitchell et al 2011 Sanjuan et al 2008
TPH1 TPH2	TPH1 T27224C TPH1 A218C THP2 C2755A	TPH1 & TPH2 code for two isoforms of Tryptophan hydroxylases (TPH), the rate limiting enzymes in serotonin synthesis and are thought to play a critical role in regulating serotonin metabolism. Under hormonal influence polymorphisms in TPH1 & TPH2 will affect enzyme activity, impacting rates of serotonin metabolism.	TPH1 27224C and TPH2 2755A alleles were associated with co-morbid perinatal major depression and anxiety disorder. (TPH1 27224C conferred a strong protective effect (odds ratio=0.27; 95% confidence interval = 0.11-0.7) while TPH2 2755A allele was found only in women with (p=0.043) and exhibited a dominant gene action (p=0.038) with an estimated disease risk of 1.73.) TPH2 haplotypes were associated with depression both during pregnancy and postpartum. No association was found between TPH1 A218C and PND at 4-6pn	Sun et al 2004 Lin et al 2009 Fasching et al 2012 Khabour et al 2013
COMT	COMTVal158Met	The polymorphism affects enzyme functionality in a trimodal fashion: high function for the Val/Val genotype; intermediate function for the Val/Met genotype and low activity for the Met/Met genotype. Difference in enzymic activity due to genotype in COMTVal158Met affect monoamine function.	AA genotype (Met/Met) was associated with PND (p=0.01) After 1,000 permutation test, the adjusted p value remained sig (p=0.05)	Alvim-Soares et al 2013
MAOA and COMT	COMTVal158Met and MAOA VNTR	The gene coding for MAOA codes for an enzyme involved in the degradation of serotonin, dopamine and noradrenalin. The VNTR polymorphism occurring in the promoter region consisting of a 30bp repeated sequence. The 3aR and 4R are transcribed 10 times more efficiently compared to other variants i.e. 2R, 3R and 5R. The combination of low variants in COMT and MAOA is also found to be associated with altered stress response. Women with this genotype may be more sensitive to the increasing stress and/or decreasing synthesis of	Women carrying low activity variants of MAOA and COMT showed increased scores at 36 weeks of pregnancy and 6 weeks postpartum but not during early pregnancy or 12 weeks postpartum.	Doornbos et al 2009

		serotonin that occur as pregnancy progresses.		
BDNF	Val66Met	Met allele is associated with impaired intracellular trafficking and secretion as well as altered human hippocampal function and smaller grey matter volumes in several brain regions.	No association between Val66Met carrier status and PND was reported. A sig. association between Met66 Carrier status and development of PND symptoms at 6 weeks postpartum was evident in mother delivering during autumn/winter.	Figueira et al 2010 Comasco et al 2011
BDNF and 5-HTTLPR		Polymorphisms in BDNF have been associated with 5-HHT availability with Val allele carriers having higher levels of availability in several regions of the brain. Moreover, serotonin transporter binding levels in the brain have been shown to increase during autumn and winter and as brain tryptophan levels decrease during the perinatal period BDNF Val66Met genotype could interact with season of delivery to influence serotonin availability and in turn the risk of depression.	No gene-gene interaction was found. A cumulative effect was detected with carriers of a greater number of 5-HTTLPR S and BDNFVal66Met Met alleles reporting higher EPDS scores if delivering during autumn/winter	Comasco et al
PRKCB	haplotype of rs2051684, rs381901 and rs198183	PRKCB is involved in the signal transduction pathways that regulate the HPA axis (Shelton 2007.)	Genotype G/G-T/T-C/C at SNPs rs2051684, rs381901 and rs198183	Costas et al 2010
HMCN1	rs2891230	This gene encodes an extracellular protein that contains four estrogen receptor-binding sites.	Genome-wide analysis showed the HMNC1 gene had the strongest association with PND symptoms. The GA genotype of SNP rs2891230 was associated with PND.	Mahon et al 2009 Alvim-Soares et al 2014
ESR1	ESR1 TA	Estrogens can act on multiple central nervous system pathways by binding to intracellular estrogen receptor encoded by ESR1and affecting transcription in target tissues and also through non-classical second messenger systems. Estrogen can modulate serotonin transmission among several of these pathways.	A sig association was reported between the upstream TA microsatellite repeat and EPDS scores (p=0.007) and the occurrences of PND.	Pinsonneault et al 2013
OXT	rs2740210 rs4813627	Maternal depression mediates the effects of early adversity on breastfeeding and these same OXT-related polymorphisms moderate this mediation. The effect of OXT genotype and early experiences will be mediated by postpartum maternal mood state.	rs2740210 interacted with early life adversity and quality of care mothers experienced in early life to predict depression (CC) rs4813627 interacted with quality of care mothers experienced in early life to predict depression (G/G)	Jonas et al 2013 Mileva-Seitz et al 2013 Mileva-Seitz et al 2013

OXTR	Methylation levels	Estrogen variation induced by pregnancy and childbirth modulates the OXT system at the OXTR with estradiol increasing OXTR gene transcription. OXTR DNA methylation will be associated with PND at functionally relevant CpGs.	Methylation levels at CpGs located on chr3 at positions 8810078 and 8810069 exhibited sig association with PND. Moderate evidence was also shown for an interaction of CpGs in the region with child abuse to mediate PND.	Kimmel et al 2016
OXTR	Genotype and methylation levels	The combined effect of genotype and methylation level affects OXTR function.	Women with the rs53576 GG genotype showed 2.63 greater odds of PND for every 10% increase in methylation level, whereas methylation was unrelated to PND amongst "A" carriers. This was only seen in women with postnatal onset of symptoms.	Bell et al 2015
HP1BP3 & TTC9B	Methylation patterns	Changes in patterns of methylation at these two genes caused by childbirth related changes in estrogen levels predicts PND with some women being more sensitive to estrogen changes than others.	Methylation levels at these two genes were able to predict PND in a cohort of women with a history of psychiatric illness with a high degree of accuracy (AUC 0.96) and with moderate success in a cohort of women both with and without a history of psychiatric illness (AUC 0.81).	Guintivano et al 2013 Osborne et al 2015

Table 3 A summary of the suggested genetic and epigenetic mechanisms and results for the statistically significant associations reported within the included literature

Table 3 summarises the associations reported in the literature and the mechanisms thought to underlie these associations in order to identify candidate genes and pathways that may be appropriate for future study.

3. Quality of the evidence presented

This area of research is relatively new and a large number of variants have been investigated with few large replication studies to date. In weighing the strength of the evidence for the associations reported, some methodological approaches and study designs within the included studies are worthy of note. The reliability of associations reported in genetic studies is often questioned due to low sample size and therefore inadequate statistical power. Indeed, many of the studies assessed in this review did not clearly report on how sample size had been determined. Nominally statistically significant results in underpowered studies have a low predictive value in reflecting real associations. Therefore, associations reported in smaller, underpowered studies must be viewed with caution until they are replicated in a larger cohort. Further to this, several studies are utilizing data from the same population, possibly inflating the strength of some findings (see table 1).

A case-control study design was frequently used in the studies to ensure a comparative sample of depressed and healthy postnatal women, but these results cannot necessarily be extrapolated to represent the general population. Additional factors that limit generalisability include recruitment of single ethnicity (Mileva-Seitz et al 2013, Doornbos et al 2009, Gelabert et al 2012, Engineer et al 2013, Tan et al 2015) and recruitment of women with a history of psychiatric illness.

The tools used to measure PND were of good quality, with 14 studies using clinical assessment to formally diagnose PND. The most common approach taken was to measure PND via a screening tool, however a number of different tools were used limiting comparability across the studies. The Edinburgh Postnatal Depression Scale was the most commonly used (N=20, 54% of included studies); it detects the level of PND symptoms with a high degree of sensitivity and specificity. However, variation in the time points at which depression was assessed

hampered synthesis of results. Furthermore, 17 of the 37 studies did not assess maternal mood during pregnancy making it difficult to determine whether the depression was of postnatal or antenatal onset, or was pre-existing.

The effect of environmental factors may be particularly pertinent in the case of PND. In addition to the changes in roles and the transition to becoming a parent, women experience the physical challenges of pregnancy and childbirth. However, only 11 of the 37 studies (30%) investigated gene-environment interaction which may account for some of the inconsistencies in results between studies. Within the studies that did assess environmental factors, various methods of measurement were used such as self-completion questionnaires or interviews. Where validated measures were used, psychometric information is given confirming their validity and reliability within the study populations.

Studies incorporating environmental factors revealed associations where studies investigating genetic carrier status alone did not. For example, carrier status of BNDF Val66Met was associated with PND only when the mother delivered in winter or autumnal months (Comasco et al 2011). In studies examining genotype alone, an interaction of the genetic variation with an environmental factor leading to increased risk for PND may have been missed. There has been little attempt to investigate gene to gene interactions within studies. Gene expression and protein levels are also not generally measured and this may be considered a limitation, as without these measures the functional consequences of genetic and epigenetic variability remain unknown. In a systematic review of the genetic variability in inflammatory markers to depression Barnes et al (2017) noted that mRNA gene-expression studies showed more reliable associations with outcomes than studies of genetic variants. Changes in mRNA and protein levels can be the consequence of genetic or epigenetic variation and can elucidate mechanisms

and pathways that are involved in PND. Studies incorporating both genetic/epigenetic assessments in combination with gene expression data and even protein levels, therefore, may be considered the gold standard in trying to establish the mechanism underlying the associations with PND.

Discussion

This review synthesizes the current literature on the emerging association between genetic variants, epigenetic modifications and PND. Identification of potential genetic and epigenetic biomarkers may potentially enhance the accuracy of current predictive models, facilitating early intervention to improve outcomes for mothers and infants. Although two large GWAS studies (N=10,893 and N=1,210,759) searching for genetic biomarkers for PND, have had limited success in eliciting specific biomarkers, this could be explained by the polygenetic nature of depression and the role that environmental factors play in its onset. The importance of environmental factors has been demonstrated in studies showing associations between PND and 5HTT carrier status in the presence of stressful life events, BDNF Met carrier status during autumnal and winter months and OXT and OXTR carrier status in the presence of childhood adversity experienced by the mother.

The associations reported in this review and summarized in Table 3 suggest that the unique physiological changes brought about by the body's adaptation to pregnancy and childbirth may influence the effect of genetic variants, and can lead to epigenetic changes that increase risk of PND. The reviews by Figueiredo et al. (2015) on depression in the perinatal period and by McEvoy et al. (2017) on premenstrual dysphoric disorder and postnatal depression support our findings that genetic and epigenetic studies reinforce support the hypothesis that hormonal change and estrogen signaling during childbirth can lead to epigenetic changes associated with increased risk of depression.

Limited associations between biological processes that have been implicated in depression at other life stages were found in association with PND. For example, associations between SNPs that impact the function of the HPA axis and PND were not found to be strong, possibly because of the dampening down of this system during pregnancy (Brunton et al 2008).

PND experienced by women with a history of depression may also be linked to different underlying biological processes, and therefore a different group of biomarkers, than PND in women with no psychiatric history. For example, the 'S' allele of the 5-HTTPLR was associated with PND specifically in women with a previous history of psychiatric illness.

Mitchel et al (2011) suggested that genetic carrier status in the 5-HTTPLR may confer a biological sensitivity to context, theorising that the S allele and the 10 allele of a tandem repeat polymorphism (STin2 VNTR in intron 2 of the SLC6A4 gene), rather than conferring risk, heightened women's sensitivity to their environment. They reported these alleles as positively associating with PND in an unfavourable environment and negatively associating in a favourable environment. This bi-directional outcome may explain some of the inconsistencies in the results from the studies investigating the 5-HTTLPR, but further studies are needed to investigate this further.

Limitations of this review

Although 37 papers were identified for inclusion, there were only a small number of papers investigating each polymorphism or epigenetic marker making it difficult to draw firm conclusions, especially if study results were inconsistent. This literature review has searched for original research from peer-reviewed journals and therefore does not include grey literature.

This may mean that further relevant studies that would have met the quality standards for inclusion have been omitted.

Conclusion

Based on the reviewed evidence, the risk for PND is unlikely to be defined by a woman's genetic profile alone. Environmental influences interact with and mediate the effect of genetic carrier status and are important in determining the overall risk of developing PND; potentially through epigenetic mechanisms. A framework based on genetic variants, epigenetic modification and environmental factors may generate useful predictive models that could assist in identifying women who have an elevated risk of PND.

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