BJPsych | The British Journal of Psychiatry (2025)
1–12. doi: 10.1192/bjp.2025.39

Review

Oestrogen receptor genes and perinatal depression symptoms: systematic review

Gianna Zorzini and Ulrike Ehlert

Background

During the perinatal period, women may be more susceptible to depressive symptoms because of fluctuating oestrogen levels. Genetic variations, epigenetic modifications and varying gene expression levels of oestrogen receptor genes may contribute to inter-individual differences in the encoded receptors' sensitivity to oestrogen, ultimately modulating the susceptibility to depressive symptoms.

Aims

The aim of this systematic review was to provide an overview of the literature on the association between oestrogen receptor genes and perinatal depression symptoms by including genetic, epigenetic and gene expression studies.

Method

A systematic search of three public databases, PubMed, PsycINFO and Web of Science, was conducted in accordance with the PRISMA guidelines (PROSPERO registration number: CRD42023447446). Two independent reviewers extracted data and assessed study quality.

Results

A total of 29 studies were finally included, of which 16 investigated genetic variants, five investigated epigenetic modifications and eight investigated gene expression levels of oestrogen receptor genes. A limited number of genetic variations were found to be associated with perinatal depression symptoms, most of them in *ESR1*. Moreover, DNA methylation marks involved in oestrogen signalling, and gene expression levels of *ESR1* and *ESR2*, were found to be associated with perinatal depression symptoms.

Conclusions

Genetic variations, epigenetic modifications and gene expression levels of oestrogen receptor genes are associated with susceptibility to perinatal depression symptoms. The underlying mechanism might be the inter-individual modulation of the encoded receptors' sensitivity to oestrogen. Future research employing more comprehensive and integrative approaches is needed to better understand the aetiology of perinatal depression symptoms.

Keywords

Oestrogen receptor; epigenetics; genetic variation; perinatal depression.

Major depression is one of the most common mental disorders, with an estimated lifetime prevalence of 10%, and affects twice as many women as men.[1–3] Various factors are hypothesised to contribute to this gender difference, which is primarily observed during the reproductive phase.[4,5] Among these, fluctuations in sex steroid hormones, particularly those associated with female reproductive transitions, are considered a major biological contributor.[6–11] One such reproductive transition occurs during the perinatal period, which spans from pregnancy until 1 year after birth and is characterised by very pronounced sex steroid fluctuations. Depression during this period can result in adverse impacts not only on the pregnant person but also on the offspring, the partner and the family.[12–14] Recent data indicate that around 40% of women exhibit depressive symptoms during the perinatal period, with a substantial proportion meeting the diagnostic criteria for depression.[15]

Perinatal depression

Over the past few years, depression during the perinatal period has become the most frequent complication of childbirth, with an estimated prevalence of 17%.[16–18] Despite a growing body of evidence, it is still debated whether depression during this period is sufficiently distinct from major depression to be defined as a separate diagnosis.[19,20] However, this discrepancy can largely be attributed to varying definitions, including the timing of onset, which can range up to 1 year after delivery.[21] For instance, the DSM-5 uses the specifier 'with peripartum onset' for a major depressive episode that is diagnosed either during pregnancy or within the first 4 weeks after delivery.[22] In comparison, the definition by the ICD-11 covers the period from pregnancy up to 6 weeks postpartum.[23] Moreover, definitions with even broader time ranges have been used, covering pregnancy and up to 1 year postpartum.[24] To accommodate the range of definitions used in the existing literature, this review refers to perinatal depression as depressive episodes that occur during pregnancy and up to 12 months postpartum.

Aetiology of perinatal depression

Although a conclusive aetiological model for perinatal depression is still lacking, it is widely recognised that biological and psychosocial factors, and interactions thereof, are involved in the pathophysiological mechanisms.[25–27] Given the overlap between fluctuations in sex steroid hormones and an increased incidence of depressive symptoms, the involvement of oestrogens and progesterone has been investigated in more detail. So far, empirical evidence has implicated progesterone, particularly its neuroactive metabolite allopregnanolone (a modulator of $GABA_A$ receptors), in perinatal depression symptoms.[28] Moreover, two neuroactive steroid $GABA_A$ modulators, brexanolone and zuranolone, seem to be effective in the treatment of perinatal depression symptoms.[29,30] In contrast, the empirical evidence on oestrogens has been inconclusive.[31] While findings on the association between perinatal depression symptoms and oestrogen levels are contradictory,[32,33] some studies have identified an increased sensitivity to oestrogen in women with

https://doi.org/10.1192/bjp.2025.39 Published online by Cambridge University Press

perinatal depression symptoms.[34–36] Therefore, a potential mediating role of oestrogen sensitivity in the aetiology of the disorder has been suggested, which warrants further investigation.

Oestrogen

Oestrogens are known to regulate reproductive functions, but are further involved in numerous other functions in both females and males[37] since their synthesis and actions are not restricted to the gonads but also occur in various extragonadal tissues.[38,39] In the brain, oestrogens are involved in molecular processes across several neurotransmitter systems that affect emotional and cognitive functions implicated in various mental disorders.[40,41] Oestrogens can interact with the dopaminergic, serotonergic, GABAergic and glutaminergic pathways by regulating neurotransmitter synthesis, release and receptor interactions.[42,43] However, oestrogens are largely bound to transport proteins, with only around 2–3% being available in the unbound state with the capacity to induce an effect in target tissues.[44]

Oestrogen receptors

Oestrogens exert their effects by binding to three oestrogen receptors: oestrogen receptor-α, oestrogen receptor-β and the G protein-coupled oestrogen receptor (GPER). Oestrogen receptors mediate the emotional and cognitive effects of oestrogen, as they are distributed in various brain regions involved in these functions.[45,46] The receptors consist of distinct protein structures that provide amino acid sequences to encode receptor functions.[47–49] Binding to oestrogen receptors initiates cell type-specific transcriptional processes and signalling mechanisms through both genomic and non-genomic pathways, which ultimately regulate gene expression.[50,51] The efficiency of oestrogen-mediated signalling and the associated biological and behavioural outcomes are regulated by the individual sensitivity to oestrogen.[52] However, oestrogen sensitivity depends on the number and activity of oestrogen receptors, which can be determined at different levels.[53]

Oestrogen receptor genes

The oestrogen receptors are encoded by three distinct genes, consisting of *ESR1* encoding oestrogen receptor-α, *ESR2* encoding oestrogen receptor-β and *GPER* encoding GPER, which are important determinants of oestrogen sensitivity.[54] So far, several genetic variations in these genes have been identified, including single nucleotide polymorphisms (SNPs), restriction fragment length polymorphisms (RFLPs), short tandem repeats (STRs) and haplotype combinations. Depending on the sequence location, genetic variations have the potential to differentially modify gene expression levels and the structure and function of the encoded receptors.[55] Furthermore, epigenetic modifications, such as DNA methylation, can alter the accessibility of the DNA without changing the DNA sequence itself, thereby mediating the transcriptional activity of the gene.[56] Research suggests that genetic variations, epigenetic modifications and varying gene expression levels of oestrogen receptor genes may lead to inter-individual differences in the receptors' sensitivity to oestrogen, which may subsequently increase susceptibility to perinatal depression symptoms.[57–59]

Scope of review

Previous reviews and meta-analyses have provided evidence that oestrogen receptor gene variants, including rs2234693 and rs9340799, may be involved in the aetiology of major depression in women.[60,61] However, these approaches did not strictly distinguish between major depression and depression that occurs during reproductive transitions. Although each of the reproductive transition phases is marked by changes in sex steroid hormones, they exhibit distinct patterns of hormonal fluctuations.[7,9,10,36] The most pronounced fluctuations occur during the perinatal period, and there is growing evidence suggesting that depression during this phase is distinguishable from major depression.[6,19–21] Considering that genetic variations, epigenetic modifications and varying gene expression levels of oestrogen receptor genes may lead to inter-individual differences in the sensitivity of the encoded receptor to oestrogen, their involvement in the aetiology of perinatal depression symptoms has been suggested.[57–59] Therefore, this systematic review aims to provide an overview of the research on the association between oestrogen receptor genes and perinatal depression symptoms by including genetic, epigenetic and gene expression studies.

Method

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[62] The review protocol was registered with the International Prospective Register of Systematic Reviews before data collection (PROSPERO; registration no. CRD42023447446). Ethics approval was not required for this systematic review.

Search strategy

An initial systematic literature search was conducted on 21 August 2023. Records were retrieved from three electronic databases: PubMed, PsycINFO and Web of Science. All data were obtained from published studies, with no restrictions on publication year or language. Potentially eligible studies published in languages other than English were translated into English and assessments were conducted using the translated version. A two-component search string with the Boolean operator 'OR' was used: (a) oestrogen receptor synonyms and components, including (epi-)genetics and gene expression, and (b) perinatal depression, including synonyms (see Supplementary Table S1 available at https://doi.org/10.1192/bjp.2025.39). A supplementary manual review of reference lists was performed to identify additional publications. The literature search was updated on 6 December 2024.

Study selection

After removal of duplicates, the remaining records were screened for eligibility using titles and abstracts. To be included, records had to meet the following criteria: (a) original research, (b) human participants and (c) female participants who were (d) pregnant or within the first year postpartum. Notably, the aim of employing a broad period, encompassing both pregnancy and the 12-month period following childbirth, was to accommodate the varying definitions found in the literature and thus to provide a comprehensive overview. The full text of records meeting these criteria was reviewed for final eligibility. The following exclusion criteria were applied: (a) no assessment of depression and/or depressive symptoms, (b) no assessment of genetic variants, epigenetic modifications or gene expression levels of oestrogen receptor genes, (c) focus on child outcomes, (d) focus on gestational/birth factors and (e) same sample. The screening was performed by two independent reviewers and any disagreements were resolved by consensus.

Data extraction

Data extraction was performed according to the guidelines suggested by Sagoo et al.[63] The first data extraction took place

https://doi.org/10.1192/bjp.2025.39 Published online by Cambridge University Press

on 28 August 2023. Two independent reviewers extracted the data using a predetermined form and categorised them according to genetic, epigenetic and gene expression studies. The genetic studies were further categorised according to two categories: (a) candidate gene studies and (b) genome-wide association studies (GWASs). The candidate gene studies were further classified according to the three oestrogen receptor genes. We extracted information on the first author, year of publication, country of origin, study design, sample characteristics (sample size, mean age, ethnicity/race), method of analysis, diagnostic criteria, time of assessment and main findings. In addition, we extracted information on genotyped SNPs and nucleotides for candidate gene studies. For epigenetic and gene expression studies, we additionally extracted information on the type of epigenetic marker or receptor gene, respectively, as well as on the specimen. Because of the limited number of included studies investigating each predictor variable (most were only investigated once) and the methodological heterogeneity of the studies, encompassing different outcome variables, diverse study designs and different measurement approaches,[64,65] we did not perform a meta-analysis, and data were analysed narratively.

Quality appraisal

To assess risk of bias, we used a checklist developed by Elwood et al[58] in accordance with the guidelines of the HuGE Review Handbook.[64] The checklist included the following items: a clearly stated objective and hypothesis, clear eligibility criteria for participants, information bias in genotyping, selection bias, information bias in assessment of environmental factors, information bias in assessment of depression, restrictions on the ethnicity of participants, replicable statistical methods, assessment of Hardy–Weinberg equilibrium (HWE), comprehensive descriptive data and genotype described. Each criterion on the checklist was rated as 'Yes' (study satisfied the criteria), 'No' (study did not satisfy the criteria) or 'NA' (information not available in the study). Only the criterion information bias in genotyping was rated additionally with 'QC' (details given of quality control procedures). To assess the quality of the evidence for each included study, the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) criteria were applied.[66] The initial confidence level was defined according to the study design, with observational studies starting at low confidence. The confidence level was raised by a number of factors, including the use of clinical ratings for perinatal depression symptoms, the inclusion of confounders, the exclusion of psychiatric comorbidities, the use of correction for multiple testing and a large sample size ($n \geq 1000$). The confidence level was lowered by factors such as failure to account for confounders, lack of correction for multiple testing, small ($n \leq 100$) or very small ($n \leq 50$) sample sizes and indirectness of assessment criteria for perinatal depression. Based on these factors, 'very low', 'low', 'moderate' and 'high' estimates (−2, −1, 0 and 1, respectively) were assigned. The final confidence level was adjusted by one or two categories if the difference between the number of factors raising or lowering confidence was two or higher or four or higher, respectively. Quality assessment was performed independently by two reviewers, and any disagreements were resolved by consensus.

Results

Study selection

The initial literature search identified a total of 2093 records, from which 561 duplicates were removed. Following an initial screening of titles and abstracts, 1220 articles that did not meet the inclusion criteria were excluded. Reasons for exclusion at this stage encompassed articles that did not cover any original research (e.g. Fernandez et al[67]), studies that investigated animal samples (e.g. Furuta et al[68]) and studies with a female sample analysed outside of the perinatal period (e.g. Mehta et al[35]). Subsequently, a total of 287 articles were evaluated for full-text eligibility. Of these, 258 were removed based on the exclusion criteria. Notably, the reasons for exclusion encompassed lack of assessment of depression and/or depressive symptoms (e.g. Thippeswamy et al[69]), lack of assessment of genetic variants, epigenetic modifications or gene expression levels of oestrogen receptor genes (e.g. Figueira et al[70]), a focus on child outcomes (e.g. Wikenius et al[71]), a focus on gestational/birth factors (e.g. Pellicano et al[72]) and the investigation of the same sample (e.g. Nguyen et al[73]). Furthermore, GWASs conducting combined analyses of multiple cohorts without reporting individual cohort findings separately were excluded (e.g. Guintivano et al[74]). Although such studies have the potential to increase statistical power, their findings are limited by methodological variability (e.g. heterogeneous definitions of perinatal depression across the cohorts). Therefore, a total of 29 studies were ultimately included in the systematic review. The studies were categorised according to genetic studies ($n = 16$), epigenetic studies ($n = 5$) and gene expression studies ($n = 8$). The genetic studies were further divided into two categories: (a) candidate gene studies ($n = 9$) and (b) GWASs ($n = 7$). Since no candidate gene study was found to investigate the association between *GPER* and perinatal depression symptoms, the studies were further divided into two categories: (a) studies examining genetic variations in *ESR1* ($n = 8$) and (b) studies focusing on genetic variations in *ESR2* ($n = 6$). The study characteristics and results of the included studies were described within these categories (see Supplementary Tables Tables S4–8). Figure 1 summarises the selection process based on the PRISMA guidelines.

Study characteristics

The 29 included studies were published between 2010 and 2024. The sample sizes ranged from 14 to 226 707. Seventeen studies conducted a genome-wide approach, while 12 studies employed a targeted approach. Nine genetic studies conducted a candidate gene approach and genotyped and tested a total of 62 genetic variations in oestrogen receptor genes, comprising 61 SNPs, of which four were RFLPs, and one STR (see Fig. 2). In addition, four haplotype combinations were tested for an association with perinatal depression symptoms. Following the recommendations of Takezawa et al[75] we avoid broad, arbitrary groupings and therefore report self-reported ethnicities as stated in the original studies to ensure an accurate description of the participants. Three studies examined Asian samples, four examined White samples, ten examined mixed-ethnicity samples, two examined European samples, one examined a Spanish sample, one examined a Japanese sample and eight studies did not provide sufficient information on ethnicity. Twenty-three studies employed a case–control design, and six studies adopted a cohort design. Eleven of the case–control studies collected longitudinal data: six collected data during pregnancy and the postpartum period and the other five collected data only during the postpartum period, spanning from 2–3 days to 12 months postpartum.[76–86] Four of the case–control studies used a cross-sectional design, collecting data within the first 12 weeks postpartum.[87–90] The remaining eight case–control studies did not report the specific assessment time point during the perinatal period.[91–98] The six cohort studies collected longitudinal data during pregnancy and postpartum, ranging from 14 weeks of pregnancy to 9 months postpartum.[99–104] The included studies applied various self-report instruments and clinical interviews to assess perinatal

https://doi.org/10.1192/bjp.2025.39 Published online by Cambridge University Press

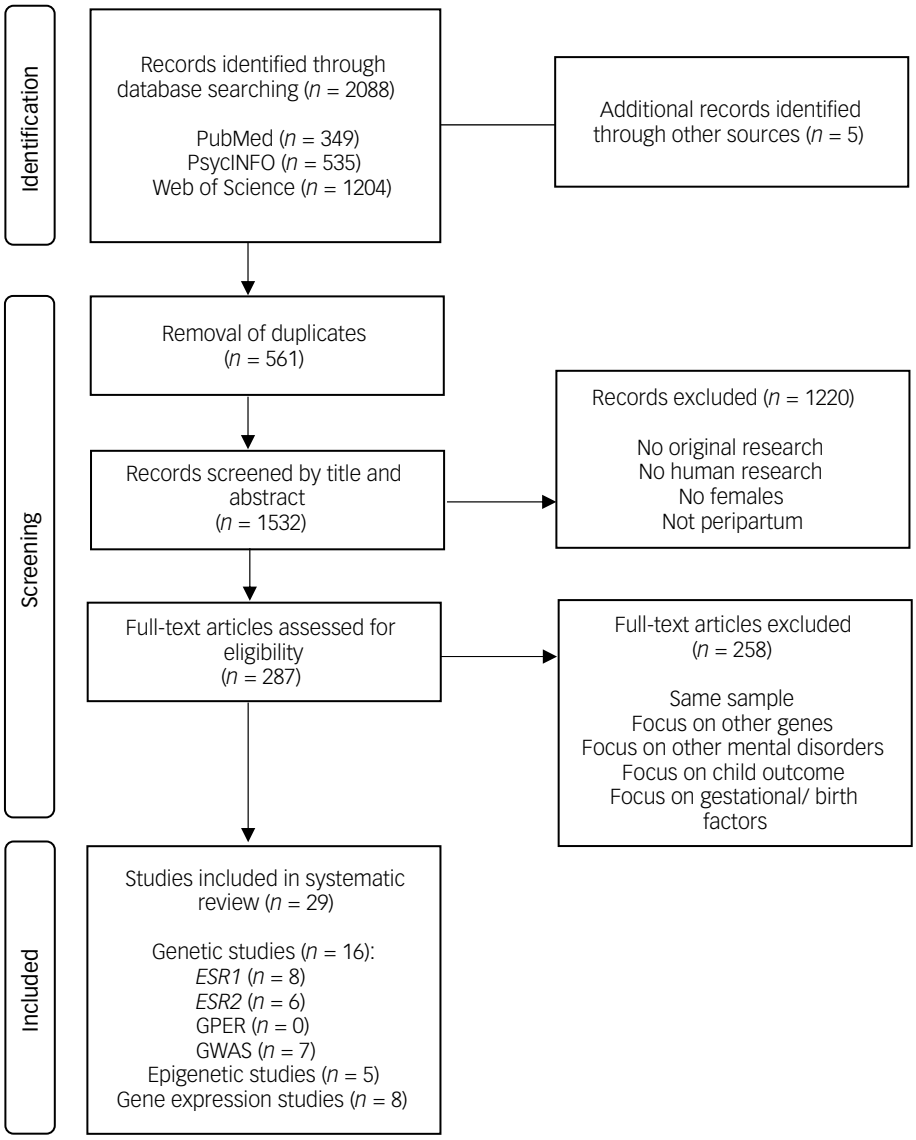

Fig. 1 PRISMA flow diagram of the studies included in the review. *ESR1*, oestrogen receptor-α gene; *ESR2*, oestrogen receptor-β gene; GPER, G protein-coupled oestrogen receptor gene; GWAS, genome-wide association study.

depression symptoms. A total of seven different self-report instruments were used; the most frequently administered self-report instrument was the Edinburgh Postnatal Depression Scale (EPDS).[105] The EPDS was employed in 22 studies, of which 16 reported a cut-off score, ranging from 8 to 20.[76,78–80,82,83,85–90,93,95–102,104]

Critical appraisal of included studies

For an overview of the risk of bias assessment, please refer to Supplementary Fig. S1 and Table S2. None of the included studies indicated a high chance of bias for the criteria 'replicable statistical methods' and 'comprehensive descriptive data'. However, most of the studies did not provide information on the assessment of environmental factors, indicating a high chance of bias for this criterion. An overview of the quality of evidence assessment is provided in Supplementary Table S3. In summary, most of the studies were attributed with a low (48.3%) level of confidence, followed by very low (27.6%) and moderate (24.1%). No study achieved a high (0.0%) level of confidence. It should be noted that an initial low confidence level was assigned to observational studies, which affected all of the included studies.

Genetic studies on oestrogen receptor gene 1

Eight candidate gene studies investigated the association between genetic variations in *ESR1* and perinatal depression symptoms.[76–78,87,88,93,94,100] These studies genotyped and tested a total of 45 genetic variations, including 44 SNPs, of which two were RFLPs and one was a STR. The most frequently investigated genetic variation was the SNP rs2077647, which was analysed in four studies. The second most frequently investigated variations (each analysed in three different studies) were the SNPs rs9340958 and rs3020434 and the RFLPs rs2234693, also known as the Pvu-II variant, and rs9340799, also known as the Xba-I variant. The third most frequently investigated variants were the SNPs rs9341052, rs3798577 and rs1801132, and one STR, the thymine-adenine repeat, which were each analysed in two studies. The remaining genetic variations were only tested once. Furthermore, three studies analysed additional haplotype combinations. A significant linkage disequilibrium was found between the haplotype combinations of rs2077647 and rs9340799, rs2077647 and rs2234693 and rs2234693 and rs9340799, but the haplotypes did not show a significant association with perinatal depression

https://doi.org/10.1192/bjp.2025.39 Published online by Cambridge University Press

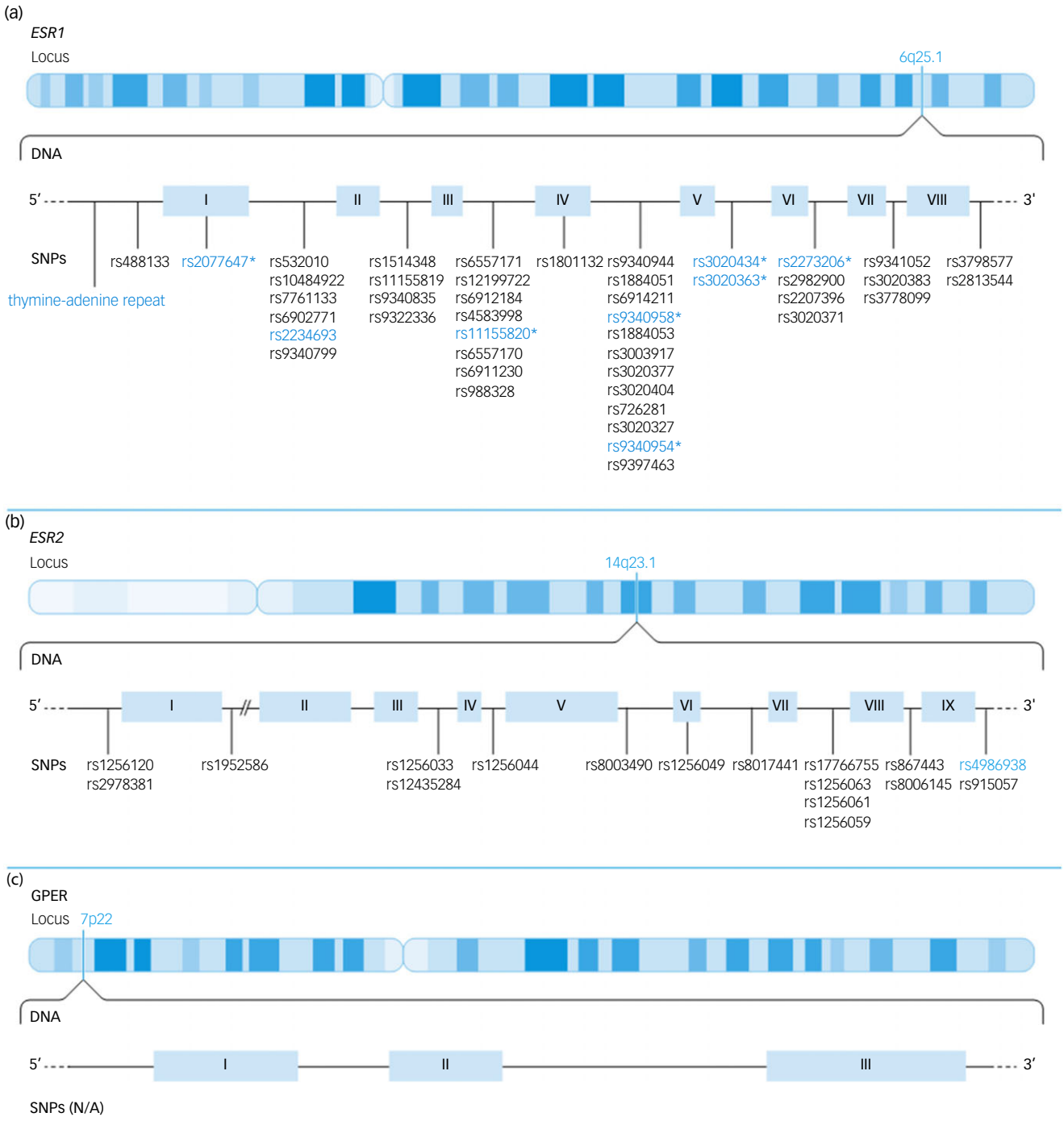

Fig. 2 The genomic structure and approximate locations of the genetic variations in (a) *ESR1*, (b) *ESR2* and (c) GPER investigated in the included candidate gene studies. *ESR1*, oestrogen receptor-α gene; *ESR2*, oestrogen receptor-β gene; GPER, G protein-coupled oestrogen receptor gene; SNPs, single nucleotide polymorphisms. Blue color indicates significant findings. *Not significant after correction for multiple testing.

symptoms.[93] Costas et al[76] found that the haplotype combination of rs9340954 and rs3020434 showed the strongest significant association with perinatal depression symptoms, although it did not withstand correction for multiple testing. Another study found that the nine investigated SNPs defined approximately six haplotype combinations, but they were not tested for an association with perinatal depression symptoms.[88] One study also tested whether the joint genotype distribution of rs2234693 and rs9340799 was associated with perinatal depression symptoms, but no significant association emerged.[78] Moreover, one study investigated potential gene–gene interactions with oestrogen receptor genes in perinatal depression symptoms, of which three interactions with the thymine-adenine repeat were found to be significant, specifically the dopamine transporter gene (*SLC6A3*) and two genes involved in serotonergic signalling (*SLC6A4* and *HTR2A*).[88] The most significant interaction was found for the thymine-adenine repeat and the *SERTLPR*, although the data were not adjusted for multiple testing.[88]

Genetic studies on oestrogen receptor gene 2

Six candidate gene studies investigated the association between genetic variations in *ESR2* and perinatal depression symptoms.[76,77,87,93,94,99] The studies genotyped and tested a total of 17 SNPs, including two

https://doi.org/10.1192/bjp.2025.39 Published online by Cambridge University Press

RFLPs. The most frequently genotyped and tested genetic variation was the RFLP rs4986938, also known as the Alu-l variant, which was examined in three studies. The second most frequently analysed genetic variation was the RFLP rs1256049, also known as the Rsa-l variant, which was examined in two studies. The remaining SNPs were genotyped and tested only once, and no haplotype combinations were constructed and tested. Notably, only one study found an association between genetic variations in *ESR2* and perinatal depression symptoms. Specifically, the RFLP rs4986938 was associated with perinatal depression symptoms, although the results were not adjusted for multiple testing.[77]

Genome-wide association studies

Seven genetic studies conducted a genome-wide approach to investigate associations with perinatal depression symptoms.[84,91,92,96–98,104] The studies examined a total of 12 distinct cohorts. A genome-wide significance for oestrogen receptor genes was reached in one study.[91] In detail, the SNP rs2347923 located in Intron 3 of *ESR1* was found to be associated with perinatal depression symptoms. Moreover, the SNP rs851981, located in the 5' untranslated region (UTR) of *ESR1*, was associated with perinatal depression symptoms after genome-wide significant loci for a latent reproductive factor, including reproductive disorders such as endometriosis, were identified and filtered for nominal significance ($p \leq 0.05$) in perinatal depression symptoms.[92]

Gene expression studies

Eight studies investigated the association between gene expression levels of oestrogen receptor genes and perinatal depression symptoms.[79,80,82,85,86,89,90,103] One of them analysed mRNA levels of *ESR1*,[82] one analysed mRNA levels of *ESR2*[103] and five employed a genome-wide approach for mRNA analysis.[79,80,85,86,89,90] Four studies employed peripheral blood samples to determine mRNA levels,[79,80,89,103] two studies investigated peripheral blood mononuclear cells (PBMCs),[85,90] one study analysed extracellular vesicles in peripheral blood[86] and one study used maternal placental tissue samples.[82] Five of the eight studies found significant associations between gene expression levels of oestrogen receptor genes and perinatal depression symptoms. In the case of mRNA levels of *ESR1*, women with perinatal depression symptoms exhibited a downregulation in maternal placental tissue and PBMCs, as well as an enrichment in peripheral blood, compared to healthy controls.[80,82,90] Furthermore, transcript levels of *ESR1* were found to be downregulated in granulocytes and upregulated in B-cells in women with perinatal depression symptoms, but this did not withstand correction for multiple testing.[89] For mRNA levels of *ESR2*, higher levels in peripheral blood were associated with increased perinatal depression symptoms.[103] Moreover, transcript levels of *ESR2* were found to be downregulated in peripheral blood and monocytes and upregulated in CD8± T-cells in women with perinatal depression symptoms, but this did not remain significant after correction for multiple testing.[89]

Epigenetic studies

Five studies investigated the association between epigenetic modifications of oestrogen receptor genes and perinatal depression symptoms.[81,83,95,101,102] Four of them analysed DNA methylation[81,83,95,101,102] while one study evaluated microRNAs.[95] Three studies investigated peripheral blood samples,[81,83,102] one study examined extracellular vesicles in peripheral blood[95] and one study analysed maternal placental tissue samples.[101] All studies investigating DNA methylation employed an epigenome-wide association analysis (EWAS).[81,83,101,102] In contrast, the study evaluating microRNAs employed a candidate approach.[95] Three of the EWAS studies investigated the methylation levels of individual CpG sites,[81,83,101] whereas one study analysed differentially methylated regions.[102] Three of the four EWAS studies found significant associations between enrichment of DNA methylation marks involved in oestrogen signalling and perinatal depression symptoms.[81,101,102] With regard to microRNAs, significantly upregulated levels of miR-211 and miR-744, which target the 3′ UTR of *ESR1* and *ESR2* and inhibit expression of these genes in plasma exosomes, were identified in women with perinatal depression symptoms.[95]

Discussion

Previous research has indicated an involvement of oestrogen receptor genes in the aetiology of depression in women. Notably, the strongest evidence was reported for an association of rs2234693 and rs9340799 with severe depressive symptoms and major depression in women.[60,61] However, these studies failed to distinguish between major depression and depression during the perinatal period. While all of these phases are characterised by changes in sex steroid hormones, they exhibit distinct patterns of hormonal fluctuations.[7,9,10,36] The most pronounced fluctuations are observed during the perinatal period, and there is accumulating evidence suggesting that depression during this phase is distinguishable from major depression.[6,19–21] Therefore, we provided an overview of the published literature on the association between oestrogen receptor genes and perinatal depression symptoms, by including genetic, epigenetic and gene expression studies. Overall, our review revealed that a limited number of genetic variations in *ESR1* and *ESR2* were associated with perinatal depression symptoms. Most of the associations were found for variations in *ESR1*, of which the RFLP rs2234693 emerged as the most frequently reported variant to show a significant association with perinatal depression symptoms. Moreover, epigenetic modifications, including DNA methylation marks involved in oestrogen signalling and gene expression levels of *ESR1* and *ESR2*, were found to be associated with perinatal depression symptoms.

When interpreting the associations between oestrogen receptor gene variants and perinatal depression symptoms, it is important to consider some mediating factors. One such factor is the specific genes and the function of their encoded receptor, since three different oestrogen receptor genes were investigated. We only report findings for *ESR1* and *ESR2*, as we found no candidate gene studies investigating the association between *GPER* and perinatal depression symptoms and no GWASs with genome-wide significance for variations in *GPER*. Despite the fact that GPERs are membrane-bound oestrogen receptors, which are expressed in various brain areas and are important mediators of oestrogen's rapid, non-genomic effects through the activation of various signal transduction pathways, their function in the brain and thus their implications for behaviour are still largely understudied.[51,106–108] Consequently, no conclusions can be drawn regarding the impact of genetic variations in *GPERs* and their associated rapid signalling pathways, which may be implicated in the aetiology of perinatal depression symptoms. However, our review revealed that *ESR1* was more frequently associated with perinatal depression symptoms than *ESR2*. On the one hand, this finding can be partially explained by the higher number of genetic variations studied in *ESR1* compared to *ESR2*, and thus a potential publication bias. On the other hand, the distinct expression patterns of the encoded receptors indicate a more important role in emotional functions and moods for oestrogen receptor-α encoded by *ESR1* than for oestrogen receptor-β encoded by *ESR2*.[45]

https://doi.org/10.1192/bjp.2025.39 Published online by Cambridge University Press

In addition to the specific gene and the function of the receptor it encodes, the type of genetic variation must also be considered, with a broad spectrum of genetic variation having already been investigated. Most of the reviewed studies analysed SNPs, including RFLPs, and only a few studies examined STRs and haplotype combinations. Overall, 11 SNPs (including two RFLPs) and one STR were found to be associated with perinatal depression symptoms.[76–78,87,88,91,92] Seven of the SNPs did not remain significant after correction for multiple testing, indicating that the initial associations may be susceptible to false positives.[76,87,88] Regarding RFLPs, one of three studies analysing rs4986938 (Alu-I) and two of three studies analysing rs2234693 (Pvu-II) found a significant association with perinatal depression symptoms[76–78,93] However, these findings were not adjusted for multiple testing, thus increasing the likelihood of false positive results. Notably, although these variants are, by definition, also SNPs, they are referred to as RFLPs because of their ability to disrupt the recognition sites of specific restriction enzymes, such as Pvu-II or Alu-I, which cut the DNA at these points.[55] Previous research linked both of these RFLPs to a risk of depression in women.[60,61,109] However, as these investigations did not strictly distinguish between major depression and depression that occurs during reproductive transitions, for the time being, it is not possible to conclude whether rs4986938 and rs2234693 may represent a shared genetic factor for both major depression and perinatal depression or whether they are specific to perinatal depression symptoms. Regarding the STR thymine-adenine repeat, one study found a significant association with perinatal depression symptoms while another detected a trend for an association.[58,61] Notably, a previous study found that the thymine-adenine repeat was in strong linkage disequilibrium with the RFLP rs2234693.[110] Considering linkage disequilibrium, single variation analyses might be insufficient, as some alleles occur at different sites more frequently than would be randomly expected.[111] For instance, while some variants in linkage disequilibrium are highly correlated, one may serve as a marker, whereas another could directly be implicated in gene expression. Analysing a single variant can therefore miss subtle or combined effects that contribute to a phenotype. Therefore, analyses including haplotypes, a combination of frequently co-occurring alleles on a chromosome, provide more information on further genetic variations.[108,112] This approach improves the robustness and reliability of results and enhances the power of association tests, particularly when multiple alleles are involved.[112,113] However, the reviewed haplotype combinations were not found to be significantly associated with perinatal depression symptoms,[76,93] although this finding should be interpreted with caution as only four different haplotype combinations were examined, which were each tested only once. Overall, although various types of genetic variations were analysed across the included candidate gene studies, the majority of the specific variants were only examined in a limited number of studies. Given that genetic variations generally predict only small differences in the phenotype,[114] a careful selection of the genetic variation to be investigated might be crucial to achieve more stable and reliable results. Moreover, genome-wide approaches may provide evidence for novel risk variants without the bias of prior hypotheses, thereby overcoming limitations of candidate gene approaches and leading to a more comprehensive understanding of the genetic architecture of perinatal depression symptoms.[115,116] Notably, both SNPs identified by the included GWASs represent novel risk variants, as they have not been investigated by the included candidate gene studies.[91,92] However, GWASs are often underpowered, since a high level of significance is needed to account for multiple testing.[115] This limitation was also evident in the included GWASs, where the majority was underpowered. Therefore, conducting meta-analyses combining different cohorts has gained considerable interest in increasing sample size and thus statistical power. However, although 20 distinct cohorts were investigated in a recent meta-analysis of GWASs of perinatal depression, no SNP achieved genome-wide significance.[74] To address the power limitation, Kiewa et al[92] employed another approach, using a two-step analysis. First, they identified genome-wide significant loci for a latent reproductive factor, including reproductive disorders such as endometriosis. Second, the loci identified were tested specifically for their association with perinatal depression symptoms, applying a significance threshold of $p \leq 0.05$. This approach reduced the multiple testing burden compared to conducting a genome-wide analysis specifically for perinatal depression. In summary, although various genetic variations have been investigated, only a small number of them have been found to be significantly associated with perinatal depression symptoms. Moreover, the majority did not withstand correction for multiple testing or were not adjusted for multiple testing, increasing the risk of false positive results. Initial evidence suggests a more important role for RFLPs such as rs2234693 in perinatal depression symptoms than for other variations in oestrogen receptor genes. However, little is known about their role and the biological pathways that potentially result in perinatal depression symptoms.[108] Moreover, it is important to note that the observed associations are based on correlations, which precludes any direct causal interpretations regarding the specific biological mechanisms that potentially explain these associations. Consequently, it may also be that these variations do not affect oestrogen signalling directly but are in linkage disequilibrium with another functional variation, which may in turn explain the significant associations with perinatal depression symptoms.

While Mendelian inheritance provides a framework for understanding how single-gene traits are transmitted over generations, the majority of complex disorders, including perinatal depression symptoms, do not follow simple Mendelian patterns and involve multiple factors.[114] Notably, none of the reviewed studies investigated potential gene–environment interactions with oestrogen receptor genes in perinatal depression symptoms. One study additionally examined the influence of environmental factors and found that a distressed partner relationship, unplanned pregnancy and a self-reported history of depression were predictors of perinatal depression.[87] However, one study examined potential gene–gene interactions with oestrogen receptor genes in perinatal depression symptoms and found that three out of seven potential gene–gene interactions with the thymine-adenine repeat were associated with perinatal depression symptoms, including the dopamine transporter gene (*SLC6A3*) and two genes involved in serotonergic signalling (*HTR2A* and *SLC6A4*).[88] Although these data were not adjusted for multiple testing, meaning that false positive results cannot be ruled out, the initial evidence suggests that various gene–gene interactions with oestrogen receptor genes may be involved in perinatal depression symptoms.

Besides genetic factors, it is also crucial to consider epigenetic modifications, as they have the potential to regulate gene transcription.[56] Only a limited number of studies ($n = 5$) were found to examine epigenetic modifications of oestrogen receptor genes in relation to perinatal depression symptoms. The majority investigated these modifications through epigenome-wide DNA methylation analysis.[81,83,101,102] Notably, none of the reviewed studies investigated methylation levels using a targeted approach. Initial evidence from the reviewed studies suggests that DNA methylation marks in regions involved in oestrogen signalling, rather than in oestrogen receptor genes directly, may be associated with perinatal depression symptoms. However, the ability to directly compare these studies is limited, since there is only a small number of studies, which employed varying methodologies,

https://doi.org/10.1192/bjp.2025.39 Published online by Cambridge University Press

including the analysis of distinct tissue types. Given the tissue-specific nature of epigenetic modifications, findings from peripheral blood may not be applicable to other tissues.[117,118] Moreover, although one study found an association between microRNAs targeting *ESR1* and *ESR2* and perinatal depression symptoms,[95] the findings were not adjusted for multiple testing, meaning that false positive results cannot be ruled out. Therefore, it is not yet possible to draw definitive conclusions regarding the involvement of epigenetic modifications of oestrogen receptor genes in the aetiology of perinatal depression symptoms. Nevertheless, initial evidence points to an involvement of epigenetic modifications related to oestrogen signalling in perinatal depression symptoms.

Furthermore, gene expression levels also warrant careful consideration, as they may offer crucial information about the functional and biological implications of the genetic variants and epigenetic modifications. While none of the genetic and epigenetic studies investigated whether these (epi-)genetic variations affected gene expression levels, a small number of studies ($n = 8$) investigated gene expression levels of oestrogen receptor genes in relation to perinatal depression symptoms. Four studies reported an association between mRNA levels of *ESR1* and perinatal depression symptoms.[80,82,89,90,103] However, the findings from one of these studies did not withstand correction for multiple testing,[89] and findings from another study were not adjusted for multiple testing,[82] indicating a higher risk of false positive results. Similarly for mRNA levels of *ESR2*, although two studies reported an association with perinatal depression symptoms, one of these did not withstand correction for multiple testing and the other did not adjust for multiple testing.[89,103] Moreover, conflicting results have been reported, with both up- and downregulation of mRNA levels. Given that gene expression levels of oestrogen receptors are known to be tissue specific,[119] comparisons between the studies are challenging and interpretations may be limited in terms of generalisability, because of the use of distinct tissue types across the reviewed studies. Furthermore, although blood is suitable for gene expression analysis, variations in collection, storage and extraction may differentially affect transcription profiles.[120] Although binding to oestrogen receptors can induce both genomic and non-genomic effects,[121,122] the studies did not examine the specific biological mechanisms implicated in the manifestation of distinct gene expression levels, meaning that no causal conclusions about the implicated pathways can be drawn. Nevertheless, initial evidence indicates that gene expression levels of *ESR1* and *ESR2* are associated with perinatal depression symptoms.

In addition, when interpreting the findings of this review, it is essential to take potential confounding factors into account. Notably, 15 studies accounted for confounding variables, most frequently age, followed by genetic ancestry. Although a previous study found no direct association between genetic ancestry and perinatal depression,[123] it is possible that differences in genetic variations may reflect population-specific differences rather than behavioural differences. This limitation is particularly relevant to the candidate gene approach, since this approach is less effective in accounting for subtle genetic ancestry differences compared to genome-wide approaches.[116]

The reviewed studies exhibited numerous methodological differences regarding the assessment of perinatal depression symptoms, which may account for some of the inconclusive findings. First, the reviewed studies employed a wide range of assessment time points, spanning from 11–14 weeks of pregnancy to 12 months postpartum. These differences reflect the current inconsistencies regarding the distinction between major depression and perinatal depression, which can largely be attributed to varying definitions of the time of symptom onset and how the postpartum period is defined.[20] Research has suggested distinct genetic factors contributing to depression during pregnancy and postpartum, with a greater impact after birth.[124,125] However, it was not possible to compare the findings regarding onset during pregnancy and onset postpartum because of the limited number of studies investigating each time period, as well as the heterogeneous study designs. As such, it cannot be ruled out that oestrogen receptor gene variants associated with perinatal depression symptoms differ depending on whether onset occurs during pregnancy or postpartum. Second, the reviewed studies employed a wide range of self-report instruments and clinical interviews to assess perinatal depression symptoms, most of which were only employed in one study and were not specifically designed for use during the perinatal period. Given that some depressive symptoms are associated with common physiological symptoms during the perinatal period, their differentiation may be challenging.[126,127] However, the most widely used screening tool was the EPDS, which was specifically designed for use during the perinatal period by excluding normative physiological perinatal symptoms associated with depressive symptoms,[105] although notably, the studies applied various cut-off values for the EPDS, ranging from 8 to 20.[76,78,79,82,83,87,88,95] Although a cut-off value of 11 has been found to maximise both sensitivity and specificity for detecting depression in pregnant and postpartum women, other cut-off values may be used to prioritise either sensitivity or specificity.[128] Moreover, the majority of the GWASs employed a retrospective assessment of perinatal depression symptoms using the EPDS, which may introduce recall bias and thus affect accuracy of the reported symptoms.[96–98,104] Overall, the assessment of perinatal depression symptoms varies widely, which makes it difficult to compare the findings and may explain some of the inconsistencies.

This is the first systematic review to provide an overview of the current literature on the association among genetic variations, epigenetic modifications and gene expression levels of oestrogen receptor genes and perinatal depression symptoms. However, some limitations need to be addressed. Despite 29 studies being included, only a small number of studies investigated each category, with 16 studies investigating genetic variations, five studies examining epigenetic modifications and eight studies analysing gene expression levels of oestrogen receptor genes. Moreover, although 16 genetic studies were identified for inclusion, nine of these employed a candidate gene approach, whereby each genetic variation was only analysed in a limited number of studies, with the majority being tested in only one study. Furthermore, the genetic studies conducting a genome-wide approach were mostly underpowered. In addition, the broad inclusion criteria in terms of study design restricted potential comparisons between the studies. Accordingly, we were unable to compare the findings for subgroups with symptom onset during pregnancy and symptom onset postpartum. Moreover, as all of the included studies employed a correlational design, we cannot draw causal conclusions regarding how the investigated markers may ultimately affect perinatal depression symptoms. Another limitation of this review lies in its primary focus on oestrogen receptor genes. As other sex steroid hormones such as progesterone also fluctuate during the perinatal period and are also associated with mood and behaviour, the sensitivity of their receptors may also be implicated in perinatal depression symptoms.[129] Since progesterone and oestrogen can exert both synergistic and antagonistic effects within the same neurotransmitter systems, a complex interplay underlying perinatal depression symptoms cannot be ruled out and warrants further investigation.[43]

To summarise, initial evidence supports the involvement of oestrogen receptor genes in perinatal depression symptoms, through a potential inter-individual modulation of the oestrogen

https://doi.org/10.1192/bjp.2025.39 Published online by Cambridge University Press

receptors' sensitivity to oestrogen. Genetic variations such as rs2234693 in *ESR1*, along with epigenetic modifications, including DNA methylation marks involved in oestrogen signalling and gene expression levels of *ESR1* and *ESR2*, may serve as future biomarkers for perinatal depression symptoms. However, the current empirical evidence is insufficient to establish these biomarkers for clinical use, and the correlational nature of the results restricts definitive conclusions about the specific biological mechanisms underlying these associations. In view of the present findings, we recommend that future research should not only replicate these findings in larger samples, with an emphasis on reducing methodological inconsistencies and exploring potential interactions, but should also conduct further functional investigations to uncover the specific biological pathways through which oestrogen receptor genes may contribute to perinatal depression symptoms. Future research also needs to explore the potential involvement of *GPER* in perinatal depression symptoms in more detail. Since non-genomic oestrogen signalling may be crucial in modulating the rapid intracellular responses to oestrogen fluctuations, a consideration of both the genomic and non-genomic effects of oestrogen may provide vital insights into how hormonal changes affect the brain and mood regulation during the perinatal period. Given the complexity of perinatal depression and its aetiology, we recommend that future studies should also employ more comprehensive and integrative approaches, such as multi-omics, to simultaneously analyse data on various genetic, epigenetic, hormonal, environmental and psychosocial factors. Such approaches will be critical in moving towards a better understanding of the aetiology of perinatal depression symptoms and in establishing reliable biomarkers.

Gianna Zorzini, Department of Clinical Psychology and Psychotherapy, University of Zurich, Zurich, Switzerland; **Ulrike Ehlert**, Department of Clinical Psychology and Psychotherapy, University of Zurich, Zurich, Switzerland

Correspondence: Ulrike Ehlert. Email: u.ehlert@psychologie.uzh.ch

First received 16 May 2024, final revision 18 Dec 2024, accepted 9 Jan 2025

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1192/bjp.2025.39

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Acknowledgements

The authors thank Sarah Mannion for proofreading the manuscript and Tara von Grebel University of Zurich, Information Technology, MELS/SIVIC, for creating Fig. 2.

Author contributions

G.Z.: conceptualisation, investigation, visualisation, interpretation of data, writing – original draft. U.E.: conceptualisation, supervision, interpretation of data, writing – reviewing and editing.

Funding

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of interest

None.

Analytic code availability

Analytic code availability is not applicable to this article as no new data were created or analysed in this study.

Research availability

Research materials of this review are available on request from the corresponding author, U.E.

References

1 Kessler RC. Epidemiology of women and depression. *J Affect Disord* 2003; **74**: 5–13.

2 Kuehner C. Why is depression more common among women than among men? *Lancet Psychiatry* 2017; **4**: 146–58.

3 Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of depression in the community from 30 countries between 1994 and 2014. *Sci Rep* 2018; 8: 2861.

4 Deecher D, Andree TH, Sloan D, Schechter LE. From menarche to menopause: exploring the underlying biology of depression in women experiencing hormonal changes. *Psychoneuroendocrinology* 2008; **33**: 3–17.

5 Hyde JS, Mezulis AH. Gender differences in depression: biological, affective, cognitive, and sociocultural factors. *Harv Rev Psychiatry* 2020; **28**: 4–13.

6 Kundakovic M, Rocks D. Sex hormone fluctuation and increased female risk for depression and anxiety disorders: from clinical evidence to molecular mechanisms. *Front Neuroendocrinol* 2022; **66**: 101010.

7 Miller LJ, Girgis C, Gupta R. Depression and related disorders during the female reproductive cycle. *Womens Health (Lond)* 2009; **5**: 577–87.

8 Payne JL. The role of estrogen in mood disorders in women. *Int Rev Psychiatry* 2003; **15**: 280–90.

9 Payne JL, Palmer JT, Joffe H. A reproductive subtype of depression: conceptualizing models and moving toward etiology. *Harv Rev Psychiatry* 2009; **17**: 72–86.

10 Serrano E, Warnock JK. Depressive disorders related to female reproductive transitions. *J Pharmacy Pract* 2007; **20**: 385–91.

11 Halbreich U. Women's reproductive related disorders (RRDs). *J Affect Disord* 2010; **122**: 10–3.

12 Letourneau NL, Dennis C-L, Benzies K, Duffett-Leger L, Stewart M, Tryphonopoulos PD, et al. Postpartum depression is a family affair: addressing the impact on mothers, fathers, and children. *Issues Ment Health Nurs* 2012; **33**: 445–57.

13 Power J, van IJzendoorn M, Lewis AJ, Chen W, Galbally M. Maternal perinatal depression and child executive function: a systematic review and meta-analysis. *J Affect Disord* 2021; **291**: 218–34.

14 Slomian J, Honvo G, Emonts P, Reginster J-Y, Bruyère O. Consequences of maternal postpartum depression: a systematic review of maternal and infant outcomes. *Womens Health (Lond)* 2019; **15**: 1745506519844044.

15 Mazza M, Avallone C, Kotzalidis GD, Marano G, Moccia L, Serio AM, et al. Depressive symptoms during pregnancy: prevalence and correlates with affective temperaments and psychosocial factors. *J Pers Med* 2023; **13**: 211.

16 Hahn-Holbrook J, Cornwell-Hinrichs T, Anaya I. Economic and health predictors of national postpartum depression prevalence: a systematic review, meta-analysis, and meta-regression of 291 studies from 56 countries. *Front Psychiatry* 2017; **8**: 248.

17 Wang Z, Liu J, Shuai H, Cai Z, Fu X, Liu Y, et al. Mapping global prevalence of depression among postpartum women. *Transl Psychiatry* 2021; **11**: 543.

18 Shorey S, Chee CYI, Ng ED, Chan YH, Tam WWS, Chong YS. Prevalence and incidence of postpartum depression among healthy mothers: a systematic review and meta-analysis. *J Psychiatr Res* 2018; **104**: 235–48.

19 Di Florio A, Meltzer-Brody S. Is postpartum depression a distinct disorder? *Curr Psychiatry Rep* 2015; **17**: 76.

20 Johann A, Ehlert U. Similarities and differences between postpartum depression and depression at other stages of female life: a systematic review. *J Psychosom Obstet Gynaecol* 2022; **43**: 340–8.

21 Batt MM, Duffy KA, Novick AM, Metcalf CA, Epperson CN. Is postpartum depression different from depression occurring outside of the perinatal period? A review of the evidence. *Focus (Am Psychiatr Publ)* 2020; **18**: 106–19.

22 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. APA, 2013.

https://doi.org/10.1192/bjp.2025.39 Published online by Cambridge University Press

23 World Health Organization. *ICD-11: World Health Organization. International Statistical Classification of Diseases and Related Health Problems* 11th ed. WHO, 2022. https://icd.who.int/.

24 O'Hara MW, Wisner KL. Perinatal mental illness: definition, description and aetiology. *Best Pract Res Clin Obstet Gynaecol* 2014; **28**: 3–12.

25 Agrati D, Lonstein JS. Affective changes during the postpartum period: influences of genetic and experiential factors. *Horm Behav* 2016; **77**: 141–52.

26 Brummelte S, Galea LAM. Postpartum depression: etiology, treatment and consequences for maternal care. *Horm Behav* 2016; **77**: 153–66.

27 Payne JL, Maguire J. Pathophysiological mechanisms implicated in postpartum depression. *Front Neuroendocrinol* 2019; **52**: 165–80.

28 Yu Y, Liang H-F, Chen J, Li Z-B, Han Y-S, Chen J-X, et al. Postpartum depression: current status and possible identification using biomarkers. *Front Psychiatry* 2021; **12**: 620371.

29 Barnes KN, Vogl CM, Nelson LA. Zuranolone: The first FDA-approved oral treatment option for postpartum depression. *Ann Pharmacother* 2024; **58**: 728–34.

30 Powell JG, Garland S, Preston K, Piszczatoski C. Brexanolone (Zulresso): finally, an FDA-approved treatment for postpartum depression. *Ann Pharmacother* 2020; **54**: 157–63.

31 Yim IS, Tanner Stapleton LR, Guardino CM, Hahn-Holbrook J, Dunkel Schetter C. Biological and psychosocial predictors of postpartum depression: systematic review and call for integration. *Annu Rev Clin Psychol* 2015; **11**: 99–137.

32 Bloch M, Daly RC, Rubinow DR. Endocrine factors in the etiology of postpartum depression. *Compr Psychiatry* 2003; **44**: 234–46.

33 Schiller CE, Meltzer-Brody S, Rubinow DR. The role of reproductive hormones in postpartum depression. *CNS Spectr* 2015; **20**: 48–59.

34 Bloch M, Schmidt PJ, Danaceau M, Murphy J, Nieman L, Rubinow DR. Effects of gonadal steroids in women with a history of postpartum depression. *Am J Psychiatry* 2000; **157**: 924–30.

35 Mehta D, Rex-Haffner M, Søndergaard HB, Pinborg A, Binder EB, Frokjaer VG. Evidence for oestrogen sensitivity in perinatal depression: pharmacological sex hormone manipulation study. *Br J Psychiatry* 2019; **215**: 519–27.

36 Soares CN, Zitek B. Reproductive hormone sensitivity and risk for depression across the female life cycle: a continuum of vulnerability? *J Psychiatry Neurosci* 2008; **33**: 331–43.

37 Nilsson S, Gustafsson J-A. Biological role of estrogen and estrogen receptors. *Crit Rev Biochem Mol Biol* 2002; **37**: 1–28.

38 Vrtačnik P, Ostanek B, Mencej-Bedrač S, Marc J. The many faces of estrogen signaling. *Biochem Med (Zagreb)* 2014; **24**: 329–42.

39 Cui J, Shen Y, Li R. Estrogen synthesis and signaling pathways during aging: from periphery to brain. *Trends Mol Med* 2013; **19**: 197–209.

40 Hwang WJ, Lee TY, Kim NS, Kwon JS. The role of estrogen receptors and their signaling across psychiatric disorders. *Int J Mol Sci* 2020; **22**: 373.

41 Krolick KN, Zhu Q, Shi H. Effects of estrogens on central nervous system neurotransmission: implications for sex differences in mental disorders. *Prog Mol Biol Transl Sci* 2018; **160**: 105–71.

42 Barth C, Villringer A, Sacher J. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. *Front Neurosci* 2015; **9**: 37.

43 Del Río JP, Alliende MI, Molina N, Serrano FG, Molina S, Vigil P. Steroid hormones and their action in women's brains: the importance of hormonal balance. *Front Public Health* 2018; **6**: 141.

44 Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. *N Engl J Med* 2002; **346**: 340–52.

45 Osterlund MK, Hurd YL. Estrogen receptors in the human forebrain and the relation to neuropsychiatric disorders. *Prog Neurobiol* 2001; **64**: 251–67.

46 Hazell GGJ, Yao ST, Roper JA, Prossnitz ER, O'Carroll A-M, Lolait SJ. Localisation of GPR30, a novel G protein-coupled oestrogen receptor, suggests multiple functions in rodent brain and peripheral tissues. *J Endocrinol* 2009; **202**: 223–36.

47 Ascenzi P, Bocedi A, Marino M. Structure-function relationship of estrogen receptor alpha and beta: impact on human health. *Mol Aspects Med* 2006; **27**: 299–402.

48 Barton M, Filardo EJ, Lolait SJ, Thomas P, Maggiolini M, Prossnitz ER. Twenty years of the G protein-coupled estrogen receptor GPER: historical and personal perspectives. *J Steroid Biochem Mol Biol* 2018; **176**: 4–15.

49 Enmark E, Gustafsson JA. Oestrogen receptors – an overview. *J Intern Med* 1999; **246**: 133–8.

50 Fuentes N, Silveyra P. Estrogen receptor signaling mechanisms. *Adv Protein Chem Struct Biol* 2019; **116**: 135–70.

51 Marino M, Galluzzo P, Ascenzi P. Estrogen signaling multiple pathways to impact gene transcription. *Curr Genomics* 2006; **7**: 497–508.

52 Champagne FA, Curley JP. Maternal regulation of estrogen receptor alpha methylation. *Curr Opin Pharmacol* 2008; **8**: 735–9.

53 Hua H, Zhang H, Kong Q, Jiang Y. Mechanisms for estrogen receptor expression in human cancer. *Exp Hematol Oncol* 2018; **7**: 24.

54 Figtree GA, Noonan JE, Bhindi R, Collins P. Estrogen receptor polymorphisms: significance to human physiology, disease and therapy. *Recent Pat DNA Gene Seq* 2009; **3**: 164–71.

55 Maney DL. Polymorphisms in sex steroid receptors: from gene sequence to behavior. *Front Neuroendocrinol* 2017; **47**: 47–65.

56 Attwood JT, Yung RL, Richardson BC. DNA methylation and the regulation of gene transcription. *Cell Mol Life Sci* 2002; **59**: 241–57.

57 McEvoy K, Osborne LM, Nanavati J, Payne JL. Reproductive affective disorders: a review of the genetic evidence for premenstrual dysphoric disorder and postpartum depression. *Curr Psychiatry Rep* 2017; **19**: 94.

58 Elwood J, Murray E, Bell A, Sinclair M, Kernohan WG, Stockdale J. A systematic review investigating if genetic or epigenetic markers are associated with postnatal depression. *J Affect Disord* 2019; **253**: 51–62.

59 Luo F, Zhu Z, Du Y, Chen L, Cheng Y. Risk factors for postpartum depression based on genetic and epigenetic interactions. *Mol Neurobiol* 2023; **60**: 3979–4003.

60 Li C, Xie M, Wang W, Liu Y, Liao D, Yin J, et al. Association between polymorphisms in estrogen receptor genes and depression in women: a meta-analysis. *Front Genet* 2022; **13**: 936296.

61 Ryan J, Ancelin M-L. Polymorphisms of estrogen receptors and risk of depression: therapeutic implications. *Drugs* 2012; **72**: 1725–38.

62 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71.

63 Sagoo GS, Little J, Higgins JPT. Systematic reviews of genetic association studies. Human Genome Epidemiology Network. *PLoS Med* 2009; **6**: e28.

64 Little J, Higgins JPT (eds). *The HuGENet HuGE Review Handbook, Version 1.0*. Hugenet, 2006 (http://www.hugenet.ca).

65 Valentine JC, Pigott TD, Rothstein HR. How many studies do you need? A primer on statistical power for meta-analysis. *J Educ Behav Stat* 2010; **35**: 215–47.

66 Schünemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008; **336**: 1106–10.

67 Fernandez JW, Grizzell JA, Wecker L. The role of estrogen receptor β and nicotinic cholinergic receptors in postpartum depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2013; **40**: 199–206.

68 Furuta M, Numakawa T, Chiba S, Ninomiya M, Kajiyama Y, Adachi N, et al. Estrogen, predominantly via estrogen receptor α, attenuates postpartum-induced anxiety- and depression-like behaviors in female rats. *Endocrinology* 2013; **154**: 3807–16.

69 Thippeswamy H, Paul P, Purushottam M, Philip M, Jain S, Chandra PS. Estrogen pathway related genes and their association with risk of postpartum psychosis: a case control study. *Asian J Psychiatr* 2017; **26**: 82–5.

70 Figueira P, Malloy-Diniz L, Campos SB, Miranda DM, Romano-Silva MA, Marco L de, et al. An association study between the Val66Met polymorphism of the BDNF gene and postpartum depression. *Arch Womens Ment Health* 2010; **13**: 285–9.

71 Wikenius E, Myhre AM, Page CM, Moe V, Smith L, Heiervang ER, et al. Prenatal maternal depressive symptoms and infant DNA methylation: a longitudinal epigenome-wide study. *Nord J Psychiatry* 2019; **73**: 257–63.

72 Pellicano GR, Carola V, Bussone S, Cecchini M, Tambelli R, Lai C. Beyond the dyad: the role of mother and father in newborns' global DNA methylation during the first month of life-a pilot study. *Dev Psychobiol* 2021; **63**: 1345–57.

73 Nguyen T-D, Harder A, Xiong Y, Kowalec K, Hägg S, Cai N, et al. Genetic heterogeneity and subtypes of major depression. *Mol Psychiatry* 2022; **27**: 1667–75.

74 Guintivano J, Byrne EM, Kiewa J, Yao S, Bauer AE, Aberg KA, et al. Meta-analyses of genome-wide association studies for postpartum depression. *Am J Psychiatry* 2023; **180**: 884–95.

75 Takezawa Y, Kato K, Oota H, Caulfield T, Fujimoto A, Honda S, et al. Human genetic research, race, ethnicity and the labeling of populations: recommendations based on an interdisciplinary workshop in Japan. *BMC Med Ethics* 2014; **15**: 33.

76 Costas J, Gratacòs M, Escaramís G, Martín-Santos R, Diego Y de, Baca-García E, et al. Association study of 44 candidate genes with depressive and

https://doi.org/10.1192/bjp.2025.39 Published online by Cambridge University Press

anxiety symptoms in post-partum women. *J Psychiatr Res* 2010; **44**: 717–24.

77 He Q, Hu J, Zhou B, Li Y. Correlation between estrogen receptor gene polymorphism and perinatal depression. *Ch J Obstet Gynecol Ped* 2017; **13**: 169–76.

78 Zou T, Zhang J, Xie Y, Chen J, Xia GY. Correlation research on Estrogen receptor α gene and Xba I Pvu II and PPD. *Int J Clin Exp Med* 2016; **9**: 4563–8.

79 Mehta D, Grewen K, Pearson B, Wani S, Wallace L, Henders AK, et al. Genome-wide gene expression changes in postpartum depression point towards an altered immune landscape. *Transl Psychiatry* 2021; **11**: 155.

80 Mehta D, Newport DJ, Frishman G, Kraus L, Rex-Haffner M, Ritchie JC, et al. Early predictive biomarkers for postpartum depression point to a role for estrogen receptor signaling. *Psychol Med* 2014; **44**: 2309–22.

81 Guintivano J, Arad M, Gould TD, Payne JL, Kaminsky ZA. Antenatal prediction of postpartum depression with blood DNA methylation biomarkers. *Mol Psychiatry* 2014; **19**: 560–7.

82 Guleria K, Suneja A, Sharma R, Banerjee BD, Bhatia MS, Chaudhary N. Association of placental tissue estrogen receptor alpha gene expression with postpartum depression in women at risk: a pilot study. *J South Asian Feder Obstetr Gynaecol* 2021; **12**: 391–401.

83 Nakamura Y, Nakatochi M, Kunimoto S, Okada T, Aleksic B, Toyama M, et al. Methylation analysis for postpartum depression: a case control study. *BMC Psychiatry* 2019; **19**: 190.

84 Tebeka S, Gloaguen E, Mullaert J, He Q, Boland A, Deleuze J-F, et al. Genome-wide association study of early-onset and late-onset postpartum depression: the IGEDEPP prospective study. *Eur Psychiatry* 2024; **67**: 1–36.

85 Segman RH, Goltser-Dubner T, Weiner I, Canetti L, Galili-Weisstub E, Milwidsky A, et al. Blood mononuclear cell gene expression signature of postpartum depression. *Mol Psychiatry* 2010; **15**: 93–100.

86 Osborne LM, Payne JL, Sherer ML, Sabunciyan S. Altered extracellular mRNA communication in postpartum depression is associated with decreased autophagy. *Mol Psychiatry* 2022; **27**: 4526–35.

87 El-Ibiary SY, Hamilton SP, Abel R, Erdman CA, Robertson PA, Finley PR. A pilot study evaluating genetic and environmental factors for postpartum depression. *Innov Clin Neurosci* 2013; **10**: 15–22.

88 Pinsonneault JK, Sullivan D, Sadee W, Soares CN, Hampson E, Steiner M. Association study of the estrogen receptor gene ESR1 with postpartum depression–a pilot study. *Arch Womens Ment Health* 2013; **16**: 499–509.

89 Guintivano J, Aberg KA, Clark SL, Rubinow DR, Sullivan PF, Meltzer-Brody S, et al. Transcriptome-wide association study for postpartum depression implicates altered B-cell activation and insulin resistance. *Mol Psychiatry* 2022; **27**: 2858–67.

90 Pan D, Xu Y, Zhang L, Su Q, Chen M, Li B, et al. Gene expression profile in peripheral blood mononuclear cells of postpartum depression patients. *Sci Rep* 2018; **8**: 10139.

91 Jiang Y, Wei D, Xie Y. Causal effects of opioids on postpartum depression: a bidirectional, two-sample Mendelian randomization study. *Front Psychiatry* 2023; **14**: 1043854.

92 Kiewa J, Mortlock S, Meltzer-Brody S, Middeldorp C, Wray NR, Byrne EM. A common genetic factor underlies genetic risk for gynaecological and reproductive disorders and is correlated with risk to depression. *Neuroendocrinology* 2023; **113**: 1059–75.

93 Tan E-C, Lim H-W, Chua T-E, Tan H-S, Lee TM, Chen HY. Investigation of variants in estrogen receptor genes and perinatal depression. *Neuropsychiatr Dis Treat* 2018; **14**: 919–25.

94 Zhang Q, Chen C, Gong S, Huang S. Correlation between ESR1 and ESR2 genetic variations and maternal postpartum depression. *Maternal Child Health Care China* 2014; **29**: 4634–7.

95 Tang J, Liu A, Chen X, Wang S. Upregulation of circulating MiR-211 and MiR-744 is related to postpartum depression via estrogen receptor 1 targeting. *J Biol Regul Homeost Agents* 2023; **37**: 3173–83.

96 Kiewa J, Meltzer-Brody S, Milgrom J, Guintivano J, Hickie IB, Whiteman DC, et al. Perinatal depression is associated with a higher polygenic risk for major depressive disorder than non-perinatal depression. *Depress Anxiety* 2022; **39**: 182–91.

97 Li X, Takahashi N, Narita A, Nakamura Y, Sakurai-Yageta M, Murakami K, et al. Identification of risk loci for postpartum depression in a genome-wide association study. *Psychiatry Clin Neurosci* 2024; **78**: 712–20.

98 Byrne EM, Carrillo-Roa T, Penninx BWJH, Sallis HM, Viktorin A, Chapman B, et al. Applying polygenic risk scores to postpartum depression. *Arch Womens Ment Health* 2014; **17**: 519–28.

99 McClain L, Farrell L, LaSorda K, Pan LA, Peters D, Lim G. Genetic associations of perinatal pain and depression. *Mol Pain* 2019; **15**: 1744806919882139.

100 Schneider MO, Pretscher J, Goecke TW, Häberle L, Engel A, Kornhuber J, et al. Genetic variants in the genes of the sex steroid hormone metabolism and depressive symptoms during and after pregnancy. *Arch Gynecol Obstet* 2023; **307**: 1763–70.

101 Lund RJ, Kyläniemi M, Pettersson N, Kaukonen R, Konki M, Scheinin NM, et al. Placental DNA methylation marks are associated with maternal depressive symptoms during early pregnancy. *Neurobiol Stress* 2021; **15**: 100374.

102 Lapato DM, Roberson-Nay R, Kirkpatrick RM, Webb BT, York TP, Kinser PA. DNA methylation associated with postpartum depressive symptoms overlaps findings from a genome-wide association meta-analysis of depression. *Clin Epigenetics* 2019; **11**: 169.

103 Redei EE, Ciolino JD, Wert SL, Yang A, Kim S, Clark C, et al. Pilot validation of blood-based biomarkers during pregnancy and postpartum in women with prior or current depression. *Transl Psychiatry* 2021; **11**: 68.

104 Pouget JG, Taylor VH, Dennis C-L, Grigoriadis S, Oberlander T, Frey BN, et al. Preliminary insights into the genetic architecture of postpartum depressive symptom severity using polygenic risk scores. *Pers Med Psychiatry* 2021; **27–8**: 100081.

105 Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1987; **150**: 782–6.

106 Hadjimarkou MM, Vasudevan N. GPER1/GPR30 in the brain: crosstalk with classical estrogen receptors and implications for behavior. *J Steroid Biochem Mol Biol* 2018; **176**: 57–64.

107 Prossnitz ER, Barton M. The G-protein-coupled estrogen receptor GPER in health and disease. *Nat Rev Endocrinol* 2011; **7**: 715–26.

108 Sundermann EE, Maki PM, Bishop JR. A review of estrogen receptor alpha gene (ESR1) polymorphisms, mood, and cognition. *Menopause* 2010; **17**: 874–86.

109 Keyes K, Agnew-Blais J, Roberts AL, Hamilton A, Vivo I de, Ranu H, et al. The role of allelic variation in estrogen receptor genes and major depression in the Nurses Health Study. *Soc Psychiatry Psychiatr Epidemiol* 2015; **50**: 1893–904.

110 Becherini L, Gennari L, Masi L, Mansani R, Massart F, Morelli A, et al. Evidence of a linkage disequilibrium between polymorphisms in the human estrogen receptor alpha gene and their relationship to bone mass variation in postmenopausal Italian women. *Hum Mol Genet* 2000; **9**: 2043–50.

111 Slatkin M. Linkage disequilibrium–understanding the evolutionary past and mapping the medical future. *Nat Rev Genet* 2008; **9**: 477–85.

112 Clark AG. The role of haplotypes in candidate gene studies. *Genet Epidemiol* 2004; **27**: 321–33.

113 Morris RW, Kaplan NL. On the advantage of haplotype analysis in the presence of multiple disease susceptibility alleles. *Genet Epidemiol* 2002; **23**: 221–33.

114 Cannon TD, Keller MC. Endophenotypes in the genetic analyses of mental disorders. *Annu Rev Clin Psychol* 2006; **2**: 267–90.

115 Tam V, Patel N, Turcotte M, Bossé Y, Paré G, Meyre D. Benefits and limitations of genome-wide association studies. *Nat Rev Genet* 2019; **20**: 467–84.

116 Duncan LE, Ostacher M, Ballon J. How genome-wide association studies (GWAS) made traditional candidate gene studies obsolete. *Neuropsychopharmacology* 2019; **44**: 1518–23.

117 Bakulski KM, Halladay A, Hu VW, Mill J, Fallin MD. Epigenetic research in neuropsychiatric disorders: the 'tissue issue'. *Curr Behav Neurosci Rep* 2016; **3**: 264–74.

118 Smith AK, Kilaru V, Klengel T, Mercer KB, Bradley B, Conneely KN, et al. DNA extracted from saliva for methylation studies of psychiatric traits: evidence tissue specificity and relatedness to brain. *Am J Med Genet B Neuropsychiatr Genet* 2015; **168B**: 36–44.

119 Grandien K, Berkenstam A, Gustafsson JA. The estrogen receptor gene: promoter organization and expression. *Int J Biochem Cell Biol* 1997; **29**: 1343–69.

120 Gautam A, Donohue D, Hoke A, Miller SA, Srinivasan S, Sowe B, et al. Investigating gene expression profiles of whole blood and peripheral blood mononuclear cells using multiple collection and processing methods. *PLoS One* 2019; **14**: e0225137.

121 Björnström L, Sjöberg M. Mechanisms of estrogen receptor signaling: convergence of genomic and nongenomic actions on target genes. *Mol Endocrinol* 2005; **19**: 833–42.

122 Thiebaut C, Vlaeminck-Guillem V, Trédan O, Poulard C, Le Romancer M. Non-genomic signaling of steroid receptors in cancer. *Mol Cell Endocrinol* 2021; **538**: 111453.

123 Guintivano J, Sullivan PF, Stuebe AM, Penders T, Thorp J, Rubinow DR, et al. Adverse life events, psychiatric history, and biological predictors of postpartum depression in an ethnically diverse sample of postpartum women. *Psychol Med* 2018; **48**: 1190–200.

https://doi.org/10.1192/bjp.2025.39 Published online by Cambridge University Press

124 Figueiredo FP, Parada AP, Araujo LF de, Silva WA, Del-Ben CM. The Influence of genetic factors on peripartum depression: a systematic review. *J Affect Disord* 2015; **172**: 265–73.

125 Samuelsen K, Ystrom E, Gjerde LC, Eilertsen EM. Kind of blue – an evaluation of etiologies for prenatal versus postnatal depression symptoms. *J Affect Disord* 2023; **335**: 305–12.

126 Halbreich U, Karkun S. Cross-cultural and social diversity of prevalence of postpartum depression and depressive symptoms. *J Affect Disord* 2006; **91**: 97–111.

127 Marcus SM. Depression during pregnancy: rates, risks and consequences. *J Popul Ther Clin Pharmacol* 2009; **16**: e15–22.

128 Levis B, Negeri Z, Sun Y, Benedetti A, Thombs BD. Accuracy of the Edinburgh Postnatal Depression Scale (EPDS) for screening to detect major depression among pregnant and postpartum women: systematic review and meta-analysis of individual participant data. *BMJ* 2020; **371**: m4022.

129 Sundström-Poromaa I, Comasco E, Sumner R, Luders E. Progesterone – friend or foe? *Front Neuroendocrinol* 2020; **59**: 100856.

https://doi.org/10.1192/bjp.2025.39 Published online by Cambridge University Press