HHS Public Access

Author manuscript

Placenta. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:

Placenta. 2020 March ; 92: 17–27. doi:10.1016/j.placenta.2020.01.008.

A Review and Meta-analysis of Omics Approaches to Study Preeclampsia

Paula A. Benny[1], **Fadhl M. Al-Akwaa**[3], **Ryan J. Schlueter**[2], **Cameron B. Lassiter**[1], **Lana X. Garmire**[3,#]

[1]University of Hawaii Cancer Center, Epidemiology, 701 Ilalo Street, Honolulu, HI 96813, USA

[2]Department of Obstetrics and Gynaecology, University of Hawaii, 1319 Punahou Street, Honolulu, HI 96826, USA

[3]Department of Computational Medicine and Bioinformatics, North Campus Research Complex, University of Michigan, 1600 Huron Parkway, Ann Arbor, MI 48105 USA

Abstract

Preeclampsia is a medical condition affecting 5–10% of pregnancies. It has serious effects on the health of the pregnant mother and developing fetus. While possible causes of preeclampsia are speculated, there is no consensus on its etiology. The advancement of big data and high-throughput technologies enables to study preeclampsia at the new and systematic level. In this review, we first highlight the recent progress made in the field of preeclampsia research using various omics technology platforms, including epigenetics, genome-wide association studies (GWAS), transcriptomics, proteomics and metabolomics. Next, we integrate the results in individual omic level and studies, and show that despite the lack of coherent biomarkers in all omics studies, inhibin is a potential preeclamptic biomarker supported by GWAS, transcriptomics and DNA methylation evidence. Using the network analysis on the biomarkers of all literatures reviewed here, we identify four striking sub-networks with clear biological functions supported by previous molecular-biology and clinical observations. In summary, omics integration approach offers the promise to understand molecular mechanisms in preeclampsia.

Introduction

Preeclampsia is a medical condition that affects 5 – 10% of pregnant mothers and accounts for 40% of fetal deaths worldwide [1]. It manifests with symptoms of hypertension (>140/90

[#]Corresponding author: Lana X. Garmire, LGarmire@med.umich.edu.

Author Contributions

LXG envisioned the project, obtained funding, supervised the project and data analysis. LXG, PAB, FMA, RJS and CBL wrote the manuscript. All authors have read, revised and approved the final manuscript.

Conflict of Interest

The authors declare no competing interests exist.

Conflict of Interest Statement

The authors declares no conflict of interest.

mm Hg), proteinuria (>0.3g in urine) and swelling [2]. Primarily diagnosed by new onset and rapidly developing hypertension in pregnancy, preeclampsia is often found late in the third trimester, after 34 weeks, and termed late-onset preeclampsia. Early onset preeclampsia is typically diagnosed prior to 34 weeks. Several clinical symptoms such as headache, vision changes, epigastric pain and shortness of breath can accompany more severe forms of the disease [3]. Laboratory abnormalities such as increased liver enzymes, thrombocytopenia, and proteinuria with kidney damage are also common in progressive preeclampsia [4]. Clinically, the most important complications of preeclampsia to prevent are maternal seizure and cerebrovascular accident [5]. The cornerstone of therapy in preeclampsia is stabilization of the mother and delivery of the fetus as the ultimate disease treatment. Because preeclampsia is such a common and pervasive disorder, understanding how it develops and if we can predict or treat it has become the focus of numerous studies.

Though several theories exist on the cause of preeclampsia, there is no consensus on its etiology and neither is there known way to prevent it. Since this disease has complex pathologic roots in placental morphology, maternal predisposition, genetic variance and molecular signalling, combating the scientific complexity of preeclampsia requires new and unique methodologies. In recent years, omics approaches have been utilized for such purposes. Omics refers to the field in biological science that aims at the collective characterization and quantification of pools of biological molecules that translate into the structure, function, and dynamics of organisms. Taking advantage of methods such as next generation sequencing, high-resolution mass spectroscopy and chip arrays, omics platforms generate immense volumes of data in a condensed period. By comparing preeclampsia samples with control samples, one can assess the molecular differences associated with the disease state. These significant molecular differences, in the forms of mRNA, SNPs, DNA methylation sites, proteins, metabolites etc, can potentially serve as biomarkers preeclampsia. Moreover, these abnormal molecular changes can help piece together the pathogenesis determinants for preeclampsia. By targeting and reverse these molecular determinants, it is hopeful to control, manage, and ultimate treat preeclampsia.

In this review, we systematically summarize the findings from various omics research approaches to study preeclampsia through a comprehensive PubMed search. The keywords “preeclampsia” and “epigenetics”, “transcriptomics”, “GWAS”, “proteomics” and “metabolomics” were entered into the PubMed search field and all 515 results returned were analyzed for relevant validated studies between the years 2000–2019. After screening for studies not reported in English and removing duplicates, this brought the total number of studies included to 58. We enumerated them by various platforms including genetics, epigenomics, transcriptomics, proteomics and metabolomics. In order to facilitate our understanding of this multi-faceted disorder, we enlist preeclampsia-associated molecules in individual studies, as well as lacking of common ones among different omic platforms and different studies. While this observation is due to many complex issues surrounding the disease, the samples and the analysis processes, we nevertheless show that by synthesizing the knowledge gained from different omics levels, it is possible to gain systematic insights into preeclampsia. We call on the urgent need for systematic multi-omics design with clinical information documentation, which help better understand the biological mechanism

associated with this heterogenous syndrome, with the ultimate goal to narrow the gap towards therapeutics interventions.

Genetics studies of Preeclampsia

Genome wide association studies (GWAS) are typically methods used to analyse effects of single-nucleotide polymorphisms (SNPs) on disease phenotypes. There is evidence that genetic factors predispose certain populations to preeclampisa. Over the years, genetics studies have evolved from the original limited capacity of analysing a handful of SNPs to high-throughput platforms, including the Illumina SNP arrays, and more recently whole exome sequencing and whole genome sequencing platforms. Put in the perspective of clinical applications, SNPs have recently been used to identify pregnancies at high risk of miscarriage [6], similarly preeclampsia-associated SNPs may have the potential to be used as a genetic diagnostic test.

We herein compiled the results from a Pubmed literature search of all the hits resulting from the search words “GWAS” and “preeclampsia”. Studies which did not perform validation experiments on their identified targets were excluded. The resulting studies are summarized in Table 1. To date, the largest preeclampsia GWAS study consisted of offspring of 4,380 cases and 310,238 controls. The authors discovered that it was the SNPs in sFlt-1 in the fetal genome that were associated with preeclampsia risk[7]. In the maternal genome, the largest preeclampsia GWAS study was the HAPO study (Hyperglycaemia and Adverse Pregnancy Outcome) where 1070 Afro-Caribbean (n=21 cases and 1049 controls), 723 Hispanic (n=62 cases and 661 controls) and 1257 European (n=50 cases and 1207 controls) mothers were enrolled in [8]. However, in this study no individual SNPs were significantly associated with preeclampsia after Bonferroni correction, despite over one million SNPs assayed. This is could be due to the overly stringent multiple hypothesis testing [8]. Or, it is likely that multiple alleles are interacting in a multifactorial disease such as preeclampsia. A polygenic risk score might be more informative in future studies.

Table 1 summarizes a list of SNPs, obtained through GWAS, which were claimed to be associated with preeclampsia. Gene set enrichment analysis on the genes in Table I which the risk SNPs reside in reveals that calcium signalling pathway is involved ($P<0.05$) with gene members APT2B, ADRA1D and PLCD3. For example, rs7579169 (T>C), located in the intergenic region near the inhibin beta B gene (INHBB) in an Australian cohort, was validated and extended in another large Asian cohort. Inhibin is a glycoprotein which lowers follicle-stimulating hormone (FSH) levels. In preeclamptic pregnancies, inhibin protein levels are magnitudes higher compared to normal pregnancies, though the reason for this observation remains unclear [9]. It is possible that these SNPs impact on promoter activity, gene expression, amino acid sequence or protein stability. Other preeclampsia associated SNPs, such as, rs12711941 (T>G), rs7576192 (A>G) and rs2681472 were also identified near the inhibin gene [10–12]. Interestingly, in a Norwegian population, rs17367504 in the methylenetetrahydrofolate reductase (MTHFR) gene was associated with protective effects against preeclampsia [13]. Given the different SNPs reported by various GWAS studies, it is of great interest to investigate if the preeclampsia-associated SNPs in each individual study can indeed be replicated, by meta-analysis of all studies that make their data public.

Epigenetics studies of preeclampsia

Epigenetics studies the inheritable changes in gene expression that do not involve any changes in the DNA sequence [14]. The most widely studied epigenetic modification is DNA methylation [15, 16]. Essentially, epigenetics causes a change in phenotype without altering genotype and is influenced by several factors including environment, age, lifestyle and genetics [17]. As DNA methylation influences gene expression and subsequent protein translation, it has the potential to be a major contributor to a disease and a mediator of environmental influences. For clinical applications, various studies have been conducted, in the hope to identify DNA methylation signals for diagnosis or treatment of preeclampsia.

We therein performed a PubMed literature search for the words “epigenetics” and “preeclampsia” and only included studies which validated their hypomethylation and hypermethylation sites. Table 2 summarizes the hypermethylated and hypomethylated regions of genes and noncoding RNAs associated with preeclampsia in epigenetic studies [15, 16, 18–24]. Given the large number of genes involved in DNA methylation changes, it is valuable to investigate if these genes are enriched in certain biological functions. Thus we conducted pathway analysis on this list of genes using ConsensusPathDB (CPDB)[25]. The pathway analysis reveals an enrichment of proteasome pathways, hippo signalling pathways, cancer pathways and hypoxia signalling pathways affected in preeclampsia. Among these genes, hypermethylation of Wnt2 was observed in two studies [15, 26], and was proposed to contribute to trophoblast and signalling dysfunction in the preeclamptic placenta [27, 28]. However, precise mechanistic elucidation of Wnt2 signalling in preeclampsia are lacking [26]. Differentially methylated loci identified by omic strategies should be mapped to genes for further validation, in order to avoid false positive results from these studies.

Besides protein coding genes, differential methylation of several microRNA (miRNA)-associated promoter regions have been reported in preeclampsia, such as miR548, miR519, miR301, miR487, miR 185, miR 329, miR194, miR376, miR486 and miR744 [14, 53]. Pathway analysis reveals miR744 and miR185 as strongly correlated with promoter activation in cancers through β-catenin, c-Jun and MMP pathways. Due to the potential of miRNAs to alter the expression of target genes, these miRNA methylation alterations are particularly interesting for further validation by larger studies.

Transcriptomics studies of preeclampsia

Gene expression profiling has provided some mechanistic insight into preeclampsia, moreover, it could provide promising “biomarkers” for this disease. Recent studies have had success identifying preeclampsia-associated transcripts in circulation, which could function as potential clinical diagnostic markers [29, 30]. We performed a PubMed literature search using the keywords “transcriptomics” and “preeclampsia” and included the studies which validated their resultant targets.

Table 3 provides a list of differentially expressed genes associated with preeclampsia. Among them, Flt-1 (fms-like tyrosine kinase-1) was the most frequently upregulated gene in preeclampsia. It is a circulating antagonist for placenta growth factor (PGF) and vascular

endothelial growth factor (VEGF), both of which promote vascular expansion in the placenta [31]. Pathway enrichment analysis of the genes in Table 3 shows that up regulated genes are associated with adipocyte regulation, retinoic acid regulation, hypoxia signalling, and transcription factor network pathways; down regulated genes are enriched in cytokine-associated pathways.

Besides protein coding genes, differential miRNA and long non-coding RNA (lncRNA) expression has been reported in preeclampsia too [32–34]. For example, lncRNA UCA-1 primarily promotes cell migration and proliferation, presumably in an attempt to remedy poor trophoblast invasion and bad uterine spiral artery remodelling [32]. Other lncRNAs reported to be associated with preeclampsia include MEG3, HOTAIR, MALAT-1 and FLT1P1 [33]. The modes of action of these lncRNAs were proposed as chromatic state regulation (HOTAIR), metastatic gene expression regulation (MALAT1), tumor suppressor (MEG3) and angiogenesis regulator (FLT1P1). Among small RNAs, miRNAs have shown to be closely relevant in preeclampsia pathogenesis [34]. The most well studied preeclampsia associated miRNA is miR-210. It is associated with hypoxic pathways and is upregulated in response to hypoxia inducible factors [35]. miR-210 promotes angiogenesis by releasing IL-1α [36]. Another miRNA linked to preeclampsia is miR-26a down-regulated in preeclampsia, which regulate the TGF-β (transforming growth factor beta) cascade pathway, also relating to angiogenesis [37].

Proteomics studies of preeclampsia

Similar to transcriptomics, proteomics also varies temporally and spatially [38]. Global proteomics has evolved by mass spectrometry. In preeclampsia, proteomics may provide candidate biomarkers for early diagnosis, or give insights on disease progression. We searched the PubMed literature using keywords “proteomics” and “preeclampsia” and compiled studies which validated their targets.

Table 4 highlights the proteomics studies of preeclampsia. Studies from plasma [39–41] and serum [42–44] from peripheral blood have shown increases in fibronectin, matrix-metalloprotease (MMP), immunomodulatory molecules, heat shock proteins, C1S (complement C1s subcomponent), AMBP (alpha 1 microglobulin/bikunin) and a decrease in RBP4. Fibronectin, MMP and heat shock proteins are associated with cellular inflammatory and wound healing processes. Increases in C1S and AMBP contribute to spiral artery remodelling [45]. Additionally, apolipoproteins were found to be unusually more abundant in preeclamptic placentas, suggesting dysregulated lipid-protein biosynthesis and lipid transport pathways [46]. Genes with protein level changes can be categorised into six pathways. Up regulated genes are frequently observed in hypoxia signalling, lipid regulation, chemical carcinogenesis, thyroid hormone synthesis and cysteine and methionine metabolism pathways; down regulated genes are often seen in peroxisome signalling pathways.

Although a promising platform, thus far there are no clinically applicable protein biomarkers existing for preeclampsia, due to small sample sizes of the studies and lack of sufficient

sensitivity and specificity required of clinical diagnostics. However, proteomics could be a useful tool for monitoring the disease or identifying at risk populations [47, 48].

Metabolomics studies of preeclampsia

Metabolomics has recently taken the spotlight in providing biomarker candidates, representing a more holistic approach to metabolites within a cell, tissue or organism [49]. It takes the platforms of mass spectrometry and NMR spectroscopy platforms. In preeclampsia, metabolomics are typically measured in blood, placenta and urine. We performed a PubMed literature search for the keywords “metabolomics” and “preeclampsia” and compiled the resulting studies.

Table 5 summarizes the differential metabolite profiles associated with preeclampsia in the literature [50–56]. Serum samples [50–53] are the most commonly used materials. In those samples, higher lipid, 3-hydroxybutyrate, arginine, phenylalanine, alanine and leucine levels and lower valine levels were detected in preeclampsia cases [50, 52, 53, 55]. Aberrant valine, leucine, arginine and phenylalanine levels are indicative of decreased amino acid biosynthesis. In urine, decreases in hippurate and increases in creatinine levels have been observed [57], suggesting aberrant kidney functions especially in kidney’s filtration processes. Aberrant metabolite profiles could be indicative of the effects of preeclampsia due to the high blood pressure associated with the disease. Metabolite profiling of placenta tissue has also been carried out by several groups [58–60]. In the preeclamptic placenta tissue, the urea cycle is affected, evident by increased glutamate and glutamine levels. Therefore, a panel of several metabolite aberrations could serve as a diagnostic biomarker set for preeclampsia identification or monitoring of preeclampsia progression. Mapping these metabolites in Table 5 to their functional pathways would provide additional insight into the biochemical processes involved in preeclampsia progression [61–63]. Metabolomic pathway enrichment analysis shows that lipid transport, neurotransmitter regulation and protein biosynthesis pathways are highly correlated to preeclampsia.

Although lots of metabolomics markers have been investigated, so far none has been selected as either predictive or diagnostic biomarkers for preeclampsia [64]. Like other omics studies mentioned earlier (proteomics and gene expression), metabolomics studies of preeclampsia also are limited by sample sizes and the heterogeneity of this disease. In fact, even in relatively well-studied field such as breast cancer, proposed metabolomics biomarkers have very little consistency across populations [65]. Knowing such challenge, future directions may focus on multi-omics studies and biological-knowledge based integration approach, in order to identify robust biomarkers for preeclampsia.

Integrative omics studies of preeclampsia

Multi-omics studies would significantly increase the robustness of discoveries in preeclampsia research. While there are several studies and repositories dedicated toward integrative multi-omic cancer research, such as The Cancer Genome Atlas (TCGA), none currently has been reported for preeclampsia. Rarely studies measured and then integrated multi-omics data from the same samples, except for two, one which validated preeclampsia

biomarkers by integrating placental mRNA expression (GEO) and proteomics profiling [66] and the other which integrated epigenetics and transcriptomics of the same preeclampsia samples [100]. Clearly, much more work needs to be done, in order to obtain coherent biomarker signatures of preeclampsia at the multi-omics level.

Nevertheless, combining biomarkers from different studies and different omics levels may still yield interesting insights, despite many issues such as that the samples in different omics studies are not on the same subjects, same samples (eg. placenta, blood), same gestational ages as well as lacking many other unknown clinical confounders. The rationale here is that all these different omics, although assayed in different technological platforms and different samples, are all to some degrees reflecting the changes in the common basic biological units - genes. Thus we integrated at the gene level the GWAS, epigenetics, transcriptomics, proteomics and metabolomics biomarker candidates, from the above reviewed reports (Figure 1). Preeclampsia-associated markers identified within each omic platform were assigned to their study (S) to create a grouping system for multi-omic level analysis of all five platforms, despite that each original study only investigated one omic type. We then combined the grouping information with individual biomarkers to generate the heterogenous graph, in which multiple types of nodes are present. One type of node (no-color) is study ID shown as the reference index, and the other types of nodes represent biomarkers identified in one or more omics types. No single gene is associated with preeclampsia across all five omics platforms. The lack of coherence could be due to many reasons, such as the heterogeneity among different populations in these studies, the multi-factorial nature of preeclampsia, and limitations of sample sizes in each study. However, one gene, inhibin, showed fairly consistent changes in GWAS, DNA differential methylation and transcriptome levels. Inhibin levels generally rise in the first trimester, fall during the second trimester and rise again in the third trimester [67]. In preeclamptic pregnancies, inhibin levels are magnitudes higher compared to normal pregnancies [9]. Consistently, hypomethylation of inhibin was observed in preeclamptic placenta [18]. Further clinical evaluation on inhibin as biomarker is certainly of great interest.

Although different genes, proteins or metabolites may show up as biomarkers in individual omics level, the biological functions that they are involved in may be shared. For example, previous we have found that pathways, a type of biological functional unit, are good surrogate biomarker features to predict breast cancer status, based upon metabolomics data set and applied to TCGA RNA-Seq validation dataset [103]. With this consideration, we examined these biomarker candidates on the background of a Protein-Protein interaction network next (Figure 2). Using Cytoscape (STRING App), we mapped the top targets within each omic platform to reveal protein-protein interaction networks which are dominant in preeclampsia. We used enzymes as the surrogates of metabolites, in order to integrate with the protein-protein interaction network. While it is also possible to use transport proteins as a surrogate for metabolites, we chose enzymes for this review study. Network analysis reveals four striking sub-networks with clear biological functions, supported by previous molecular-biology and clinical observations. The green network is composed of proteins associated with oxidant-antioxidant pathways (PRDX1, PRDX3, SOD, HSPE1, INVS, NOX5). This likely corresponds to the events facilitating the hypoxic microenvironment in preeclampsia. The blue network is composed of protein-protein interactions between

proteasome pathways, cytokine release and inflammation (PSMA1, PSMA8, NFKB1, NFKB2, IL8). This sub-network explains the activated inflammatory response in preeclampsia. The yellow sub-network includes genes involved in protein transport, protein regulation and extracellular matrix remodelling pathways (TIMP3, TTR, SERPINA1, APO3, RBP4, AMBP, CST3, CXCL, VIM). This sub-network could be especially important in explaining the pathology observed in the preeclamptic placenta. The purple sub-network is comprised of protein-protein interactions associated with the angiogenesis and cell proliferation pathway (NCAM, FLT1, PGF, GRB2, PDGF, FGF14). Reduced spiral artery formation and reduced angiogenesis, hallmarks of preeclampsia, are likely manifested by these genes. Despite such emerging patterns, we should point out that one caveat of the network analysis here is that we have combined studies in placenta and blood together, thus the PPI based on blood biomarkers is inferred.

Therefore, even though the biomarkers were identified by different studies and at different omic level, integrative analysis on the protein-protein interaction networks of these biomarkers reveals coherent and coordinated biological functions that are otherwise much less clear in the individual omic studies.

Limitations and perspectives

Large amounts of omics data related to preeclampsia are accruing with the advancement of technologies. There is strong evidence that preeclampsia is a complex disease that involves programming changes at DNA, epigenetic, transcriptomic, protein and metabolite levels. Clinically, the application of understanding how each of these elements affects the process of the disease state may be able to provide insights into treatment and prevention. Omics approaches can open the door for new studies and research with focus on therapeutic approaches in the comparison of patients with and without preeclampsia [101, 102]. For instance, we already know that low-dose aspirin prevents early onset preeclampsia, but exactly how and why this prevention takes place is postulated, leaving room for omics studies to find out at what level the medication could be working. This is only one example of how future studies could determine and then lead to advances in how we treat and prevent preeclampsia by understanding the disease in a more stepwise molecular state.

As an effort to demonstrate the known and unknowns in preeclampsia omics field, we conducted a comprehensive literature review on the various studies at different omic levels. This review has presented the challenges in identifying robust biomarkers in preeclampsia. Many reasons may contribute to the observed lack of consistency in various omics studies. Besides sample size, the heterogeneity and the lack of detailed understanding of the heterogeneity of this syndrome, both at the clinical and molecular levels, likely play a part. The differing results obtained from experiments shows the importance of rigor in study design, on selecting sample type, sample site, type of omic platform and stage in disease to break through current limitations in understanding the etiology and effect of heterogeneous medical conditions such as preeclampsia. Performing matched mother-baby dyad sampling and multi-omics studies will increase useful information, relevance and perspective obtained from these omics approaches. Finally, we would like to call on community effort to share detailed description on clinical outcomes (eg. severity of preeclampsia, availability of

medical record data) and the omics data at the raw data level. Harmonization of data, data collection, data sharing and development of public databases would equip investigators with advanced tools to improve the feasibility of multi-omic approaches toward more rigorous diagnosis and treatment of preeclampsia. Previously, only a very few databases have been created to archive significant findings from “Big Data” for preeclampsia studies. dbPEC collected and curated thousands of articles from PubMed, to generate a list of genes associated with preeclampsia [68]. PESNPdb is another database focused exclusively on SNPs associated with preeclampsia [69]. The vast amount of information from other earlier omics studies awaits to be re-collected, re-synthesized and integrated to understand preeclampsia. All of these aspects, once implemented, will enable better powered and more accurate biomarker discoveries at the subtype level.

Nevertheless, we showed that a systematic and multi-omic analysis approach, even at the post-statistics level and among very different populations of limited sizes, has the potential merit to unravel the general molecular mechanisms of preeclampsia coherently. These pathways are candidate targets for future therapeutic interventions for treating and controlling preeclampsia. Thus, our review and meta-study demonstrates the proof-of-principle to gain systematic molecular information on preeclampsia, by orchestrating multiple dimensions of omics data.

Acknowledgements

Dr. Lana X Garmire’s research is supported by grants K01ES025434 awarded by NIEHS through funds provided by the trans-NIH Big Data to Knowledge (BD2K) initiative (http://datascience.nih.gov/bd2k), P20 COBRE GM103457 awarded by NIH/NIGMS, R01 LM012373 and LM 012907 awarded by NLM, and R01 HD084633 awarded by NICHD to LX Garmire. Funding was also provided in part by the Department of Obstetrics and Gynecology, University of Hawaii. The authors thank all members of the Garmire Group for their helpful discussions.

References

1. Sibai B, Dekker G, and Kupferminc M, Pre-eclampsia. Lancet, 2005 365(9461): p. 785–99. [PubMed: 15733721]
2. Mustafa R, et al., A comprehensive review of hypertension in pregnancy. J Pregnancy, 2012 2012: p. 105918. [PubMed: 22685661]
3. Villanueva Egan LA, Bohorquez Barragan ME, and Alanis Lopez P, [Factors related to the diagnosis of HELLP syndrome in patients with severe preeclampsia]. Ginecol Obstet Mex, 2004 72: p. 394–9. [PubMed: 15526555]
4. Roberts JM, et al., Vitamins C and E to prevent complications of pregnancy-associated hypertension. N Engl J Med, 2010 362(14): p. 1282–91. [PubMed: 20375405]
5. Zamorski MA and Green LA, Preeclampsia and hypertensive disorders of pregnancy. Am Fam Physician, 1996 53(5): p. 1595–610. [PubMed: 8623688]
6. Wang Y, et al., Clinical application of SNP array analysis in first-trimester pregnancy loss: a prospective study. Clin Genet, 2017 91(6): p. 849–858. [PubMed: 27883173]
7. McGinnis R, et al., Variants in the fetal genome near FLT1 are associated with risk of preeclampsia. Nat Genet, 2017 49(8): p. 1255–1260. [PubMed: 28628106]
8. Zhao L, Bracken MB, and DeWan AT, Genome-wide association study of pre-eclampsia detects novel maternal single nucleotide polymorphisms and copy-number variants in subsets of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study cohort. Ann Hum Genet, 2013 77(4): p. 277–87. [PubMed: 23551011]
9. Ree PH, et al., Early detection of preeclampsia using inhibin a and other second-trimester serum markers. Fetal Diagn Ther, 2011 29(4): p. 280–6. [PubMed: 21252475]

10. Wang Q, et al., Single nucleotide polymorphisms near the inhibin beta B gene on 2q14 are associated with pre-eclampsia in Han Chinese women. Eur J Obstet Gynecol Reprod Biol, 2015 193: p. 127–31. [PubMed: 26313529]
11. Wan JP, et al., The common single-nucleotide polymorphism rs2681472 is associated with early-onset preeclampsia in Northern Han Chinese women. Reprod Sci, 2014 21(11): p. 1423–7. [PubMed: 24642721]
12. Johnson MP, et al., Genome-wide association scan identifies a risk locus for preeclampsia on 2q14, near the inhibin, beta B gene. PLoS One, 2012 7(3): p. e33666. [PubMed: 22432041]
13. Thomsen LC, et al., The antihypertensive MTHFR gene polymorphism rs17367504-G is a possible novel protective locus for preeclampsia. J Hypertens, 2017 35(1): p. 132–139. [PubMed: 27755385]
14. Dupont C, Armant DR, and Brenner CA, Epigenetics: definition, mechanisms and clinical perspective. Semin Reprod Med, 2009 27(5): p. 351–7. [PubMed: 19711245]
15. Yeung KR, et al., DNA methylation profiles in preeclampsia and healthy control placentas. Am J Physiol Heart Circ Physiol, 2016 310(10): p. H1295–303. [PubMed: 26968548]
16. Anton L, et al., Differential methylation of genes associated with cell adhesion in preeclamptic placentas. PLoS One, 2014 9(6): p. e100148. [PubMed: 24963923]
17. Feil R and Fraga MF, Epigenetics and the environment: emerging patterns and implications. Nat Rev Genet, 2012 13(2): p. 97–109. [PubMed: 22215131]
18. Blair JD, et al., Widespread DNA hypomethylation at gene enhancer regions in placentas associated with early-onset pre-eclampsia. Mol Hum Reprod, 2013 19(10): p. 697–708. [PubMed: 23770704]
19. Ferreira JC, et al., WNT2 promoter methylation in human placenta is associated with low birthweight percentile in the neonate. Epigenetics, 2011 6(4): p. 440–9. [PubMed: 21474991]
20. Ching T, et al., Genome-wide hypermethylation coupled with promoter hypomethylation in the chorioamniotic membranes of early onset pre-eclampsia. Mol Hum Reprod, 2014 20(9): p. 885–904. [PubMed: 24944161]
21. Chu T, et al., Comprehensive analysis of preeclampsia-associated DNA methylation in the placenta. PLoS One, 2014 9(9): p. e107318. [PubMed: 25247495]
22. Hogg K, et al., Early onset pre-eclampsia is associated with altered DNA methylation of cortisol-signalling and steroidogenic genes in the placenta. PLoS One, 2013 8(5): p. e62969. [PubMed: 23667551]
23. Jia RZ, et al., Screening for differential methylation status in human placenta in preeclampsia using a CpG island plus promoter microarray. Int J Mol Med, 2012 30(1): p. 133–41. [PubMed: 22552323]
24. Yuen RK, et al., DNA methylation profiling of human placentas reveals promoter hypomethylation of multiple genes in early-onset preeclampsia. Eur J Hum Genet, 2010 18(9): p. 1006–12. [PubMed: 20442742]
25. Kamburov A, et al., The ConsensusPathDB interaction database: 2013 update. Nucleic acids research, 2013 41(Database issue): p. D793–D800. [PubMed: 23143270]
26. Liu Y and Ma Y, Promoter Methylation Status of WNT2 in Placenta from Patients with Preeclampsia. Med Sci Monit, 2017 23: p. 5294–5301. [PubMed: 29109390]
27. Zhang Z, et al., Association of Wnt2 and sFRP4 expression in the third trimester placenta in women with severe preeclampsia. Reprod Sci, 2013 20(8): p. 981–9. [PubMed: 23322712]
28. MacDonald BT, Tamai K, and He X, Wnt/beta-catenin signaling: components, mechanisms, and diseases. Dev Cell, 2009 17(1): p. 9–26. [PubMed: 19619488]
29. Struwe E, et al., Microarray analysis of placental tissue in intrauterine growth restriction. Clin Endocrinol (Oxf), 2010 72(2): p. 241–7. [PubMed: 19548955]
30. Whitehead CL, et al., Placental specific mRNA in the maternal circulation are globally dysregulated in pregnancies complicated by fetal growth restriction. J Clin Endocrinol Metab, 2013 98(3): p. E429–36. [PubMed: 23337725]
31. Kendall RL and Thomas KA, Inhibition of vascular endothelial cell growth factor activity by an endogenously encoded soluble receptor. Proc Natl Acad Sci U S A, 1993 90(22): p. 10705–9. [PubMed: 8248162]

32. Gormley M, et al., Preeclampsia: novel insights from global RNA profiling of trophoblast subpopulations. Am J Obstet Gynecol, 2017.
33. Song X, et al., Dysregulation of LncRNAs in placenta and pathogenesis of preeclampsia. Curr Drug Targets, 2017.
34. Morales-Prieto DM, et al., Elsevier Trophoblast Research Award Lecture: origin, evolution and future of placenta miRNAs. Placenta, 2014 35 Suppl: p. S39–45. [PubMed: 24378039]
35. Biro O, Nagy B, and Rigo J Jr., Identifying miRNA regulatory mechanisms in preeclampsia by systems biology approaches. Hypertens Pregnancy, 2017 36(1): p. 90–99. [PubMed: 27835046]
36. Luo R, et al., Hypoxia-inducible miR-210 contributes to preeclampsia via targeting thrombospondin type I domain containing 7A. Sci Rep, 2016 6: p. 19588. [PubMed: 26796133]
37. Brooks SA, et al., miRNAs as common regulators of the transforming growth factor (TGF)-beta pathway in the preeclamptic placenta and cadmium-treated trophoblasts: Links between the environment, the epigenome and preeclampsia. Food Chem Toxicol, 2016 98(Pt A): p. 50–57. [PubMed: 27375191]
38. Graves PR and Haystead TA, Molecular biologist's guide to proteomics. Microbiol Mol Biol Rev, 2002 66(1): p. 39–63; table of contents. [PubMed: 11875127]
39. Kim SM, et al., Expression changes of proteins associated with the development of preeclampsia in maternal plasma: A case-control study. Proteomics, 2016 16(10): p. 1581–9. [PubMed: 27001287]
40. Kolla V, et al., Quantitative proteomic (iTRAQ) analysis of 1st trimester maternal plasma samples in pregnancies at risk for preeclampsia. J Biomed Biotechnol, 2012 2012: p. 305964. [PubMed: 22570525]
41. Blumenstein M, et al., A proteomic approach identifies early pregnancy biomarkers for preeclampsia: novel linkages between a predisposition to preeclampsia and cardiovascular disease. Proteomics, 2009 9(11): p. 2929–45. [PubMed: 19444803]
42. Lu Q, et al., Serum markers of pre-eclampsia identified on proteomics. J Obstet Gynaecol Res, 2016 42(9): p. 1111–8. [PubMed: 27279411]
43. Liu C, et al., Proteomic analysis of human serum for finding pathogenic factors and potential biomarkers in preeclampsia. Placenta, 2011 32(2): p. 168–74. [PubMed: 21145106]
44. Rasanen J, et al., Comprehensive maternal serum proteomic profiles of preclinical and clinical preeclampsia. J Proteome Res, 2010 9(8): p. 4274–81. [PubMed: 20568817]
45. Goldberg M, et al., Synthesis of complement proteins in the human chorion is differentially regulated by cytokines. Mol Immunol, 2007 44(7): p. 1737–42. [PubMed: 17005253]
46. Jarvie E, et al., Lipotoxicity in obese pregnancy and its potential role in adverse pregnancy outcome and obesity in the offspring. Clin Sci (Lond), 2010 119(3): p. 123–9. [PubMed: 20443782]
47. Horgan RP and Kenny LC, 'Omic' technologies: genomics, transcriptomics, proteomics and metabolomics. The Obstetrician & Gynaecologist, 2011 13(3): p. 189–195.
48. Mischak H, et al., Epidemiologic design and analysis for proteomic studies: a primer on -omic technologies. Am J Epidemiol, 2015 181(9): p. 635–47. [PubMed: 25792606]
49. Fanos V, et al., Metabolomics application in maternal-fetal medicine. Biomed Res Int, 2013 2013: p. 720514. [PubMed: 23841090]
50. Bahado-Singh RO, et al., Metabolomic determination of pathogenesis of late-onset preeclampsia. J Matern Fetal Neonatal Med, 2017 30(6): p. 658–664. [PubMed: 27569705]
51. Austdal M, et al., First Trimester Urine and Serum Metabolomics for Prediction of Preeclampsia and Gestational Hypertension: A Prospective Screening Study. Int J Mol Sci, 2015 16(9): p. 21520–38. [PubMed: 26370975]
52. Koster MP, et al., First-Trimester Serum Acylcarnitine Levels to Predict Preeclampsia: A Metabolomics Approach. Dis Markers, 2015 2015: p. 857108. [PubMed: 26146448]
53. Bahado-Singh RO, et al., Validation of metabolomic models for prediction of early-onset preeclampsia. Am J Obstet Gynecol, 2015 213(4): p. 530 e1–530 e10. [PubMed: 26116099]
54. Bahado-Singh RO, et al., Metabolomics and first-trimester prediction of early-onset preeclampsia. J Matern Fetal Neonatal Med, 2012 25(10): p. 1840–7. [PubMed: 22494326]

55. Odibo AO, et al., First-trimester prediction of preeclampsia using metabolomic biomarkers: a discovery phase study. Prenat Diagn, 2011 31(10): p. 990–4. [PubMed: 21744367]
56. Dunn WB, et al., Changes in the metabolic footprint of placental explant-conditioned culture medium identifies metabolic disturbances related to hypoxia and pre-eclampsia. Placenta, 2009 30(11): p. 974–80. [PubMed: 19775752]
57. Kenny LC, et al., Robust early pregnancy prediction of later preeclampsia using metabolomic biomarkers. Hypertension, 2010 56(4): p. 741–9. [PubMed: 20837882]
58. Austdal M, et al., Metabolic profiles of placenta in preeclampsia using HR-MAS MRS metabolomics. Placenta, 2015 36(12): p. 1455–62. [PubMed: 26582504]
59. Walejko JM, et al., Global Metabolomics of the Placenta Reveals Distinct Metabolic Profiles between Maternal and Fetal Placental Tissues Following Delivery in Non-Labored Women. Metabolites, 2018 8(1).
60. Bahado-Singh R, et al., Integrated Proteomic and Metabolomic prediction of Term Preeclampsia. Sci Rep, 2017 7(1): p. 16189. [PubMed: 29170520]
61. Huang S, et al., Novel personalized pathway-based metabolomics models reveal key metabolic pathways for breast cancer diagnosis. Genome Med, 2016 8(1): p. 34. [PubMed: 27036109]
62. Alakwaa FM, Chaudhary K, and Garmire LX, Deep Learning Accurately Predicts Estrogen Receptor Status in Breast Cancer Metabolomics Data. J Proteome Res, 2018 17(1): p. 337–347. [PubMed: 29110491]
63. Alakwaa F, Huang S, and Garmire L, Lilikoi: an R package for personalized pathway-based classification modeling using metabolomics data. bioRxiv, 2018.
64. Nobakht MGBF, Application of metabolomics to preeclampsia diagnosis. Syst Biol Reprod Med, 2018: p. 1–16.
65. Huang S, et al., Novel personalized pathway-based metabolomics models reveal key metabolic pathways for breast cancer diagnosis. Genome Medicine, 2016 8(1): p. 34. [PubMed: 27036109]
66. Liu LY, et al., Integrating multiple ‘omics’ analyses identifies serological protein biomarkers for preeclampsia. BMC Med, 2013 11: p. 236. [PubMed: 24195779]
67. Muttukrishna S, et al., Measurement of serum concentrations of inhibin-A (alpha-beta A dimer) during human pregnancy. Clin Endocrinol (Oxf), 1995 42(4): p. 391–7.
68. Triche EW, et al., Bioinformatic approach to the genetics of preeclampsia. Obstet Gynecol, 2014 123(6): p. 1155–61. [PubMed: 24807322]
69. Tuteja G, et al., PESNPdb: a comprehensive database of SNPs studied in association with pre-eclampsia. Placenta, 2012 33(12): p. 1055–7. [PubMed: 23084601]
70. Zhao L, et al., Genome-wide association study identifies a maternal copy-number deletion in PSG11 enriched among preeclampsia patients. BMC Pregnancy Childbirth, 2012 12: p. 61. [PubMed: 22748001]
71. Sandrim VC, et al., Circulating microRNA expression profiles in pre-eclampsia: evidence of increased miR-885–5p levels. BJOG, 2016 123(13): p. 2120–2128. [PubMed: 26853698]
72. Sitras V, et al., Differential placental gene expression in severe preeclampsia. Placenta, 2009 30(5): p. 424–33. [PubMed: 19249095]
73. Tsai S, et al., Transcriptional profiling of human placentas from pregnancies complicated by preeclampsia reveals disregulation of sialic acid acetylesterase and immune signalling pathways. Placenta, 2011 32(2): p. 175–82. [PubMed: 21183218]
74. Yong HE, et al., Genome-wide transcriptome directed pathway analysis of maternal pre-eclampsia susceptibility genes. PLoS One, 2015 10(5): p. e0128230. [PubMed: 26010865]
75. Brew O, Sullivan MH, and Woodman A, Comparison of Normal and Pre-Eclamptic Placental Gene Expression: A Systematic Review with Meta-Analysis. PLoS One, 2016 11(8): p. e0161504. [PubMed: 27560381]
76. Mary S, et al., Placental Proteomics Provides Insights into Pathophysiology of Pre-Eclampsia and Predicts Possible Markers in Plasma. J Proteome Res, 2017 16(2): p. 1050–1060. [PubMed: 28030762]
77. Gharesi-Fard B, Zolghadri J, and Kamali-Sarvestani E, Proteome differences of placenta between pre-eclampsia and normal pregnancy. Placenta, 2010 31(2): p. 121–5. [PubMed: 19954843]

78. Park JS, et al., Identification of proteomic biomarkers of preeclampsia in amniotic fluid using SELDI-TOF mass spectrometry. Reprod Sci, 2008 15(5): p. 457–68. [PubMed: 18579854]
79. Yang JI, et al., The Proteomic Analysis of Human Placenta with Pre-eclampsia and Normal Pregnancy. J Korean Med Sci, 2015 30(6): p. 770–8. [PubMed: 26028931]
80. Ma K, et al., A proteomic analysis of placental trophoblastic cells in preeclampsia-eclampsia. Cell Biochem Biophys, 2014 69(2): p. 247–58. [PubMed: 24343450]
81. Shi Z, et al., Comparative proteomics analysis suggests that placental mitochondria are involved in the development of pre-eclampsia. PLoS One, 2013 8(5): p. e64351. [PubMed: 23671712]
82. Kim YN, et al., Toward a better understanding of preeclampsia: Comparative proteomic analysis of preeclamptic placentas. Proteomics Clin Appl, 2007 1(12): p. 1625–36. [PubMed: 21136660]
83. Webster RP, et al., Differences in the proteome profile in placenta from normal term and preeclamptic preterm pregnancies. Proteomics Clin Appl, 2007 1(5): p. 446–56. [PubMed: 21136696]
84. Zhang W, et al., Detergent-Insoluble Proteome Analysis Revealed Aberrantly Aggregated Proteins in Human Preeclampsia Placentas. J Proteome Res, 2017 16(12): p. 4468–4480. [PubMed: 28965414]
85. Erez O, et al., The prediction of late-onset preeclampsia: Results from a longitudinal proteomics study. PLoS One, 2017 12(7): p. e0181468. [PubMed: 28738067]
86. Jin X, et al., Proteomics analysis of human placenta reveals glutathione metabolism dysfunction as the underlying pathogenesis for preeclampsia. Biochim Biophys Acta, 2017 1865(9): p. 1207–1214.
87. Mary S, et al., Tubulointerstitial nephritis antigen-like 1 protein is downregulated in the placenta of pre-eclamptic women. Clin Proteomics, 2017 14: p. 8. [PubMed: 28344540]
88. van den Berg CB, et al., Elevated levels of protein AMBP in cerebrospinal fluid of women with preeclampsia compared to normotensive pregnant women. Proteomics Clin Appl, 2017 11(1–2).
89. Buhimschi IA, et al., Proteomic profiling of urine identifies specific fragments of SERPINA1 and albumin as biomarkers of preeclampsia. Am J Obstet Gynecol, 2008 199(5): p. 551 e1–16. [PubMed: 18984079]
90. Ariff A, et al., Analysis of the Epigenome in Multiplex Pre-eclampsia Families Identifies SORD, DGKI, and ICA1 as Novel Candidate Risk Genes. Front Genet. 2019 10:227. [PubMed: 30941163]
91. Wang T, et al., Epigenome-wide association data implicate fetal/maternal adaptations contributing to clinical outcomes in preeclampsia. Epigenomics. 2019 11(9):1003–1019. [PubMed: 31091979]
92. Gray KJ, et al., Gene-Centric Analysis of Preeclampsia Identifies Maternal Association at PLEKHG1. Hypertension. 2018 72(2):408–416. [PubMed: 29967039]
93. Feng Y, et al., Application of iTRAQ proteomics in identification of the differentially expressed proteins of placenta of pregnancy with preeclampsia. J Cell Biochem. 2019 120(4):5409–5416. [PubMed: 30506707]
94. Tarca AL, et al., The prediction of early preeclampsia: Results from a longitudinal proteomics study. PLoS One. 2019 14(6):e0217273. [PubMed: 31163045]
95. Ding W, et al., Isobaric tag for relative and absolute quantitation based quantitative proteomics reveals unique urinary protein profiles in patients with preeclampsia. J Cell Mol Med. 2019 23(8):5822–5826. [PubMed: 31232531]
96. Ling Y, et al., Screening of serum biomarkers of preeclampsia by proteomics combination with bioinformatics. Hypertens Pregnancy. 2019 38(3):184–192. [PubMed: 31284791]
97. Kawasaki K, et al., Metabolomic Profiles of Placenta in Preeclampsia. Hypertension. 2019 73(3):671–679. [PubMed: 30595122]
98. Liu Y, et al., Metabolomics revealed decreased level of omega-3 PUFA-derived protective eicosanoids in pregnant women with pre-eclampsia. Clin Exp Pharmacol Physiol. 2019 46(8):705–710 [PubMed: 30983029]
99. Sovio U, et al., 4-Hydroxyglutamate is a novel predictor of pre-eclampsia. Int J Epidemiol. 2019 pii: dyz098 10.1093/ije/dyz098.

100. Leavey K, et al., Epigenetic regulation of placental gene expression in transcriptional subtypes of preeclampsia. Clin Epigenet 10, 28 (2018).

101. Leavey K, et al., Unsupervised Placental Gene Expression Profiling Identifies Clinically Relevant Subclasses of Human Preeclampsia. Hypertension. 2016 68(1):137–47. [PubMed: 27160201]

102. Leavey K, et al., Large scale aggregate microarray analysis reveals three distinct molecular subclasses of human preeclampsia. PLoS One. 2015 10(2):e0116508. [PubMed: 25679511]

103. Huang S, Chong N, Lewis NE, Jia W, Xie G, Garmire LX. Novel personalized pathway-based metabolomics models reveal key metabolic pathways for breast cancer diagnosis. Genome Med. 2016 8(1):34. [PubMed: 27036109]

Highlights

We review recent progress in preeclampisa using various omics technology platforms.

We show that in general coherent preecalmpsia biomarkers are lacking in all omics studies.

Using network systems biology approach, we identify four sub-networks related to preeclampisa.

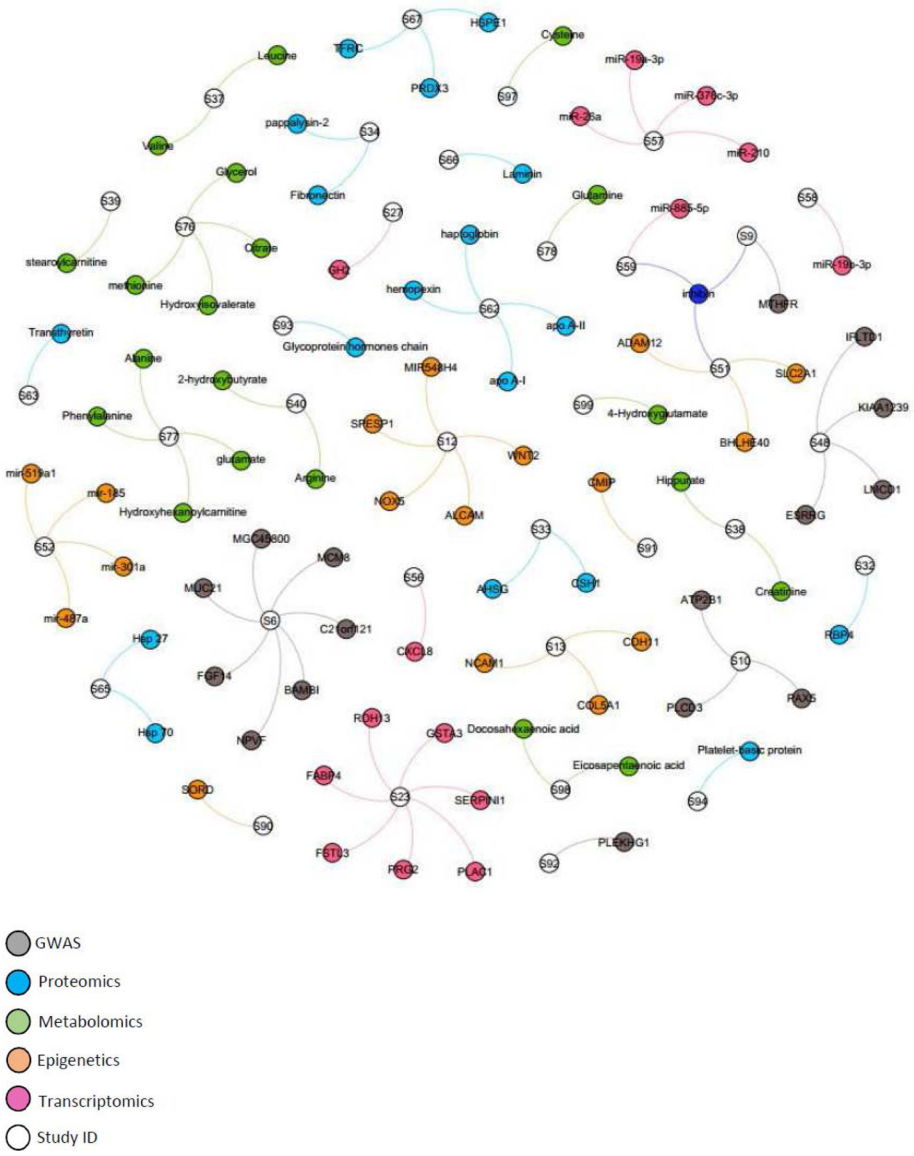

Figure 1.

Bipartite graph merging all omics platforms used to study preeclampsia. A bipartite group is composed of two types of nodes. One type of nodes depicts the biomarkers found in different omic-type studies. Omic-type is annotated by node color as indicated in the plot: Grey = GWAS, orange = Methylation, pink = Transcriptomics, blue = Proteomics, bright green = metabolomics. The other type of nodes, labelled as S, signifies the study information.

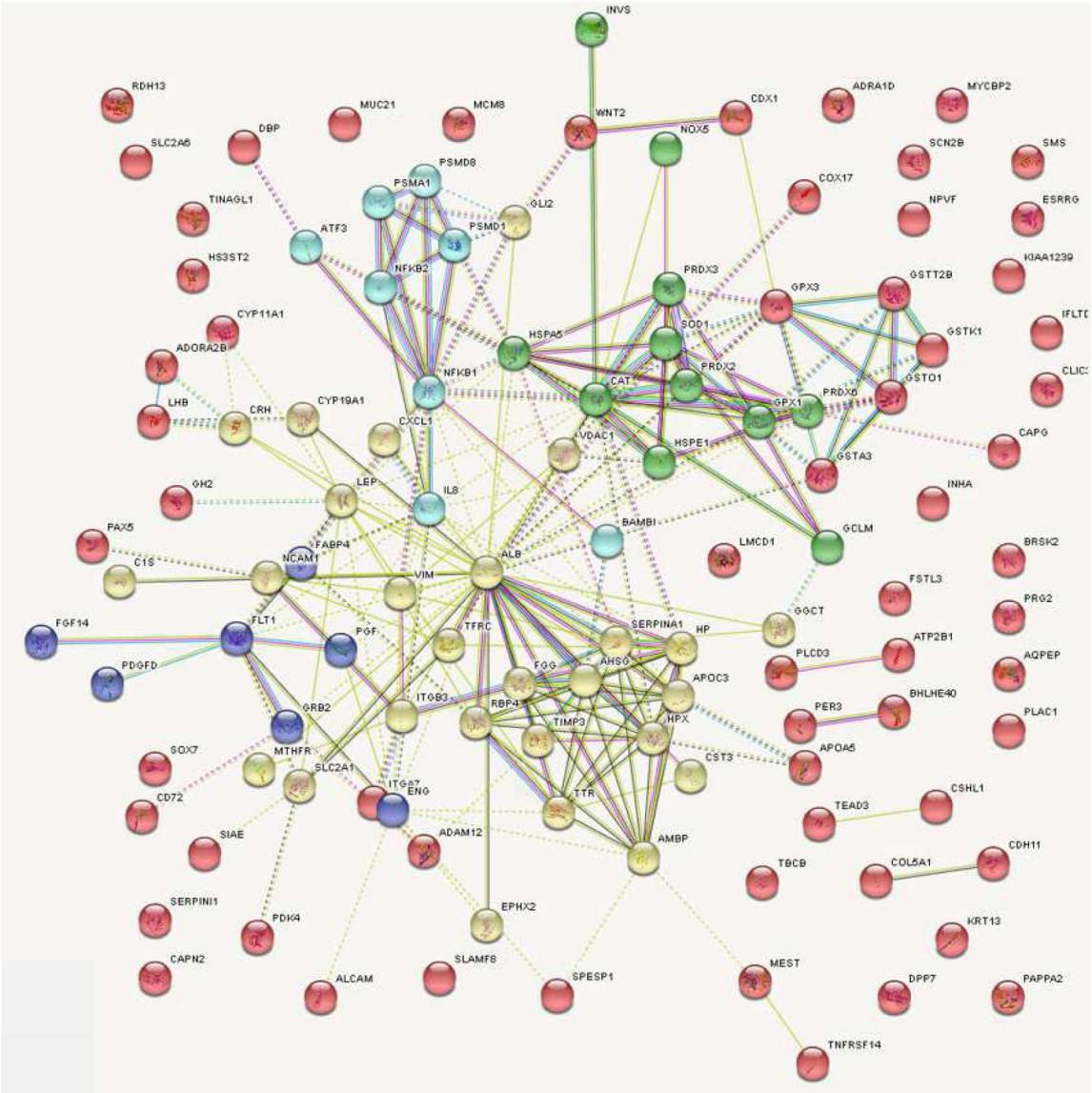

Figure 2.

Protein-protein interaction network (STRING database) generated by combining all biomarkers of different omic types, reviewed earlier in the report. The network is done using Cytoscape visualization. Four dominant sub-networks associated with preeclampsia are shown (blue, green, yellow, purple), each enriched with biological functions. Antioxidant pathway involving PRDX2, PRDX3, HSPE1, GCLM and SOD1 (green). Proteasome and cytokine signalling pathway involving PSMA1, PSMD8, NFKB1, NFKB2 (blue). Protein regulation and transport pathways involving C1s, TFRC, CXCL1, TTR, TIMP3 (yellow). Angiogenesis signalling pathway involving FLT1, PGF, FGF, ENG (purple). The other red targets are still associated with preeclampsia but not within the four dominant sub-networks.

Table 1.

List of SNPs extracted from several preeclampsia GWAS reports. Gene of interest, sample origin (mother or child), study size, gestational age and severity of preeclampsia were included.

SNPs	Gene	Reference	Sample Origin (mother, child)	Study size (Case/control)	Gestational Age (preeclampsia, control in weeks) *
rs17367504a	MTHFR	[13]	Mother	1006/816	^
rs7579169	INHIBIN	[12]	Mother	538/540	^
rs17249754a	ATP2B1	[13]	Mother	1006/816	^
rs16933812a	PAX5	[13]	Mother	1006/816	^
rs12946454a	PLCD3	[13]	Mother	1006/816	^
rs1426409	KIAA1239	[70]	Mother	177/116	^
rs17686866	ESRRG	[70]	Mother	177/116	^
rs9831647	LMCD1	[70]	Mother	177/116	^
rs10743565	IFLTD1	[70]	Mother	177/116	^
rs11617740	FGF14	[8]	Mother	137/2,986	^
rs2839440	C21orf121	[8]	Mother	137/2,986	^
rs12641856	MGC45800	[8]	Mother	137/2,986	^
rs4815879	MCM8	[8]	Mother	137/2,986	^
rs28360974	MUC21	[8]	Mother	137/2,986	^
rs1248993	BAMBI	[8]	Mother	137/2,986	^
rs975369	NPVF	[8]	Mother	137/2,986	^
rs1556832	ADRA1D	[8]	Mother	137/2,986	^
rs11600901	SCN2B	[8]	Mother	137/2,986	^
rs7322722	MYCBP2	[8]	Mother	137/2,986	^
rs10989019	INVS	[8]	Mother	137/2,986	^
rs4769613	FLT1	[7]	Child	4,380/310,238	<34,37## >34,39#
rs9478812	*PLEKHG1*	[3]	Mother	877/2004	###

early-onset preeclampsia

late-onset preeclampsia

severe preeclampsia

mild preeclampsia

^ not specified

* Type of preeclampsia

Table 2.

List of hyper- and hypo-methylated regions associated with preeclampsia. Gene of interest, region, methylation status, characteristics, coordinates, study size, gestation age were included.

Gene/ Region	Methylation status	Reference	Sample origin	Analyse type	Characteristic	Coordinates/ Accension	Study size	Gestational Age (preeclampsia, control in weeks) *
WNT2	Hyper	[15] [19]	Fetal placenta	Region	TSS	chr7:116963492–116964841	8/16	35,37 ^
SPESP1	Hyper	[15]	Fetal placenta	Region	TSS, 5′-UTR, body	chr15:69202400–69223895	8/16	35,37 ^
NOX5	Hyper	[15]	Fetal placenta	Region	TSS, 5′-UTR, body	chr15:69222400–69223895	8/16	35,37 ^
MIR548H4	Hyper	[15]	Fetal placenta	Region	TSS, 5′-UTR, body	chr15:69222400–69223895	8/16	35,37 ^
ALCAM	Hyper	[15]	Fetal placenta	Region	Body	chr3:105087718–105088546	8/16	35,37 ^
CDH11	Hyper	[16]	Fetal placenta	Site		cg26624576	31/14	35,37 ^
COL5A1	Hyper	[16]	Fetal placenta	Site		cg14237069	31/14	35,37 ^
NCAM1	Hypo	[16]	Fetal placenta	Site		cg20857767	31/14	35,37 ^
INHIBIN	Hypo	[18]	Fetal placenta	Site	5’UTR	cg11079619	20/20	31,37 ##
BHLHE40	Hypo	[18]	Fetal placenta	Site	Body	cg20971407	20/20	31,37 ##
SLC2A1	Hypo	[18]	Fetal placenta	Site	Body	cg01924561	20/20	31,37 ##
ADAM12	Hypo	[18]	Fetal placenta	Site	Body	cg02494582	20/20	31,37 ##
mir-519a1	Hyper	[20]	Chorioamniotic membrane		Promoter		30/17	32,38##
mir-301a	Hyper	[20]	Chorioamniotic membrane		Promoter		30/17	32,38##
mir-487a	Hyper	[20]	Chorioamniotic membrane		Promoter		30/17	32,38 ##
mir-185	Hyper	[20]	Chorioamniotic membrane		Promoter		30/17	32,38 ##
mir-329	Hyper	[20]	Chorioamniotic membrane		Promoter		30/17	32,38 ##
mir-194	Hyper	[20]	Chorioamniotic membrane		Promoter		30/17	32,38 ##

Gene/ Region	Methylation status	Reference	Sample origin	Analyse type	Characteristic	Coordinates/ Accension	Study size	Gestational Age (preeclampsia, control in weeks) *
mir-376a1	Hyper	[20]	Chorioamniotic membrane		Promoter		30/17	32,38 ##
mir-486	Hyper	[20]	Chorioamniotic membrane		Promoter		30/17	32,38 ##
mir-744	Hyper	[20]	Chorioamniotic membrane		Promoter		30/17	32,38 ##
GRB2	Hypo	[20]	Chorioamniotic membrane		Promoter		30/17	32,38 ##
ATF3	Hypo	[20]	Chorioamniotic membrane		Promoter		30/17	32,38 ##
NFKB2	Hypo	[20]	Chorioamniotic membrane	Region	Promoter	NM_001077493	30/17	32,38 ##
PSMA1	Hypo	[20]	Chorioamniotic membrane		Promoter		30/17	
PMSE1	Hypo	[20]	Chorioamniotic membrane		Promoter		30/17	32,38 ##
PSMD1	Hypo	[20]	Chorioamniotic membrane		Promoter		30/17	32,38 ##
PSMD8	Hypo	[20]	Chorioamniotic membrane	Region	Promoter, Body	NM_002812	30/17	32,38 ##
PAPPA2	Hypo	[21]	Maternal Placenta	Site	Not Reported	cg10994126	9/24	35,37 ##
CRH	Hyper	[22]	Placenta				19/19	31,37## 37,39#
CYP11A1	Hypo	[22]	Placenta				19/19	31,37## 37,39#
3β-HSD type 1	Hypo	[22]	Placenta				19/19	31,37## 37,39#
TEAD3	Hypo	[22]	Placenta				19/19	31,37## 37,39#
CYP19	Hypo	[22]	Placenta				19/19	31,37## 37,39#
CAPN2	hypo	[23]	Placenta	Region	Promoter	824	9/9	35,37 ^
EPHX2	hypo	[23]	Placenta	Region	Promoter	2053	9/9	35,37 ^
ADORA2B	hyper	[23]	Placenta	Region	Promoter	136	9/9	35,37 ^

Gene/ Region	Methylation status	Reference	Sample origin	Analyse type	Characteristic	Coordinates/ Accension	Study size	Gestational Age (preeclampsia, control in weeks) *
SOX7	hyper	[23]	Placenta	Region	Promoter	83595	9/9	35,37 ^
CXCL1	hyper	[23]	Placenta	Region	Promoter	2919	9/9	35,37 ^
CDX1	hyper	[23]	Placenta	Region	Promoter	1044	9/9	35,37 ^
GLI2	hypo	[24]	Fetal placenta	Region	Promoter	GLI2_E90_Fa	4/5	30,37 ## 37,39 #
KRT13	hypo	[24]	Fetal placenta	Region	Promoter	KRT13_P676_Fa	4/5	30,37 ## 37,39 #
MEST	hypo	[24]	Fetal placenta	Region	Promoter	MEST_E150_Fa	4/5	30,37 ## 37,39 #
TIMP3	hypo	[24]	Fetal placenta	Region	Promoter	TIMP3_P690_Ra	4/5	30,37 ## 37,39 #
CAPG	hypo	[24]	Fetal placenta	Region	Promoter	CAPG_E228_Fa	4/5	30,37 ## 37,39 #
SORD		[90]	Placenta				7,4	^
DGKI		[90]	Placenta				7,4	^
ICA1		[90]	Placenta				7,4	^
CMIP		[91]	Placenta				32,30	33,37 ##

early-onset preeclampsia

late-onset preeclampsia

severe preeclampsia

mild preeclampsia

^ not specified

* Type of preeclampsia

Table 3.

List of the RNA transcripts associated with preeclampsia. Gene symbol, transcript fold change, tissue of origin, study size, gestational age and severity of preeclampsia were included.

Gene symbol	Reference	Fold change	Tissue	Study size	Gestational Age (preeclampsia, control in weeks) *
PRG2	[32]	6.4	syncytiotrophoblasts severe preeclampsia (placenta)	4/4	27,37 ###
FSTL3	[32]	3.7	syncytiotrophoblasts severe preeclampsia (placenta)	4/4	27,37 ###
FABP4	[32]	3.5	syncytiotrophoblasts severe preeclampsia (placenta)	4/4	27,37 ###
RDH13	[32]	3.1	syncytiotrophoblasts severe preeclampsia (placenta)	4/4	27,37 ###
PLAC1	[32]	−3.4	syncytiotrophoblasts severe preeclampsia (placenta)	4/4	27,37 ###
SERPINI1	[32]	−4.4	syncytiotrophoblasts severe preeclampsia (placenta)	4/4	27,37 ###
GSTA3	[32]	−4.8	syncytiotrophoblasts severe preeclampsia (placenta)	4/4	27,37 ###
CXCL8	[32]	3.5	cytotrophoblasts Severe preeclampsia (placenta)	3/4	27,37 ###
GH2	[32]	−14.2	cytotrophoblasts Severe preeclampsia (placenta)	3/4	27,37 ###
miR-210	[24]	2.452	Placenta (full thickness)	16/16	30,29## 37,38#
miR-26a	[37]	−164.655	Placenta (full thickness)	16/16	^
miR-376c-3p	[71]	down	Circulating exosomes	5/4	35,35 ^
miR-19a-3p	[71]	down	Circulating exosomes	5/4	35,35 ^
miR-19b-3p	[71]	down	Circulating exosomes	5/4	35,35 ^
miR-885–5p	[71]	up	Circulating exosomes	5/4	35,35 ^
sFLT1	[72]	2.6	Placenta (full thickness)	21/21	34,39 ###
ENG	[73]	1.852919237	Placenta (full thickness)	23/37	33,37 ^
INHIBIN A	[73] [74] [75]	3.0	Placenta (full thickness)	21/21	33,37 ^
SIAE	[73]	1.354912795	Placenta (full thickness)	23/37	33, 37 ^
PAPPA2	[73]	2.9	Placenta (full thickness)	21/21	33, 37 ^
BRSK2	[73]	8.6	Placenta (full thickness)	21/21	33, 37 ^
FLJ90650	[73]	10.0	Placenta (full thickness)	21/21	33, 37 ^
LEP	[73]	40.0	Placenta (full thickness)	21/21	33, 37 ^
LHB	[73]	4.1	Placenta (full thickness)	21/21	33, 37 ^
PDGFD	[73]	−2.3	Placenta (full thickness)	21/21	33, 37 ^

Gene symbol	Reference	Fold change	Tissue	Study size	Gestational Age (preeclampsia, control in weeks) *
COX17	[73]	−4.3	Placenta (full thickness)	21/21	33, 37 ^
HS3ST2	[74]	−1.39	Maternal Placenta (Decidual basalis)	60/65	32,39 ^
TNFRSF14	[74]	−1.35	Maternal Placenta (Decidual basalis)	60/65	32,39 ^
SLC2A6	[74]	−1.32	Maternal Placenta (Decidual basalis)	60/65	32,39 ^
DPP7	[74]	−1.22	Maternal Placenta (Decidual basalis)	60/65	32,39 ^
CD72	[74]	−1.21	Maternal Placenta (Decidual basalis)	60/65	32,39 ^
PER3	[74]	−1.20	Maternal Placenta (Decidual basalis)	60/65	32,39 ^
DBP	[74]	−1.20	Maternal Placenta (Decidual basalis)	60/65	32,39 ^
PDK4	[74]	1.72	Maternal Placenta (Decidual basalis)	60/65	32,39 ^
HS3ST2	[74]	−1.39	Maternal Placenta (Decidual basalis)	60/65	32,39 ^

early-onset preeclampsia

late-onset preeclampsia

severe preeclampsia

mild preeclampsia

^ not specified

* Type of preeclampsia

Table 4.

List of proteins associated with preeclampsia. Proteins, fold changes, sample origin, sample size of studies, gestational age and severity of preeclampsia were also included.

Protein	Fold change	Reference	Sample origin	Sample size	Gestational Age (preeclampsia, control in weeks) *
apolipoproteins A-I	↑ 2	[76]	Plasma^	25/25^	38,39^
	↑	[77]	Placenta	5/5	35,37 ^
	↑	[78]	Amniotic fluid	18/16	36,36^
apolipoproteins and A-II	↑ 2	[76]	plasma	25/25	38,39^
haptoglobin	↓ −1.8	[76]	plasma	25/25	38,39^
hemopexin	↓ −1.8	[76]	plasma	25/25	38,39^
Fibronectin	↑ 2.1	[44]	serum	30/58	35,40### 39,40####
RBP4	↓	[42]	serum	10/10	36,38 ###
Hsp 27	↑ ↑	[79]	Placenta Placenta	5/5 10/10	35,37^
Hsp 70	↓	[79]	placenta	5/5	35,37^
Laminin	↑ 0.18	[80]	placenta trophoblastic cells	1/1	^
HSPE1	↑ 5.86	[81]	placenta	4/4	36,37^
PRDX3	↑ 5.01	[81]	placenta	4/4	36,37^
TFRC	↑ 3.9	[81]	placenta	4/4	36,37^
Chorionic somatomammotropin hormone	↑	[43]	serum	5/5	36,38^
Transthyretin	↑	[77] [43]	Placenta Serum	5/5 5/5	35,37 ^
Plasma retinol-binding protein 4	↑	[43]	serum	5/5	36,38^
Alpha-2-HS-glycoprotein	↑	[43]	serum	5/5	36,38^
pappalysin-2	↓ −1	[44]	serum	30/58	35,40### 39,40####
choriogonadotropin-beta	↓ −7.6	[44]	serum	30/58	35,40### 39,40####
apolipoprotein C-III	↑ 2.1	[44]	serum	30/58	35,40### 39,40####
cystatin-C	↑ 6.5	[44]	serum	30/58	35,40### 39,40####

Protein	Fold change	Reference	Sample origin	Sample size	Gestational Age (preeclampsia, control in weeks) *
vascular endothelial growth factor receptor-1	↓ −8.4	[44]	serum	30/58	35,40$^{\#\#\#}$ 39,40$^{\#\#\#\#}$
endoglin	↓ −1	[44]	serum	30/58	35,40$^{\#\#\#}$ 39,40$^{\#\#\#\#}$
chloride intracellular channel 3	↑	[77]	placenta	5/5	35,37 $^{\wedge}$
protein disulphide isomerase	↑	[77]	placenta	5/5	35,37 $^{\wedge}$
peroxiredoxin 2	↓	[77]	placenta	5/5	35,37 $^{\wedge}$
peroxiredoxin 3	↓	[77]	placenta	5/5	35,37 $^{\wedge}$
Hsc 70	↓	[77]	placenta	5/5	35,37 $^{\wedge}$
SOD-1	↓	[77]	placenta	5/5	35,37 $^{\wedge}$
actin gamma 1 propeptide	↓	[77]	placenta	5/5	35,37 $^{\wedge}$
chain A of enoyl-coenzyme A hydratase	↓	[77]	placenta	5/5	35,37 $^{\wedge}$
HSP gp96	↓	[77]	placenta	5/5	35,37 $^{\wedge}$
fibrinogen gamma chain	6.4	[41]	plasma	39/57	38,40 $^{\wedge}$
SBBI42	↑	[78]	amniotic fluid	18/16	36,36 $^{\wedge}$
Chaperonin (heatshock protein 60	↑ 223	[82]	placenta	8/8	33,36 $^{\wedge}$
Glutathione S-transferase	↑ 177	[82]	placenta	8/8	33,36 $^{\wedge}$
Voltage-dependent anion channel	↑ 185	[82]	placenta	8/8	33,36 $^{\wedge}$
ER-60protease	↑ 179	[82]	placenta	8/8	33,36 $^{\wedge}$
Chain H, Cathepsin D at pH 7.5	↑ 245	[82]	placenta	8/8	33,36 $^{\wedge}$
Catalase	↑	[83]	placenta	3/3	29,38 $^{\wedge}$
glucose-regulated protein	↑	[83]	placenta	3/3	29,38 $^{\wedge}$
Endothelial monocyte- activating polypeptide	↓	[83]	placenta	3/3	29,38 $^{\wedge}$
ENG	↑ 3.21	[84]	placenta	10/10	35,39 $^{\wedge}$
VIM	↓ −1.58	[84]	placenta	10/10	35,39 $^{\wedge}$
MMP-7	↑ 1.4	[85]	plasma	76/90	38,39$^{\#\#\#}$ 38,39$^{\#\#\#\#}$
PlGF	↓ −1.1	[85]	plasma	76/90	38,39$^{\#\#\#}$ 38,39$^{\#\#\#\#}$
SOD1	↑ 222.39	[86]	placenta	20/20	$^{\wedge}$
SMS	↑ 323.31	[86]	placenta	20/20	$^{\wedge}$

Protein	Fold change	Reference	Sample origin	Sample size	Gestational Age (preeclampsia, control in weeks) *
GSTK1	↑ 90.64	[86]	placenta	20/20	^
GPX1	↑ 25.18	[86]	placenta	20/20	^
GPX3	↑ 5.80	[86]	placenta	20/20	^
GCLM	↑ 0.66	[86]	placenta	20/20	^
GGCT	↑ 1.26	[86]	placenta	20/20	^
GSTT2B	↑ 0.83	[86]	placenta	20/20	^
NFKB1	↑ 67.84	[86]	placenta	20/20	^
Q9GZM7	↓ 1.6	[87]	placenta	25/25	^
Protein AMBP (P02760)	↑ 1.8	[88]	cerebrospinal fluid	43/55	30,38^
Complement C1s subcomponent	↑	[39]	plasma	13/13	^
P01009	↑	[89]	urine	114/92	36,33### 36,33####
P02768	↑	[89]	urine	114/92	36,33### 36,33####
Glycoprotein ormonesα chain	↑1.7	[93]	Placenta	20,20	37,37^
Apolipoprotein A-I	↑1.3	[93]	Placenta	20,20	37,37^
Solute carrier organic anion	↑1.3	[93]	Placenta	20,20	37,37^
transporter family member	↓0.79	[93]	Placenta	20,20	37,37^
Platelet-basic protein	↓0.77	[93]	Placenta	20,20	37,37^
MMP - 7	↑1.9	[94]	Plasma	90,33	31,39##
Transferrin	↑3	[95]	Urine	7,7	^
Complement factor B	↑2	[95]	Urine	7,7	^
pregnancy-specific beta-1-glycoprotein 2	↓2	[7]	Serum	5,7	33,38^

early-onset preeclampsia

late-onset preeclampsia

severe preeclampsia

mild preeclampsia

^ not specified

* Type of preeclampsia

Table 5.

List of metabolites associated with preeclampsia. Metabolites, fold changes sample origin, study size, gestational age and severity of preeclampsia were also included.

Metabolite dysregulation	Fold change	Reference	Sample origin	Case/controls	Gestational Age (preeclampsia, control in weeks) *
Valine	↓ −1.27	[50]	maternal serum	59/115	#
Leucine	↑ 1.16	[50]	maternal serum	59/115	#
Hippurate	↓	[51]	urine	26/561	38,40^
Creatinine	↑	[51]	urine	26/561	38,40^
Stearoylcarnitine	↑ 0.829	[52]	maternal serum	167/500	31,40## 37,40#
Arginine	↑ 1.02	[53]	maternal serum	50/108	##
2-hydroxybutyrate	↑ 1.08	[53]	maternal serum	50/108	##
Citrate	↑ 0.06	[54]	maternal plasma	30/60	##
Glycerol	<0.001	[54]	maternal plasma	30/60	##
Hydroxyisovalerate	↑ 0.01	[54]	maternal plasma	30/60	##
Methionine	↑ 0.024	[54]	maternal plasma	30/60	##
Hydroxyhexanoylcarnitine	↑ 0.78	[55]	maternal serum	41/41	35,39^
Alanine	↑ 0.78	[55]	maternal serum	41/41	35,39^
Phenylalanine	↑ 0.80	[55]	maternal serum	41/41	35,39^
Glutamate	↑ 0.79	[55]	maternal serum	41/41	35,39^
	↑ 0.76	[56]	placenta	6/6	^
Glutamine	↑ 0.42	[56]	placenta	6/6	^
Cysteine	↑0.64	[97]	Placenta	10,10	##,#
eicosapentaenoic acid	↑2	[98]	Plasma	10,10	37,38^
docosahexaenoic acid	↑1.4	[98]	Plasma	10,10	37,38^
4-Hydroxyglutamate	↑3	[99]	Serum	194,325	35,40## 39,40#

early-onset preeclampsia

late-onset preeclampsia

severe preeclampsia

mild preeclampsia

^ not specified

* Type of preeclampsia