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Epigenetic processes during preeclampsia and effects on fetal development and chronic health

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Abstract

Preeclampsia (PE), the leading cause of maternal and fetal morbidity and mortality, is associated with poor fetal growth, intrauterine growth restriction (IUGR) and low birth weight (LBW). Offspring of women who had PE are at increased risk for cardiovascular (CV) disease later in life. However, the exact etiology of PE is unknown. Moreover, there are no effective interventions to treat PE or alleviate IUGR and the developmental origins of chronic disease in the offspring. The placenta is critical to fetal growth and development. Epigenetic regulatory processes such as histone modifications, microRNAs and DNA methylation play an important role in placental development including contributions to the regulation of trophoblast invasion and remodeling of the spiral arteries. Epigenetic processes that lead to changes in placental gene expression in PE mediate downstream effects that contribute to the development of placenta dysfunction, a critical mediator in the onset of PE, impaired fetal growth and IUGR. Therefore, this review will focus on epigenetic processes that contribute to the pathogenesis of PE and IUGR. Understanding the epigenetic mechanisms that contribute to normal placental development and the initiating events in PE may lead to novel therapeutic targets in PE that improve fetal growth and mitigate increased CV risk in the offspring.

Introduction

Preeclampsia (PE), the leading cause of maternal and fetal morbidity and mortality, affects 5–7% of pregnancies in the United States and is responsible for over 70000 maternal deaths and 500000 fetal deaths worldwide each year [1]. PE is characterized by gestation-specific hypertension with systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg and proteinuria ≥ 300 mg/24 h [1,2]. Typically, PE occurs in two stages where placental dysfunction occurs first without any observable symptoms followed by a symptomatic phase as early as the 20th week of gestation [3]. PE is associated with a variety of pathophysiological processes including impaired implantation, placenta ischemia, systemic inflammation and endothelial dysfunction [2,4,5]. The placenta plays a vital role in the etiology of PE in the mother and placental dysfunction in PE has a lifelong adverse effect on future cardiovascular (CV) well-being in the mother and her child [6,7]. Placental

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Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

ischemia leading to dysregulation in placental homeostasis is the initiating factor for PE [2] and is the leading cause of intrauterine growth restriction (IUGR) in the Western world [8]. Numerous studies demonstrate that hypertension during pregnancy is associated with increased BP and CV risk in offspring [9–15]. However, despite decades of research, to date there are no effective therapeutic interventions to treat PE [16,17] or alleviate IUGR and the developmental origins of chronic disease in the offspring [18]. Clinically, the cornerstone of therapy in PE remains stabilization of the mother and early delivery of fetus, which results in preterm birth or low birth weight (LBW), also associated with increased CV risk in offspring [19]. Yet, any therapeutic intervention administered to the mother must provide benefit without compromising placental perfusion, fetal development and CV health in the offspring.

There are many theories that exist regarding the origins of PE. Although there is no exact consensus [20], the placenta is considered as a necessary component in the development of PE [20]. During normal pregnancy, placental cytotrophoblasts (CTs) invade the spiral arteries of the myometrium resulting in vascular remodeling that involves disorganization of the smooth muscle layer in order to ensure adequate delivery of nutrients to the developing fetus [20]. Disruption of placentation in PE leads to placenta ischemia [20,21], hypoxia, inflammation, the generation of oxidative stress and IUGR [2,22]. Yet, the exact molecular mechanisms that contribute to the development of placental dysfunction and impaired fetal growth in PE are not clear.

Several angiogenic mechanisms are involved in the pathogenesis of PE including an imbalance of pro-angiogenic and anti-angiogenic factors. Up-regulation of anti-angiogenic factors such as soluble fms-like tyrosine-1 (sFlt-1) and soluble endoglin (sEng) in the placenta contribute to abnormal placental vascularization [23,24]. Increased production of an agonistic autoantibody directed against the angiotensin (ANG II) type 1 (AT1) receptor (AT1-AA) in PE [25] is linked to increased production of sFlt-1 [26] and endothelin [27]. Experimental studies indicate that increases in the AT1-AA contribute to increased BP, higher levels of endothelin and decreased levels of vasodilators such as nitric oxide (NO) [28]. Collectively, these studies indicate that an imbalance in these factors contribute to the development of maternal endothelial dysfunction in PE.

Epigenetic processes play a critical role in gene expression during placental development and function [29,30]. Epigenetic processes, or how the environment influences changes in gene expression without altering the DNA sequence, is one mechanism by which gestational hypoxia, allows adaptive responses to change in the placental environment in PE. However, studies examining the importance of epigenetic regulation in the etiology of PE and IUGR are very limited, especially mechanistic studies using well-established experimental models. Numerous studies suggest that a number of epigenetic mechanisms are involved in the regulation of gene expression during development and in differentiated tissues [31–34]. As reviewed by Apically et al., these mechanisms include DNA methylation, biogenesis, and the action of noncoding RNAs such as microRNAs (miRNAs) and histone modification [35]. Epigenetic changes can also occur in response to cellular signaling, environmental factors and normal cellular process and thus, play a role in all facets of cellular functions

such as replication, cell progression damage repair, transcription, metabolism, migration and survival [36].

In this review, we will provide a comprehensive evaluation of known epigenetic regulations reported to contribute to normal placental development and placental dysfunction in PE and IUGR (Figure 1). These include epigenetic mechanisms such as DNA methylation, miRNAs and histone modifications. Recent publications are identifying potential mechanisms by which changes in maternal nutrition, maternal stress and/or other maternal environmental exposures including toxic substances can alter the expression of imprinted genes during pregnancy influencing fetal development [33,34,37]. Identification of epigenetic-based targets related to PE may identify potential biomarkers for diagnosis for the onset of PE, as well as classifying PE according to severity [38,39]. Important to the field of developmental programming of chronic disease, knowledge gained by understanding the importance of epigenetic alterations in PE that result in placental dysfunction and IUGR may lead to the identification of potential targets and novel therapeutic approaches to alleviate fetal growth restriction and mitigate increased risk for chronic disease in the offspring.

Developmental programming of chronic disease: historical perspective

The theory of Developmental Origins of Health and Disease (DOHaD) states that exposure to a suboptimal prenatal and early postnatal environment during critical periods of early life or development led to an increased risk of chronic diseases [40]. In 1989, Dr. David Baker demonstrated an inverse correlation between birthweight and BP in children [41] followed by a second study that reported an inverse relationship between birth weight and subsequent death later in life from coronary heart disease [42] highlighting that events in early life have long-lasting effects on CV health. The current literature surrounding the theory of developmental origins of long-term health reaches far beyond CV disease. Diabetes, obesity, metabolic syndrome, asthma and psychiatric diseases are all associated with poor fetal growth due to an impoverished *in utero* environment [43]. Therefore, considering the burden of CV disease alone, it is clear that adverse events during prenatal life including fetal exposure to PE have great potential to affect the chronic health of our population. The underlying etiology of developmental origins of chronic diseases including CV risk is multifactorial and in PE, involves many complex mechanisms such as fetal malnutrition and exposure to placental hypoxia.

Developmental programming of chronic disease: origins in PE

PE alters normal placental development during pregnancy resulting in short- and long-term complications for both the mother and the offspring. The placenta is the primary interface between the mother and fetus and plays a large role in regulating nutrient supply to the developing fetus [22,44]. Nutrients responsible for proper fetal development include oxygen, glucose, amino acids and fatty acids, which are all under tight regulatory mechanisms [44,45]. These regulatory mechanisms include epigenetic modifications such as DNA methylation and demethylation, miRNAs and histone modifications, which can alter placental development resulting in alterations in nutrient supply in PE [46]. LBW due to fetal undernutrition is an underlying cause of asymmetric growth and increased CV risk in

later life [47]. Placental dysfunction that occurs in response to placental hypoxia during PE altering fetal oxygen delivery to fetus also contributes to IUGR [48].

Developmental programming of chronic disease: clinical relevance

Numerous clinical and experimental studies report an inverse relationship between adverse events in early life such as PE and later chronic disease including CV risk. Offspring from women with PE have higher BP [7]. Experimental models that mimic the etiology of PE provide proof of principle and demonstrate sex- and age-specific differences in increased BP and CV risk in the IUGR offspring [49–51]; an observation also reported in offspring from human PE [9–15,18,52]. Yet, the origins of placental dysfunction, the critical mediator of poor fetal growth and the causative event in the *in-utero* programming of increased CV risk in the offspring, remains unclear.

Compelling evidence suggests that the time of development extending from conception, pregnancy, birth and infancy is very sensitive to interactions between the genome and the environment and contributes to lifelong consequences in the offspring [53,54]. As shown by both animal and human studies, early translation patterns of the genome play a major role in regulating one's life trajectories that condition an individual for greater risk for chronic diseases [55–60]. During development, environmental stimuli determine not only short-term, but also long-term and transgenerational heritable traits due to epigenetic imprinting [58,61]. Thus, epigenetic processes play a major role in the regulation of placental development and the physiology of the fetus in normal pregnancy and PE [29].

DNA methylation

DNA methylation, the most common epigenetic mechanism, is the process of adding additional methyl groups co-valently to a cytosine that usually lies in cytosine-phospho-guanine (CpG) dinucleotide sites. CpG sites occur with high frequency in genomic regions called CpG islands and are common targets for transcription factors [62]. Almost half of the human genome including many housekeeping genes contain CpG islands [63]. DNA methylation is a biochemical process performed by DNA methyltransferases (DNMTs), enzymes that play important roles in development and growth in all high-level organisms [62]. DNA methylation is a heritable epigenetic marker that is linked to many important physiological processes such as gene regulation, genomic imprinting and repression of transposable elements [62]. It also plays a critical role in many important cellular functions including embryonic development, transcription, chromatin structure and X-chromosome inactivation [62]. DNMT1 is the predominant mammalian DNA methylating enzyme responsible for the restoration of hemi-methylated sites into fully methylated site referred to as maintenance methylation. DNMT3A and DNMT3B are mainly involved in DNA methylation of new sites also referred to as *de novo* methylation. DNA methylation inhibits transcription or post-transcriptional RNA degradation resulting in gene silencing of its downstream targets [64].

DNA methylation during PE: role of the placenta

Many studies reveal altered gene expression in placentas from women with PE [65]. In a study by Vaiman et al. the promoters of numerous transcription factors that play a major role in cell responses to inflammation, hypoxia, DNA damage and cell proliferation were either up- or down-regulated [65] suggesting important roles for these genes in the etiology of PE. Up- or down-regulation of gene expression in PE may involve in part, epigenetic changes that arise in response to the abnormal placental environment. The placenta in PE is characterized by hyperoxia and an increase in reactive oxygen species (ROS) [66]. Mayne et al. identified 62 sites of aberrant DNA methylation that were associated with accelerated placental aging in early PE [67]. Therefore, oxidative stress could be driving the accelerated aging phenotype of trophoblast cells, which could be one of the many mechanisms disrupted in the placental environment in women with PE [68]. Most studies that report changes in DNA methylation related to gene expression of factors critical to placental development in PE are correlative [69]. One example from a recent study by Almomani et al. using stringent analysis of publicly available DNA methylation datasets showed significant differential methylation of CpG island methylator phenotype (CMIP) in two different validated PE cohorts [69]. However, using a cell line derived from first trimester human extra-villous trophoblast cells (EVTs), the HTR8/SVneo cell line, Wang et al. demonstrated that inhibition of CMIP using a small interfering RNA (siRNA) inhibitor was associated with increased expression of vascular endothelial growth factor A (VEGFA), VEGFC, *hypoxia-inducible factor 1*-α (HIF1α) and RELA proto-oncogene RelA [70]. Increased expression of these genes is indicative of hypoxia and an imbalance of angiogenic/anti-angiogenic factors critical to the etiology of PE. Collectively, these studies indicate that epigenetic changes are associated with markers of hypoxia and placental insufficiency, hallmarks of PE.

Other studies suggest a direct importance for DNA methylation in trophoblast differentiation. Placental adenosine levels are elevated in patients with PE [71]. Huang et al. reported elevated adenosine-induced DNA hypomethylation in cultured human trophoblasts and in a mouse model of PE induced by exogenous autoantibodies [72]. Through a genetic deletion that prevented an increase in adenosine in their mouse model of PE, Huang et al. also demonstrated that a reduction in adenosine prevented the features of PE including increased BP in conjunction with amelioration of hypomethylation of trophoblasts [72]. Findings from this study suggest that adenosine, a critical signaling molecule that becomes dysregulated in response to hypoxia, contributes to abnormal trophoblast invasion via epigenetic processes related to changes in DNA methylation of targeted tissues critical to the pathogenesis of PE. Changes in gene expression are also linked to early events with a critical role for homeobox gene regulation. The homeobox gene family (HOX) plays a significant role in placental development. HOX genes show variable methylation patterns across gestation, with a trend towards an increase in methylation over the length of gestation [73]. Of the many HOX genes, TLX1, HOXA10 and DLX5, showed an increase in DNA methylation that corresponded to decreases in mRNA expression in late pregnancy [74,75]. Down-regulation of these genes using siRNA in cell culture in primary villous CTs from uncomplicated term pregnancies led to a loss of proliferation and an increase in the differentiation markers [74]. Yet, Zadora et al. reported that placental expression of DLX5

is up-regulated in approximately 70% of a patient cohort with PE [75]. Furthermore, Zadora et al. showed that up-regulation of DLX5 in first semester trophoblast cells was associated with a reduction in cell proliferation [75]. Collectively, these studies suggest that DNA methylation is involved in proper placental development but in a manner, that is gestational timing specific.

DNA methylation also plays a role in placental physiology. For example, the regulation of the plasma concentration of biologically active vitamin D is epigenetically uncoupled during pregnancy [73]. Biologically active vitamin D regulates immunomodulation, calcium homeostasis, cellular differentiation and apoptosis [76]. During pregnancy, DNA methylation down-regulates promoter activity of vitamin D hydroxylase (CYP24AI) abolishing vitamin D-mediated feedback activation [73], allowing for significantly elevated levels of vitamin D in the maternal circulation and playing a positive role in pregnancy progression. Vitamin D deficiency increases the risk of PE [77]; yet vitamin D dietary intake does not differ in PE. A study from Anderson et al. reported that changes in DNA methylation were associated with changes in protein expression for placental genes involved in the regulation of vitamin D metabolism [78] providing support for the importance of DNA methylation as a mediator of placental dysfunction in PE.

DNA methylation during PE: severity and onset of disease

Genome-wide studies are another approach that show different methylation patterns in placenta from women who have early-onset or late-onset PE, suggesting a difference in the etiology of these two types of PE [79–81]. Early-onset PE demonstrates an increase in genome-wide hypermethylation changes when compared with late-onset PE women [81]. Furthermore, Yeung et al. identified 303 differentially methylated regions in women with PE, with 214 of them being hypermethylated and 89 of them being hypomethylated [82]. Genes, which were found to be located within these hypermethylated areas using the Kyoto Encyclopedia of Genes and Genomes pathway database resource, were revealed to be associated with ATP transport, steroid hormone biosynthesis, cellular senescence and apoptosis [82]. Further annotations of cluster analysis from Yeung et al. study showed alterations in clusters in HOX genes, Wnt Family Member 2 (Wnt2) signaling, fertilization and implantation genes, ROS signaling and cell adhesion [82]. Wnt2 expression is decreased in women with PE [83]. Mice deficient in Wnt2 have placental defects such as a high rate of fetal loss, reduced vascularization and poor remodeling of the spiral arteries [84]. Therefore, increased placental DNA methylation is reported for the Wnt2 promoter region in PE implicating a potential mechanism for the decrease in proper trophoblast invasion and remodeling of the spiral arteries.

Metalloproteinases (MMPs) are a group of well-characterized proteins, which are involved in trophoblast invasion and angiogenesis during pregnancy [85]. This family of proteins consist of 23 Zn^{2+}- and Ca^{2+}-dependent proteases, which degrade the extracellular matrix [85] with dysregulation of MMP expression associated with placental disorders such as PE [86]. A decrease in MMP2 and MMP9 is associated with a reduction in spiral artery remodeling in early gestation [87]. Methylation of the promoter for MMP9 is elevated in women with PE suggesting a potential mechanism involved in the down-regulation of

MMP9 and hence, a contributor to shallow trophoblast invasion [88]. The methylation pattern for placental TIMP3, an MMP inhibitor is reduced in early onset PE [89]. Moreover, TIMP3 may be able to inhibit angiogenesis by blocking VEGF binding to its receptor, resulting in impaired vascular development [90]. Many other placental genes involved in tumor suppression, cell adhesion, cell differentiation, trophoblast differentiation and/or invasion and cell signaling are altered by DNA methylation in PE. These genes include hypomethylation of SERPINB5 [91], DLX5 [89], FN1 [92], NDRG1 [92], BHLHE40 [79], INHBA [79], CYP11A1 [93], SH3PXD2A [94] and NCAM1 [95] and hypermethylation of insulin-like growth factor 1 (IGF-1) [96], CDX1 [97], WNT2 [82], CDH11 [95] and COL5A1 [95]. Although the direct importance of altered methylation status in PE placentas is not clear, these studies highlight the need for future studies to explore cause and effect for the importance of DNA methylation as a contributor to the etiology and severity of PE.

DNA methylation: fetal growth and chronic disease

The risk of chronic disease can also occur in pregnancies not complicated by PE. Placenta 11-β-hydroxysteroid dehydrogenase (11BHSD) converts active cortisol into an inactive form, and is the proposed mechanism thought to protect the fetus from overexposure to maternal glucocorticoids. Jahnke et al. reported that maternal stress during pregnancy was associated with an increase in methylation of placenta 11BHSD that was associated with a decrease in placental 11BHSD expression and exaggerated cortisol reactivity to stress in infants [98]. Using a placental epigenome-wide association study, Tekola-Aylel et al. identified birthweight-associated CpGs that were associated with lower birth weight and Type 2 diabetes in adulthood [99]. Collectively, these studies suggest that alterations in placental DNA methylation may contribute to fetal growth and the developmental origins of chronic disease.

DNA demethylation

In addition to methylation, demethylation contributes to trophoblast differentiation and development. Jumonji C domain-containing protein 6 (JMJD6) serves as a novel oxygen sensor and histone demethylase. Alahari et al. reported that placental JMJD6 demethylase activity is significantly reduced in PE in conjunction with a reduced expression of von Hippel Lindau (VHL), a critical mediator of proper placental development [100]. Using a model of pharmacologically induced hypoxia in the pregnant mouse, Alahari et al. demonstrated that disruption of JMJD6 and VHL were associated with impaired placental morphology and fetal growth suggesting that changes in oxygen tension moderate epigenetic regulation of VHL expression contributing to impaired placental development [100]. As stated above, an increase in methylation of the MMP9 promoter is associated with a decrease in MMP9 expression and impaired trophoblast invasion in PE. Li et al. reported that binding of the ten-eleven translocation (TET2) enzyme results in down-regulation of MMP9 [88] implicating the importance of demethylation and the TET2-MMP9 pathway in the etiology of PE.

miRNA

Non-coding RNAs (ncRNAs) are defined as an RNA molecule that is not translated into a protein product. There are several classes of ncRNAs; however, our review will focus on the importance of miRNAs [101]; a small RNA, which is reported to play a major role in placental development, physiology and pathology. miRNAs, as epigenetic modulators are a single-stranded RNA molecule consisting of 19–24 nucleotides, and their mode of action is primarily by degrading targeted mRNA transcripts or inhibiting translation of mRNA into a protein product [101]. A large number of miRNAs detected in the placenta are expressed from a gene cluster located on chromosome 19 (C19MC) [102,103]. This cluster contains 46 intronic miRNA genes, which express 58 miRNA species. In the human placenta, the expression of C19MC miRNAs are detected as early as 5 weeks of gestation [104]. Several miRNAs from the C19MC cluster are increased in vascular CTs compared with EVTs [105]. Overexpression of the C19MC cluster in the EVT cell line HTR8/Svneo results in reduced migration suggesting a potential role for the C19MC cluster as a mediator of decreased trophoblast migration, a reduction in spiral artery remodeling and placental ischemia in PE [105]. Chromosome 14 miRNA cluster (C14MC), another miRNA cluster found in the placenta, includes miR-127, miR-345, miR-370, miR-431 and miR-665, which are involved in the regulation of key physiological process such as immune suppression, anti-inflammatory response and also hypoxia-induced response [106]. However, unlike C19MC, C14MC expression decreases as pregnancy progresses [106] indicating that up- or down-regulation of numerous miRNAs contribute to proper placental development and function.

Many miRNAs also contribute to placental development by regulating genes associated with the regulation of trophoblast fate, invasion and differentiation. These include Let-7a, miR-17, miR-106a, miR-106b, miR-145, miR-155, miR-377, miR-141-3p, miR-200a-3p and miR-431, [107,108]. For example, miR-431 inhibits trophoblast invasion by inhibiting the expression of the ZEB1, a transcription factor critical to cellular differentiation and embryonic development [109]. miR-155 increases placental ROS by inhibiting the expression of the endothelial nitric oxide synthase (eNOS) gene [110]. miR-106a inhibits trophoblasts differentiation by targeting estrogen synthases, and by targeting a member of the Cytochrome P450 Family, CYP19A1 in addition to Glial Cells Missing Transcription Factor 1 (GCM1), which are responsible for mediating trophoblast differentiation [111]. miR-34 targets the serine protease inhibitor SERPINA3, a gene involved in the regulation of placental regulation and is often dysregulated in placental disorders such as PE [112]. To conclude, miRNAs contribute to a diverse array of placenta processes including trophoblast physiology, differentiation and invasion.

miRNA and PE

One of the first studies related to miRNAs in PE published in 2007 reported that placental miR-210, miR-155 and miR-200b were up-regulated in women with PE [113]. The first global transcriptomic analysis of miRNAs was performed using microarray technology in 2009. In this study, comparison of gene expression profiles from women with severe PE to controls showed that 11 miRNAs were up-regulated and 23 were down-regulated

[114]. Furthermore, among these miRNAs, their expression was organized into unique chromosome clusters. Down-regulated placental clusters in PE included 13q31.3, 14q32.31, Xq26.2 and Xq26.3, while up-regulated placental clusters included 19q13.42 [114]. The goal of these initial studies was to identify an miRNA regulatory network that could lead to a better understanding of miRNA–gene interactions that contribute to aberrant placental development and the pathogenesis of PE [115]. Many similar studies followed; yet direct correlation remained a critical missing component hindering potential importance and identification of targets for treatment and prevention.

miRNA: placental angiogenesis

Clinical and experimental studies indicate an important role for placental angiogenesis during pregnancy that ensures adequate blood flow from the placenta to the fetus providing substrates for normal fetal development [116]. Therefore, any disruption in angiogenesis in the placenta that contributes to impaired fetal growth resulting in LBW can contribute to increased CV risk in the offspring [116]. Numerous miRNAs involved in angiogenesis that target pro-angiogenic factors are dysregulated in PE. Li et al. reported that miR-144 and miR-29a are overexpressed in PE [117]. Studies by Zhao et al. reported that miR-16 and miR-144 are increased in women with PE [118]. Using reporter assays, Zhao et al. showed that miR-16 and miR-144 targeted VEGFA [118], a positive regulator of angiogenesis and major contributor to vascular endothelial cell growth, blood vessel production and vascular permeability [119]. Wang et al. also showed that miR-16 is up-regulated in women with PE, and importantly, that overexpression of miR-16 in decidua-derived mesenchymal stem cells (dMSCs) reduced viability and proliferation activity [120]. Transfection of dMSCs with an anti-miRNA-16 showed increased viability [120]. Collectively, these studies implicate a potential role for miRNAs in the pathogenesis of PE (Table 1).

Ephrin B2, an Ephrin ligand, and Ephrin type B receptor 4 (EPHB4), an Ephrin receptor, interact to mediate vascular cell adhesion, repulsion and migration [121,122]. The pro-angiogenic functions of Ephrin-B2 are carried out by regulating the internalization and signaling of VEGF receptor 2 (VEGFR2) and VEGFR3 [121]. Wang et al. reported that placental miR-17, miR-20a and miR-20b are up-regulated in PE [123]. Furthermore, using *in silico* analysis, they showed that miRNA target prediction databases identified EPHB4 as a target gene of miR-17, miR-20a and miR-20b; and importantly, that Ephrin B2 was a direct target of miR-20b as determined by luciferase reporter activity [123] (Table 1). Other targets identified by *in silico* analysis included other genes that are important in placental angiogenesis including HIF1α, VEGFA, MMP2, TIMP2, interleukin-8 (IL-8), and transforming growth factor β (TGF-β) [124]. HIF1α, a transcription factor induced in response to hypoxia, regulates genes such as VEGFA highlighting its importance in the regulation of placental remodeling in normal pregnancy and a potential role in the pathogenesis of PE. MMP2 and TIMP2 also play a major role in remodeling of the spiral arteries in early gestation and are critical in the regulation of the extracellular matrix during the initial angiogenic response in early gestation add [125–127]. Therefore, in PE increases in miR-17, miR-20a and miR-20b may act in conjunction to down-regulate many genes involved in angiogenesis such as HIF1α, VEGFA, MMP2, TIMP2, IL-8 and TGF-β,

inhibition of factors critical to cellular matrix remodeling and trophoblast proliferation, invasion and remodeling of the spiral arteries (Table 1).

Unlike miR-144, miR-29a, miR-17, miR-20a and miR-20b, which are up-regulated in PE and associated with anti-angiogenic properties, placental miR-126 is down-regulated in PE [128]. Numerous studies indicate that miR-126 exhibits pro-angiogenic properties [129–131]. Fish et al. and Harris et al. reported that overexpression of miR-126 is associated with down-regulation of vascular cell adhesion molecule-1 (VCAM-1), in addition to down-regulation of other targets such as sprout-related EVH1 domain containing protein 1 (SPRED1) and phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2) [129,130] (Table 1). VCAM-1 is a master regulator of angiogenesis, whereas SPRED1 and PIK3R2 play a major role in the VEGF pathway [129,131]. Fish et al. also reported that knockdown of miR-126 in mouse embryonic endothelial cells is associated with impaired vascular integrity [129]. Hong et al. reported that a decrease in miRNA-126 expression in PE is associated with a reduction in VEGF expression [132] (Table 1). Collectively, these studies suggest that the VEGF pathway is regulated at different levels by miRNA-126, and that miRNA-126 is inversely associated with angiogenic properties in PE [128] (Table 1).

miRNA: placental renin–angiotensin system

In normal pregnancy renin, aldosterone and ANG II are increased while pregnant women remain normotensive because they are desensitized to ANG II-mediated vasoconstriction [133]. In contrast, studies report sensitivity to ANG II is enhanced in PE despite no additional increase in circulating ANG II [134]. An immune-mediated pathway that involves increased production of an AT1R-specific agnostic antibody, the AT1-AA [135] is the culprit and exogenous administration of AT1-AAs from pregnant women in a pregnant rodent results in hypertension, proteinuria, placental abnormalities and glomerular endotheliosis [136] implicating its importance in the pathophysiology of the disease. The binding of AT1-AAs to the AT1R induces production of sFlt-1 and sEng [135,137]. AT1-AAs also induce apoptosis in the placentas of pregnant mice, human villous placental explants and trophoblast cells [137]. In women with PE, increased levels of AT1-AAs are also associated with increases in sFlt-1 and decrease in VEGF [137]. In addition, AT1-AAs also are linked to increased IL-6 production, endothelin and stimulation of placental oxidative stress [138].

miRNAs contribute to regulation of the RAS and production of the AT1-AA. Teng et al. reported that miR-155 binds directly to the 3′UTR of AT1R [139]. They also demonstrated that targeted disruption and down-regulation of miR-155 was associated with increased AT1R expression and enhanced ANG II-mediated activation of phospo-ERK1/2 (Table 2). However, miR-155 expression in PE is controversial. Although, while some studies report that miR-155 is decreased in PE [140], many more show an increase in placental miR-155 [113,132,140] suggesting tissue-specific expression of miR-155 and timing of gestation may influence the critical role of this miRNA in the etiology of PE (Table 2). To add to the complexity, regulation of AT1R and AT1-AA involves other miRNAs. Sansom et al. indicate that miR-802 directly interacts with AT1R within the intestinal epithelium [141]. However, there are no reports linking miR-802 with PE. Moreover, several studies report that circulating and placental levels of miRNA-181a are up-regulated in PE [142–

144]. A report by Liu et al. showed that up-regulation of placental miRNA-181a in PE is associated with an increase in mRNA expression of IL-6 [142], a factor also correlated to AT1-AA in PE [145,146] and the well-established and clinically relevant Reduced Uterine Perfusion Pressure (RUPP) model of PE [147] (Table 2). Moreover, Liu et al. showed that miR-181a enhances mRNA expression of IL-6 by activating p38 and c-Jun N-terminal kinase (JNK) signaling pathways [142]. Whether these findings are correlative, or indicative of importance is not clear but highlights the complexity of PE and that additional studies are warranted to understand the importance of miRNAs in the pathogenesis of PE. AT1-AA and BP are increased in response to infusion of IL-6 in the pregnant rat [145] suggesting that IL-6 stimulates production of AT1-AA, and that the activation of AT1R meditates IL-6-induced PE. miR-1301, which is found to be decreased in women with PE, results in the up-regulation of IL-6 production and leads to an increase in AT1-AA levels [148]. In addition, a decrease in miR-1301 is associated with an increase in maternal BP [148] (Table 2). Taken together, these studies provide significant support for miRNA involvement in RAS dysregulation during PE.

miRNAs: placental NO production

NO is a biological product synthesized from L-arginine by NOS. NO is a major regulator of vascular resistance and hemodynamic changes during normal pregnancy and PE. In normal pregnancy there is an increase in NO and NOS [149]. Choi et al. reported that circulating levels of NO, placental NOS activity and nitrate and nitrite are significantly lower in PE [149]. Weber et al. using human endothelial cells demonstrated that shear stress is associated with increased expression of miR-21 [150]. In this study, phosphorylation of eNOS and NO production are increased suggesting activation of the NO-NOS pathway [150]. Interestingly, women with PE show an increase in miR-221 and miR-222, but show a decrease in NO production [144].

Placental levels of miRNA-155 are also increased in PE [113,140], miRNA-155 is indicated to contribute to the regulation of eNOS [110]. Kim et al. showed that overexpression of miR-155 in HUVECs is associated with a decrease in eNOS expression and NO production whereas inhibition of miR-155 is associated with an increase in eNOS [110] (Table 3). Shen et al. also showed that miR-155 is overexpressed in sera from women with PE [151]. This study also demonstrated that exposure of human placenta-derived BeWo cells to sera from women with PE suppresses eNOS expression by miRNA-155 targeting the 3′UTR of eNOS [151] (Table 3). Thus, these studies suggest a causative role for miRNA-155 in the pathogenesis of PE. Yet, Kim et al. reported that up-regulation of serum levels of sEng, sFlt-1 and PIGF were associated with increased circulating levels of NO despite an increase in serum levels of miR-155 [110]. Only circulating, not placenta-specific differences in these factors were reported in this study highlighting that the contribution of miR-155 may be tissue-specific. Thus, findings from these studies suggest that down-regulation of placental eNOS by miRNA-155 may contribute to decreased placental NO production resulting in IUGR and increased CV risk in offspring.

miRNAs: regulation of trophoblast function

One of the leading causes of IUGR in PE is inadequate trophoblast invasion and remodeling of the spiral arteries. Numerous studies demonstrate that miR-195, miR-376c or miR-378a-5p promote proliferation and invasion in trophoblast cells and placental explants by targeting components of the TGF-β pathway that include the Activin type II receptor (ActRIIA), activin receptor-like kinase 5 (ALK5) and Nodal [152–154]; respectively. MiR-195 and miR-376 are down-regulated in women with PE [155,156]. Bai et al. showed that miR-195 is down-regulated in PE [152] (Table 4). Moreover, this study reported that targeting of ActRIIA by overexpression of miR-195 in HTR8/SVneo cells promoted cell invasion [152]. Fu et al. demonstrated that circulating and placental levels of miR-376c are reduced in women with PE [153]. Moreover, this study showed that overexpression of miR-376c in HTR8/SVneo cells promoted trophoblast cell proliferation, migration and invasion by suppressing ALK5, Nodal and the TGF-β pathway [153] (Table 4). Luo et al. showed that inhibition of miRNA-378a-5p in placental explants decreased trophoblast cell invasion and placental explant outgrowth by suppressing the TGF-β/Nodal/ALK pathways [154] (Table 4). Taken together, these studies suggest that suppression of these miRNAs may be one mechanism that contribute to a reduction in proliferation and invasion of the spiral arteries in PE.

Although these studies implicate an important role for miR-195, miR-376c and 378a-5p, other studies indicate an important role for other miRNAs including miR-299, miR-181a and miR-134. Targets of these miRNAs include HDAC 2, IGF2 and integrin β1 (ITGβ1), factors that play a pivotal in placental biology [157,158,159,160]. Expression of miR-299 is elevated in women with PE [157]. Furthermore, this study by Gao et al. showed that overexpression of miR-299 in HTR-8/SVneo cells suppressed HDAC2 expression in conjunction with suppression of trophoblast cell invasion and migration [157] (Table 4). Wu et al. reported that suppression of HTR-8/SVneo cell invasion and migration involved inhibition of IGF2 by miR-181a [158]. Keniry et al. reported that suppression of cell proliferation also involved targeting of IGF2 by miR-675, the functional component of H19, an ncRNA that exerts its functionality by serving an miRNA precursor [159] (Table 4). Zou et al. reported miR-134 suppressed trophoblast cell infiltration by targeting ITGβ1, an effect that was abolished with miR-134 inhibition [160] (Table 4). PE is associated with up-regulation of circulating and placental miR-181a and miR-134 [142–144,158,160] suggesting critical roles for these miRNAs in the etiology of PE. Yet, other miRNAs are also indicated in the regulation of trophoblast cell invasion and migration highlighting the complexity of placental development and the pathogenesis of PE

Li et al. showed that up-regulation of miR-29b induced trophoblast apoptosis and inhibited trophoblast invasion and angiogenesis in HTR-8/SVneo and BeWo cells by directly binding to the 3′UTR of myeloid cell leukemia sequence 1 (Mcl-1), MMP2, VEGFA and ITGβ1 [161] (Table 4). Importantly, this study also showed an inverse relationship with miR-29b and these target genes in PE [161] suggesting clinical relevance for this miRNA in the pathogenesis of PE. Wang et al. reported that miR-20a is up-regulated in placentas from women with PE [162]. This study, using the trophoblast cell line JEG-3 cells, also reported that overexpression of miR-20a resulted in inhibition of cell proliferation and migration by

suppression of Fork head Box Protein A1 (FOXA1) mRNA and protein expression [162] (Table 4).

Niu et al. reported that miR-30a is overexpressed in placentas of patients with PE and that up-regulation of miR-30 in HTR-8/SVneo cells suppressed IGF-1 mRNA and protein expression in association with increased apoptosis PE [163]. This study also demonstrated that overexpression of miR-30A in JPEG cells reduced cell invasion [163] (Table 4). Gao et al. showed that overexpression of miR-4421 involved down-regulation of the aldosterone synthase gene (CYP11B2) resulting in inhibition of trophoblast proliferation and blockade of cell cycle progression [164] Placental miR-4421 is also highly expressed in PE [164] suggesting a role for yet another miRNA in the etiology of impaired placental development in PE. Although reporting of increased expression of miRNAs in PE is correlative, use of trophoblast cell lines such as HTR-8/SVneo or JPEG provide evidence for a causative role. However, use of cell lines may not mimic the physiology of the placenta in PE implicating that additional studies are needed to confirm the importance of miRNAs in the etiology of placental dysfunction in PE. Clearly, the mechanisms that regulate placental trophoblast invasion are complex in normal pregnancy and even more so in PE. To conclude, numerous studies to date suggest that miRNAs play a major role in placental development by regulating placental angiogenesis, the RAS, NOS and NO production, and the regulation of trophoblast function during normal pregnancy and aberrant placenta development in PE.

Histone modifications

Histone modifications are an epigenetic process, which modify histone proteins by enzymes that include post-translational modifications such as histone methylation, acetylation, phosphorylation and ubiquitination. Histone modifications alter gene expression by modifying the degree of chromatin compaction [165], in particular by acetylation of histone H3 and H4 on specific lysine (K) and arginine (A) residues [165]. Histone lysine methylation can lead to activation or inhibition depending on the location of methylation. For example, methylation of Histone H3 Lysine 9 (H3K9), H3K27 and H4K40 are considered inactivation markers and are associated with condensed and transcriptionally inactive chromatin, whereas methylation of H3K4 and H3K36 are considered activation markers and are associated with active transcription [166]. Acetylation at the N-terminal of lysine residues is carried out by histone acetylase (HATS) and are generally associated with activation of the chromatin; whereas histone deacetylation (HDAC) of lysine residues is carried out by HDACs and leads to chromatin condensation and inactivation of gene transcription [165].

Epigenetic modifications, including histone modifications, are altered in response to changes in the environment. During pregnancy, epigenetic modifications can occur in response to hypoxia, an important regulator of placental and fetal development [167]. Utilizing both *in vitro* and *in vivo* approaches, Wellman et al. reported that hypoxia up-regulates histone demethylase Jumonji domain containing 1A (JMJD1A) [167]. Regulation of HDAC2 is also controlled in response to hypoxia [167]. For both, HIF1α plays a critical role in the regulation of these hypoxia-regulated HDACs [167,168] resulting in epigenetic modifications to the DNA packaging protein Histone H3 and transactivation of target

genes, which could further aggravate the PE phenotype [167,169]. HIF1α also plays an important role in trophoblast differentiation by different mechanisms suggesting that cross-talk between HIF1α and HDACs is required for normal trophoblast differentiation [169,170]. Trophoblast fusion is an essential step that maintains syncytiotrophoblasts, a specialized layer of epithelial cells that are in direct contact with maternal blood. Syncytin, a major regulator of *syncytiotrophoblast formation*, is controlled by several different pathways including regulation by the placenta-specific transcription factor, glial cell missing a (GCMa). Regulation of GCMa involves HATS and HDACs [171] with acetylation of GCMa controlled by the cAMP Response Element-Binding Protein (CREB) to activate the cAMP/PKA pathway to stimulate trophoblast fusion [171]. MMPs and TIMPS are also major regulators of trophoblast invasion with differential expression of MMPS and TIMPS associated with H3K9/29me3 [172]. Thus, numerous studies indicate that histone modifications play a critical role in normal placental development. However, few studies address the importance of histone modifications in PE. Using human placental cell lines and placentas from the RUPP rodent model of placental insufficiency, Eddy et al. reported acetylation of histone H3 is decreased and DNA methylation is significantly increased in response to oxygen conditions that mimic hypoxia and placental ischemia in PE suggesting that epigenetic processes within the placenta are modulated by hypoxia [173]. Chymase, a non-ACE angiotensin-converting enzyme implicated in inflammation and vascular dysfunction is elevated in women with PE [174]. Wang et al. showed that inhibition of HDAC is associated with an increase in chymase expression suggesting that alterations in HDAC expression could contribute to placental dysfunction in PE [174]. Clearly, epigenetic processes such as histone modifications contribute to normal placental development. Yet, their role in PE remains unclear highlighting the need for additional studies in order to fully understand how histone modifications not only play a role in the onset and progression of PE, but also the development of IUGR, which is associated the developmental origins of chronic disease in the offspring.

Genomic imprinting

Mammals have imprinted genes which are found to regulate placental development and fetal growth [175]. Most mammals express their autosomal genes co-dominantly from two parental chromosomes. However, in genomic imprinting the allele inherited from one parent is suppressed through epigenetic processes resulting in an imprinted, or mono-allelic expression that is specific to one parent of origin [175]. Mono-allelic expression is the result of differential epigenetic processes including DNA methylation, histone modification and miRNAs [176]. Recent reports suggest there are close to 200 genes that are subjected to imprinted expression [176,177]. The placenta in particular is important in the physiological event of imprinting because of its role in regulation of fetal growth and development. Zadora et al. reported that due to a loss of imprinting, DLX5 is up-regulated in PE and associated with impaired proliferation [75]. Barbaux et al. identified Down Syndrome Cellular Adhesion Molecule (DSCAM) as an imprinted gene in human placenta [177] suggesting a role for promotion of fetal growth. Moore et al. reported that genetic imprinting that silences one of the parental alleles contributes to fetal growth with paternally expressed genes such as IGF-1 and its receptor facilitating fetal growth, whereas maternally expressed

genes such as Pleckstrin homology-like domain family A member 2 (*PHLDA2)* acts negatively to reduce fetal growth [178]. Bi-allelic overexpression of PHLDA2 (or expression on both alleles) in the mouse is associated with an increase in placental development during mid- to late-gestation [179,180]. However, a single copy of PHLDA2 in a transgene mouse is associated with a reduction in the placental junctional zone and a decrease in glycogen content, both factors associated with IUGR [181]. In humans, PHLDA2 expression in the placenta correlates with birth weight [181]. Collectively, these studies suggest a role for imprinted genes in the etiology of PE and IUGR. However, much more research is warranted to determine if imprinted PE associated genes exist in the human genome.

Clinical relevance: IUGR and the developmental origins of chronic disease

The DOHaD theory includes the study of how the environment during fetal life programs an increased risk for chronic diseases across the lifespan. The placenta serves as the boundary between the maternal and fetal circulations and thus, plays a vital role in the delivery of nutrients including oxygen to the developing fetus [182]. The placenta is sensitive to environmental stressors including hypoxia and numerous studies implicate epigenetic processes as potential mediators of impaired placental development in PE. PE is a leading contributor to IUGR and numerous preclinical models that mimic the pathogenesis of PE demonstrate that IUGR offspring exhibit sex- and age-specific increases in BP and CV risk [49,183–185]. Therefore, epigenetic processes that result in the disruption of normal placental development may be the underlying mechanisms that link placental dysfunction to IUGR and the developmental origins of chronic disease (Figure 1).

A systematic review and meta-analysis of the literature by Ladzam et al. in 2012 reported that children born to PE women have an increased BP even in young childhood [12]. Moreover, in addition to increased BP, BMI was also increased [12]. Geelhoed et al. showed that increased BP in children born to mothers with PE was independent of familial adiposity [11]. An extensive systemic review by Hoodbhoy et al. in 2021 also reported lower birth weight in children of mothers with PE associated with increased systolic and diastolic BP [186]. Moreover, using the Helsinki birth cohort, Kajanite et al. reported that the risk of stroke is almost double in adult offspring [187].

Numerous preclinical models that mimic the etiology of PE also demonstrate CV risk is elevated in offspring exposed to placental insufficiency, prenatal hypoxia or excess sFlt-1, hallmarks of PE. Using the RUPP rodent model of PE induced by placental ischemia, the initiating event in PE, Alexander et al. showed that male IUGR offspring develop a significant increase in BP in young adulthood whereas female counterparts remain normotensive [49]. However, female IUGR offspring from RUPP dams do not stay normotensive across their lifespan; BP is increased in female IUGR offspring by 12 months of age [188]. Moreover, female IUGR exhibit early reproductive aging [189] which is also reported in LBW women [190]. Other models of developmental insult including fetal exposure to a maternal low protein diet report similar findings implicating common outcomes despite differences in fetal insult [191]. In another rodent model of PE induced via exposure to maternal hypoxia, male but not female IUGR offspring demonstrate vascular dysfunction in young adulthood [182]; however, male and female IUGR offspring develop

pulmonary hypertension by 12 months of age although only male IUGR offspring exhibit left ventricular hypertrophy [192]. The prevalence of hypertension is significantly elevated in LBW women by the age of 50 [193], suggesting that age exacerbates increased CV risk that originates *in utero*. Clearly, understanding the etiology of placental dysfunction is warranted in order to identify novel therapeutic targets for PE that also benefit the developmental fetus mitigating increased risk CV.

Recent studies indicate that epigenetic processes also contribute to the etiology of increased CV/renal risk in IUGR offspring after birth. For example, in a model of fetal insult induced by placental insufficiency, Doan et al. reported that Dnmt3a expression and imprinted gene cyclin-dependent kinase inhibitor 1C (Cdkn1c) expression are decreased in IUGR offspring at embryonic day 20 and post-natal day 1 [194]. Lv et al. miR-206 inhibits potassium voltage-gated channel subfamily A member 5 in pulmonary arterial smooth muscle cells in a rat model of IUGR associated with chronic hypoxia-induced pulmonary artery hypertension [195]. In addition, Ke et al. showed that IUGR induced via bilateral uterine ligation was associated with sex-specific and gestational day differences in DNA methylation and histone acetylation [196] suggesting that epigenetic processes are altered in IUGR offspring in a manner that is sex-specific. Bogdarina et al. reported that fetal exposure to maternal low protein diet is associated with undermethylation of the adrenal AT1B receptor in offspring that exhibit an increase in BP by 4 weeks of age [197]. However, in this study, undermethylation of the adrenal AT1B receptor was reversed by maternal exposure to an 11 β-hydroxylase inhibitor, implicating a role for maternal glucocorticoids via epigenetic processes in the developmental programming of chronic disease [197]. Taken together, these findings suggest that epigenetic mechanisms that occur in the placenta and the developing fetus during embryonic life and in IUGR offspring after birth may contribute to the developmental origins of increased CV/renal disease.

Conclusion

Epigenetic processes are known mediators of changes in gene expression. Over the past 20 years, numerous studies have investigated the role of epigenetic processes in the pathogenesis of PE, with a special emphasis on aberrant placental development. However, despite these studies the exact importance of histone modifications, miRNAs and DNA methylation in normal placenta development or their relative importance in complications related to the pathophysiology of PE and IUGR are not clear. Numerous studies suggest that epigenetic processes that are important in the regulation of trophoblast migration and invasion may be major contributors to placental dysfunction in the etiology of PE and IUGR (Figure 1). Yet, many limitations remain. Most epigenetic studies in PE have focused on ischemia in the placenta and have not investigated the influence of anti-angiogenic and inflammatory cytokines, which also have the potential to induce epigenetic changes in a global manner effecting all organ systems. Another limitation involves the few studies that have investigated the importance of epigenetic mechanisms that contribute to increased CV/renal risk in the IUGR offspring. Furthermore, there is growing evidence that PE is associated with an increased risk for future heart failure, coronary heart disease, stroke and death due to coronary heart diseases in the mother [198]. Epigenetic studies exploring increased CV risk in the mother post-partum are even more limited. Thus, understanding

how epigenetic processes contribute to maternal and fetal health during pregnancy and beyond are critical to improving the chronic health of these individuals. A comprehensive understanding of the importance epigenetic regulation in PE in the placenta as well as other organs will help identify clinical biomarkers for diagnostic and therapeutic targets in PE in order to provide benefit to the mother and her offspring, during pregnancy and across their lifespan.

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Abbreviations

ActRIIA	activin type II receptor
ALK5	activin receptor-like kinase 5
ANG II	angiotensin
AT1	ANG II type 1
BP	blood pressure
CMIP	CpG island methylator phenotype
CpG	cytosine-phospho-guanine
CT	cytotrophoblast
CV	cardiovascular
C14MC	chromosome 14 miRNA cluster
C19MC	gene cluster located on chromosome 19
dMSC	decidua-derived mesenchymal stem cell
DNMT	DNA methyltransferase
DOHaD	Developmental Origins of Health and Disease
eNOS	endothelial nitric oxide synthase
GCMa	glial cell missing a
HIF1α	*hypoxia-inducible factor 1-α*
HOX	homeobox gene family
HUVEC	human umbilical vain endothelial cells
IGF-1	insulin-like growth factor 1

IL-8	interleukin-8
ITGβ1	integrin β1
IUGR	intrauterine growth restriction
JMJD6	Jumonji C domain-containing protein 6
LBW	low birth weight
MMP	metalloproteinase
miRNA	microRNA
ncRNA	non-coding RNA
NO	nitric oxide
NOS	nitric oxide synthase
PE	preeclampsia
PIK3R2	phosphoinositide-3-kinase regulatory subunit 2
RAS	renin angiotensin system
ROS	reactive oxygen species
RUPP	reduced uterine perfusion pressure
sEng	soluble endoglin
sFlt-1	soluble fms-like tyrosine-1
siRNA	small interfering RNA
SPRED1	sprout-related EVH1 domain containing protein 1
TGF-β	transforming growth factor β
TIMP	tissue inhibitor of metalloproteinase
VCAM-1	vascular cell adhesion molecule-1
VEGFA	vascular endothelial growth factor A
VHL	von Hippel Lindau
Wnt2	Wnt Family Member 2
11BHSD	11-β-hydroxysteroid dehydrogenase

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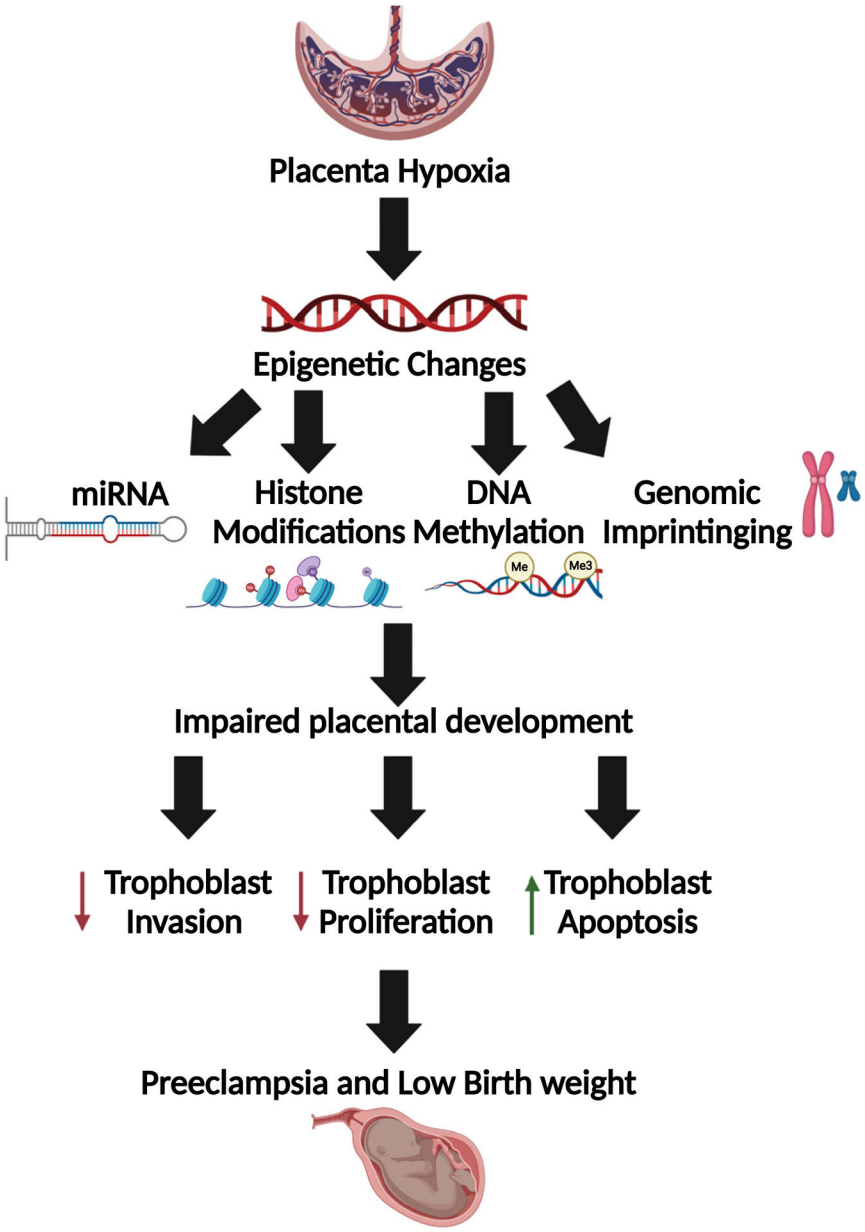

Figure 1. The pathogenies of IUGR

Summary of the effects of placental ischemia on fetal growth and how adaptive changes in epigenetic regulations such as DNA methylation, miRNAs and histone modifications as the result of placenta ischemia result in IUGR in offspring.

Table 1

Displays the differential expressed miRNAs during PE, which play a major role in placental angiogenesis

Placental angiogenesis			
miRNA	**Expression level**	**Target gene expression**	**Outcome**
miRNAs up-regulated during PE			
miR-144	Up-regulated	Down-regulation of VEGFA	Decrease trophoblast viability and proliferation
miR-16	Up-regulated	Down-regulation of VEGFA	Decrease trophoblast viability and proliferation and invasion
miR-17	Up-regulated	Down-regulation of VEGFA, HIF1α, MMP2, TIMP2, IL-8 and TGF-β, and EPHB4	Decrease trophoblast viability and proliferation and invasion
miR-20a	Up-regulated	Down-regulation of VEGFA, HIF1α, MMP2, TIMP2, IL-8 and TGF-β, and EPHB4	Decrease trophoblast viability and proliferation and invasion
miR-20b	Up-regulated	Down-regulation of Ephrin B2 and EPHB4	Impaired vascular development
miRNA down-regulated during PE			
miR-126	Down-regulated	VCAM-1, SPRED1, PIK3R2	Decrease in pro-angiogenic factors

Table 2

Displays the differentially expressed miRNAs during PE, which play a major role in the placental renin–angiotensin system

Placental Renin Angiotensin System			
miRNA	**Expression level**	**Target gene expression**	**Outcome**
miRNAs up-regulated during PE			
miR-155*	Up-regulated	Down-regulation of AT1R	Impaired development for offspring
miR-181a	Up-regulated	Up-regulation of IL-6 and AT1-AA	Increased sensitivity for AT1R
miRNA down-regulated during PE			
miR-1301	Down-regulated	Upregulation of IL-6	Increase in AT1-AA production

*Some studies show down-regulation of miR-155 during PE.

Table 3

Displays the differential expressed miRNAs during PE, which play a major role in placental NO

Placental NO			
miRNA	**Expression level**	**Target gene expression**	**Outcome**
miRNA up-regulated during PE			
miR-155 *	Up-regulated	Down-regulation of eNOS	Decreased bioavailability of NO

* Some studies show down-regulation of miR-155 during PE.

Table 4

Displays the differentially expressed miRNAs during PE, which play a major role in regulation of trophoblast function

Regulation of trophoblast function			
miRNA	**Expression level**	**Target gene expression**	**Outcome**
miRNA up-regulated during PE			
miR-29b	Up-regulated	Down-regulation of MCL-2, MMP2, and VEGFA	Decrease in trophoblast invasion
miR-30	Up-regulated	Down-regulation of IGF-1	Decrease in trophoblast invasion
miR-134	Up-regulated	Down-regulation of ITGβ-1	Decrease in trophoblast invasion
miR-299	Up-regulated	Down-regulation of HDAC2	Decrease in trophoblast invasion and migration
miR-181a	Up-regulated	Down-regulation of IGF2	Decrease in trophoblast invasion and migration
miR-675	Up-regulated	Down-regulation of IGF2	Decrease in trophoblast invasion and migration
miR-20a	Up-regulated	Down-regulation of FOXA1	Decrease in trophoblast invasion and migration
miR-4421	Up-regulated	Down-regulation of CYP11B2	Decrease in trophoblast proliferation and blockade of cell cycle
miRNAs down-regulated during PE			
miR-195	Down-regulated	Decrease in TGF-β, ACTRIIA and ALK5	Decrease in trophoblast invasion
miR-376c	Down-regulated	Decrease in TGF-β, ACTRIIA and ALK5	Decrease in trophoblast invasion
miRNA-378a-5p	Down-regulated	Decrease in TGF-β/Nodal/ALK	Decrease in trophoblast proliferation and invasion