

Epigenetic Modifications of Preeclamptic Placenta-A Systematic Review

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Abstract

We searched OVID, PubMed and Web of Science, using MSH terms related to epigenetic changes, placenta, and preeclampsia, limiting the results to humans, English language, non-review articles, and publications between 2004 to 2014. 51 out of 207 studies met selection criteria for full data extraction. Array and profiling studies were included only if their results were validated by other methods. Next, 23 of 42 articles satisfied methodological quality criteria, including gestational age-matching and/or controlling or adjusting for confounders. Then, studies with a total score <10 out of 15 quality assessment points were excluded. MicroRNAs and genes resulting from review were investigated for interactions using Ingenuity Pathways Analysis.

Ten studies met the inclusion criteria for our review: 3 concerning DNA methylation and 7 studies regarding miRNA. There were no studies on histone modification by acetylation. Seventeen differentially regulated miRNAs were identified, with three reported in two studies. Nine miRNAs were upregulated, six downregulated, one was either upregulated or downregulated depending on the severity of preeclampsia, and one had conflicting results. Our review observed nine genes that were hypomethylated, one hypermethylated, while one was found not different between groups.

IPA's microRNA analysis revealed that 16 miRNA from our list could be targeting 8,005 mRNAs. miRNAs were associated with 3 networks and 1 toxicity phenotype, hypomethylated genes with 2 networks and 5 toxicity, and one hypermethylated gene was not associated with any networks, while its toxicity list included regulation of mitochondria and renal necrosis. The common toxicity phenotype within upregulated miRNAs, downregulated miRNAs, and hypermethylated genes was associated with regulation of mitochondria.

Our review spotlights the gaps in knowledge about histone modifications associated with the preeclamptic placenta, emphasizes the importance of verifying the array results by other methods, and stresses the need to meticulously design future studies to included comparable samples groups.

Keywords: miRNA; Methylation; DNA; Placenta; Preeclampsia

Abbreviations: PE: Preeclampsia; BP: Blood Pressure; miRNA: microRNAs; EOPET: Early Onset Preeclampsia; LOPET: Late Onset Preeclampsia

Introduction

Epigenetics refers to changes in gene expression that occur without alterations in DNA sequence. These modifications can occur through various mechanisms, but most significantly, by post-transcriptional gene regulation. This form of gene regulation includes decreased gene expression through DNA methylation, silenced gene translation through microRNAs, or histone modification by acetylation, methylation, or phosphorylation. Some enzymes associated with these changes are DNA methyltransferase (DMT), Histone Acetyltransferase (HAT), Histone Methyltransferase (HMT), Histone Deacetylase (HDAC), and Histone Demethylase (HDM) [1,2].

Pregnancy, according to recent literature, is a setting in which epigenetic changes are active. Pregnancy involves significant changes in a woman's life-hormonal fluctuations, physical appearance, social adjustments, nutrition modifications, behavioral alterations, etc. Epigenetic modifications, especially during pregnancy complications, are significant as they may lead to an altered placental phenotype [2].

The quality of in utero environment is important for both the mother and fetus in later life. The idea of fetal programming, where placental environment can alter the offspring's risk of developing disease later as an adult, demonstrates the need for further insight into the specific epigenetic changes that develop during pregnancy [3].

The placental environment induced by preeclampsia has recently become the highlight of epigenetic changes in pregnancy. Preeclampsia (PE) is a life threatening medical condition that not only affects the

mother, but also endangers the fetus. More specifically, preeclampsia is the development of new onset hypertension during the second half of pregnancy that is often accompanied by new onset proteinuria. Preeclampsia may also be associated with various other signs and symptoms, including headaches, visual disturbances, epigastric pain, and rapid development of edema. According to the American Congress of Obstetricians and Gynecologists, the diagnostic criteria includes the development of hypertension, defined as a persistent systolic blood pressure (BP) of 140 mm Hg or higher or a diastolic BP of 90 mm Hg or higher after 20 weeks of gestation in a previously normotensive woman. Proteinuria is defined by the excretion of 300 mg or more of protein in a 24 hour urine collection (or this amount extrapolated from a timed collection). In the absence of proteinuria, the diagnosis of preeclampsia can be made if new onset hypertension occurs with new onset of any one of the following: thrombocytopenia with a platelet count less than 100,000/microliter, renal insufficiency defined as serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease, impaired liver function observed as elevated blood concentrations of liver transaminases to twice normal concentration, pulmonary edema, and cerebral or visual symptoms [4].

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Several studies have focused on DNA methylation changes seen in the placenta, a highly important factor in the success of fetal development. DNA methylation is an epigenetic process during which methyl groups are inserted into DNA, leading to the inhibition of transcription [5]. When the fetus is exposed to dangerous environmental factors, it can respond with significant alterations towards its growth via DNA methylation. For example, one study found that maternal smoking is associated with changes in DNA methylation of the RUNX1 gene, exerting a detrimental effect on the health of the fetus-the RUNX1 gene has been associated with childhood asthma and airway hyperresponsiveness [3].

Another form of placental epigenetics is witnessed in histone modification. Histone acetylation works to alter gene expression through post-replication chromatin assembly using specific enzymes as previously mentioned, such as HAT and HDAC. Environmental factors also play an important role here as they promote histone acetylation changes during crucial cell cycle steps [6].

Finally, microRNAs (miRNA) also hold a heavy hand in mediating placental epigenetic changes. These short, non-coding RNA segments act as silencers of post-transcriptional gene expression by base pairing with, rather than degrading, mRNA. By targeting mRNA, they are able to upregulate or downregulate gene expression, without altering the gene itself [2]. The regulation of placental development by miRNAs has been shown through the control of trophoblast cell proliferation, migration, invasion, apoptosis, and angiogenesis [7].

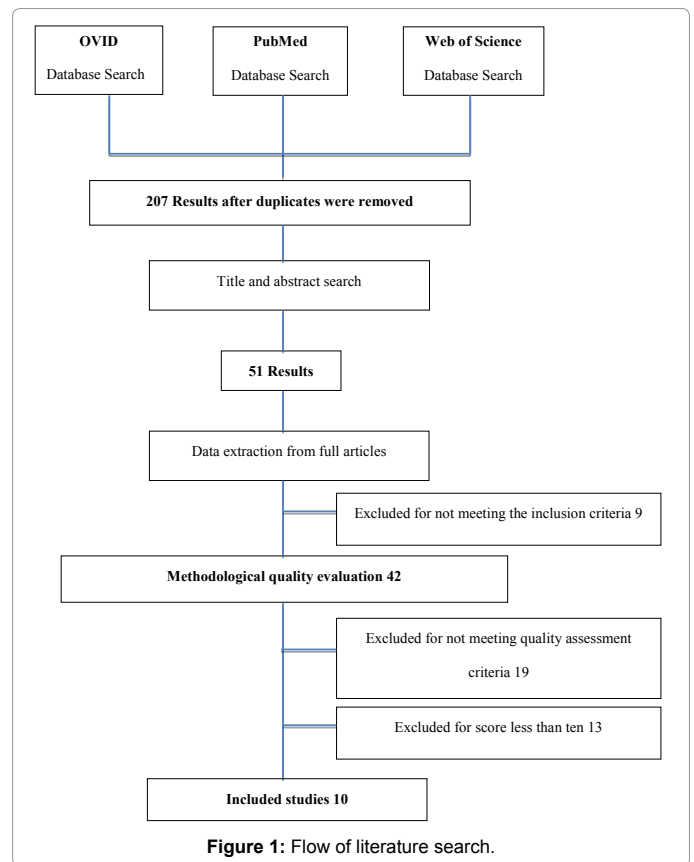
To our current knowledge, there are no existing systematic reviews of the knowledge accumulated on all epigenetic modifications in the preeclamptic placenta, including miRNA, DNA methylation and histone modification by acetylation. Here we compiled the current literature using a rigorous systematic review method that have identified the most robust of these studies in hopes of detecting both the key discoveries as well as identifying the biggest gaps in knowledge for future studies.

Materials and Methods

We systematically searched three electronic databases, Medline (OVID), Medline (PubMed) and Web of Science, using the medical subject headings (epigenetic or DNA methylation or microRNA or miRNA or histone or acetylation) AND placenta AND preeclampsia. The initial database search yielded 81 articles from OVID, 104 from PubMed and 114 from Web of Science, for a total of 299 results. Search results were limited to humans, English language, last ten-year period (2004-2014), and non-review articles (Figure 1), after which 207 articles remained.

Two authors (C.R. and E.B.) then independently screened titles and abstracts for the following pre-determined selection criteria: 1. population-pregnant women; 2. exposure-preeclampsia; 3. comparison-no preeclampsia; 4. outcome-epigenetic change; 5. type of study design-case-control observational; 6. sample type-placenta. Studies were excluded if they were reviews not previously removed from database search or did not include the use of preeclamptic placentas. Any questionable abstracts were kept for data extraction. After searching titles and abstracts and excluding those that did not fit the selection criteria, a total of 51 articles remained.

Data from each full article were then extracted by two independent reviewers (total of 5 reviewers). Any disagreements were resolved through consensus. Following full data extraction, an additional 9 articles were excluded for not studying the epigenetic changes specified (DNA methylation, miRNA, histone modification and acetylation)



PARAMETER	SCORE
Population is clearly defined	1/0
Inclusion criteria are clearly stated	1/0
Exclusion criteria are clearly stated	1/0
PE vs CTR matched or P>0.05 for maternal characteristics: BMI (1/0), age (1/0), weight (1/0), smoking (1/0), ethnicity (1/0)	1/2/3/4/5/0
PE vs CTR matched or P>0.05 gestational age	1/0
PE vs CTR matched or P>0.05 birth weight	1/0
Statistical methods appropriate	1/0
Statement of diagnostic criteria for PE (exposure)	1/0
Measurement of epigenetic change conducted (outcome)	1/0
Were results adjusted and controlled for confounders?	1/0
Limitations of experimental study identified	1/0
Total max score	15

PE-Preeclampsia; CTR-Control; BMI: Body Mass Index

Table 1: Quality assessment parameters and scores.

[8-11], for not validating results of genome wide, profiling and global methylation by other methods [12], for using primary cell tissue culture for placenta [13], for not using placental samples [14], for including only patients with specific miRNA [15], and for not presenting comparisons between control and preeclamptic patients [16]. This left us with 42 articles for methodological quality evaluation after data extraction.

As there are no formal quality assessment approaches for this type of study, we developed our own based on the literature in placenta and epigenetics (Table 1). Moreover, gestational age is a large determinant in the epigenetics of the placenta. Studies have shown that epigenetic levels in the placenta change over the course of gestation, possibly due to changing and cumulative environmental factors [17,18]. Further, it has been speculated that such epigenetic changes are a risk factor

for preterm birth, which demonstrates the need to control for these variables [19]. For an article to be included in our final analysis, it had to fulfill the criteria of gestational age-matching and/or be controlled or adjusted for confounders. Nineteen additional studies did not satisfy those criteria and were also excluded. Based on the review articles and to obtain the most vigorous systematic review, an arbitrary decision was made to include articles with a total score of at least 10 out of 15 maximal points. Quality scores of all included studies are presented in Table 2.

To determine if other molecules interact with the molecules on our list and to see how likely it is that these molecules interact together, Ingenuity Pathways Analysis (IPA; Ingenuity Systems Inc, Redwood City, CA) was used. Four separate Core Analyses were conducted-for upregulated miRNA, downregulated miRNA, hypermethylated genes, and hypomethylated genes. Datasets were filtered for species (human) and confidence (experimentally observed) and included molecules only with direct relationships.

The Core Analysis generates networks, calculates Functions and Canonical Pathways, etc. for the molecules on the list. Networks are scored based on the number of Network Eligible Molecules they

contain. The score is a numerical value used to rank networks according to their degree of relevance to the Network Eligible Molecules in the dataset. The score takes into account the number of Network Eligible Molecules in the network and its size, as well as the total number of Network Eligible Molecules analyzed and the total number of molecules in the Ingenuity Knowledge Base that could potentially be included in networks. The higher the score is, the lower the probability of finding the observed number of Network Eligible Molecules in a given network by random chance. Core Analysis also generated a Top Toxicity List -the relevant toxicity phenotypes and clinical pathology endpoints associated with the dataset. The IPA generated lists of Top Networks and Top Toxicity (Tox) are presented in Tables 5-7.

Results

Figure 1 summarizes the process of literature search. Ten studies met the inclusion criteria for our review. The characteristics of included studies are presented in Table 3. Among included studies, there were three studies on DNA methylation and seven studies on miRNA. Our search did not identify any studies on histone modification by acetylation in preeclamptic placentas.

Study	Population is clearly defined	Inclusion criteria are clearly stated	Exclusion criteria are clearly stated	PE vs CTR matched or P>.05 for maternal characteristics	PE vs CTR matched or P>.05 for gestational age	PE vs CTR matched or P>.05 for birth weight	Statistical methods	Statement of diagnostic criteria for PE (exposure)	Measurement of epigenetic change conducted (outcome)	Were results adjusted and controlled for confounders?	Limitations of experimental study identified	Total score
Bai [35]	1	1	1	2	1	0	1	1	1	0	1	10
Czikk [26]	1	1	1	2	0	0	1	1	1	1	1	10
Gao [36]	1	1	1	2	1	0	1	1	1	0	1	10
Hu [24]	1	1	1	2	1	1	1	1	1	0	1	11
Li [23]	1	1	1	2	1	1	1	1	1	0	0	10
Muralimanoharan [25]	1	1	0	2	1	1	1	1	1	0	1	10
Xiang [37]	1	1	1	2	0	0	1	1	1	1	1	10
Yan [38]	1	1	1	2	1	0	1	1	1	0	1	10
Yuen [39]	1	1	1	1	1	1	1	1	1	0	1	10
Zhu [22]	1	1	0	2	1	1	1	1	1	1	1	11

PE: Preeclampsia; CTR: Control

Table 2: Quality scores of included studies.

Study	Number of PE and CTR Placentas Studied							miRNA studied	DNA methylation studied	Gestational age at delivery(in weeks) PE	Gestational age at delivery(in weeks) Control
	Total	PE	CTR	Mild PE	Severe PE	EOPET	LOPET				
Bai [35]	32	15	17					miR-195		37.42 ± 2.57	38.86 ± 1.2
Czikk [26]	59	18					14		DUSP9	30.1 ± 2.2	32.3 ± 2.2
Gao [36]	48		24			10	14			27.9 ± 3.3 EOPET 27.9 ± 3.3 LOPET	28.6 ± 2.5
Hu [24]	50		26		24			miR-16, miR-29b, miR-195, miR-26b, miR-181a, miR-335 and miR-222		37 ± 0.2	38.8 ± 0.4
Li [23]	50	24	26					miR29-b		37	38.8
Muralimanoharan [25]	12	6	6					miR-210		38.1 ± 1.3	38.7 ± 1.1
Xiang [37]	79	48	31						CGI34, LEP, SP1, LP1, CEBPalpha	35.34 ± 3.07	39.38 ± 1.19
Yan [38]	24	12	12					mir-126		35.54 ± 3.77	37.5 ± 1.76
Yuen [39]	22		5			4	4		CAPG, GLI2, KRT1, TIMP3	24.86-34	25.86-33.71
Zhu [22]	34		11	8	15			miR-518b, miR-18a, miR-363, miR-542-3p, miR-210, miR-152, miR-411, miR-377		37.6 ± 1.4	37.5 ± 2.2

PE: Preeclampsia; CTR: Control; EOPET: Early Onset Preeclampsia; LOPET: Late Onset Preeclampsia

Table 3: Characteristics of the included studies.

Study	miRNA investigated	miRNA		p-value	Target gene
		Upregulated	Downregulated		
Bai [35]	miR-195		√	<0.05	ActRIIA
Gao [36]	miR-675		√ (EOPET)	<0.05	NOMO1
Hu [24]	miR-16, miR-29b, miR-195, miR-26b, miR-181a, miR-335 and miR-222	√ (severe PE)		<0.05	
Li [23]	miR29-b	√		<0.001	MCL1, MMP2, VEGF, ITGB1
Muralimanoharan [25]	miR-210	√ (severe PE)		<0.05	ISCU
Zhu [22]	miR-210	√ (severe PE)	√ (mild PE)	<0.05	
Zhu [22]	miR-152	√ (mild and severe)		<0.05	
Zhu [22]	miR-518b	√ (severe PE)		<0.05	
Zhu [22]	miR-18a, miR-363, miR-542-3p		√ (severe PE)	<0.05	
Zhu [22]	miR-411, miR-377		√ (mild and severe PE)	<0.05	
Yan [38]	mir-126		√	<0.05	PIK3R2 gene

PE: Preeclampsia; EOPET: Early Onset Preeclampsia

Table 4: Results of miRNA studies.

Studies	DNA methylation studied	DNA Methylation			p-value
		Hypomethylated	Hypermethylated	No Change	
Czikk [26]	DUSP9			√	
Yuen [39]	CAPG, GLI2, KRT13, TIMP3	√			<0.05
Xiang [37]	LEP, SP1, LP1, CEBPalpha	√			<0.05
Xiang [37]	CGI34		√		<0.05
Xiang [37]	SH3PXD2A	√			<0.05

Table 5: Results of DNA methylation studies.

ID	Symbol	Number of mRNA Targets
miR-126	miR-126a-3p (and other miRNAs w/seed CGUACCG)	111
miR-152	miR-148b-3p (and other miRNAs w/seed CAGUGCA)	1200
miR-195	miR-16-5p (and other miRNAs w/seed AGCAGCA)	2022
miR-16	miR-16-5p (and other miRNAs w/seed AGCAGCA)	2022
miR-181a	miR-181a-5p (and other miRNAs w/seed AAGGUGC)	1499
miR-18a	miR-18a-5p (and other miRNAs w/seed AAGGUGC)	695
miR-210	miR-210-3p (miRNAs w/seed UGUGCGU)	284
miR-222	miR-221-3p (and other miRNAs w/seed GCUACAU)	807
miR-26b	miR-26a-5p (and other miRNAs w/seed UCAAGUA)	1104
miR-29b	miR-29b-3p (and other miRNAs w/seed AGCACCA)	1495
miR-335	miR-335-5p (and other miRNAs w/seed CAAGAGC)	639
miR-377	miR-377-3p (miRNAs w/seed UCACACA)	1229
miR-411	miR-411-5p (and other miRNAs w/seed AGUAGAC)	339
miR-518b	miR-518a-3p (and other miRNAs w/seed AAAGCGC)	210
miR-542-3p	miR-542-3p (miRNAs w/seed GUGACAG)	795
miR-675	miR-675-5p (and other miRNAs w/seed GGUGCGG)	461
miR-363	miR-92a-3p (and other miRNAs w/seed AUUGCAC)	1137

Table 6: mRNA targets of miRNA.

Several groups of sampled preeclamptic placentas were studied, which are defined as follows. Preterm preeclampsia was defined as delivery of placentae between 26-33 weeks gestation and term preeclampsia was defined as delivery of placentae between 34-40 weeks gestation [20]. Early onset preeclampsia (EOPET) was defined as symptoms arising earlier than 34 weeks gestation and late onset preeclampsia (LOPET) as symptoms arising at 34 weeks gestation or later [21]. Mild PE was defined as maternal systolic BP of 140 mm Hg and/or diastolic BP of 90 mmHg on two occasions separated by 6 hours and significant proteinuria after 20 weeks of gestation, while severe PE was defined as either severe hypertension (systolic BP of 160 mmHg and/or diastolic BP of 110 mm Hg on at least two occasions 6 hours apart) plus mild proteinuria or mild hypertension plus severe proteinuria [22].

Our review revealed 17 differentially regulated miRNAs (Table 4). Three of the miRNAs (29b, 195 and 210) were evaluated in two studies (Table 4) [22-25,35]. Of the 17 miRNAs nine were upregulated, six down regulated, one (miRNA-210) was either upregulated or downregulated depending on the severity of PE, and one (miRNA-195) was found upregulated in one study [24] and downregulated in another [35].

Eleven genes from studies included in this review were found to be methylated—nine of them were hypomethylated and one-hypermethylated (Table 5). Methylation pattern of DUSP9 was reported as having no difference between PE and control placentas; however, mRNA of this gene was found to be significantly downregulated [26].

IPA's microRNA Target Filter analysis of miRNA list generated by our review revealed that 16 miRNA from our list could be targeting 8,005 mRNAs. Numbers of mRNAs that could be affected by specific miRNA modifications are shown in Table 6. Both downregulated and upregulated miRNAs were associated with 3 networks and 1 tox phenotype, hypomethylated genes with 2 networks and 5 tox, and the one hypermethylated gene was not associated with any networks, while its tox list included regulation of mitochondria and renal necrosis (Tables 7 and 8). None of the Top Networks were overlapping between the three separate analyses for upregulated miRNAs, downregulated miRNAs, and hypomethylated genes (Table 7). The common Tox phenotype for three of the groups (upregulated miRNAs, downregulated mRNAs, hypermethylated genes) was associated with regulation of mitochondria (Table 8).

Discussion

To date, this is the first systematic review of published studies on epigenetic modifications associated with preeclampsia, where epigenetic changes were validated by several methods. Ten studies, printed within the past ten years and available through three different databases, withstood vigorous scientific and quality analysis. Placental epigenetic changes associated with exposure to preeclampsia included

	Top Associated Network Functions	Score
Downregulated miRNA	Cell Cycle, Cell Death and Survival, Tumor Morphology	8
	Cancer, Cellular Development, Cellular Growth and Proliferation	3
	Gene Expression, Cellular Development, Nervous System Development and Function	3
Upregulated miRNA	Cardiovascular Disease, Organismal Injury and Abnormalities, Reproductive System Disease	14
	Cell Morphology, Digestive System Development and Function, Endocrine System Development and Function	3
	Cell Death and Survival, Drug Metabolism, Molecular Transport	3
Hypomethylated DNA	Embryonic Development, Organ Development, Organismal Development	17
	Cell-to-Cell Signaling and Interaction, Cell Death and Survival, Connective Tissue Development and Function	3

Table 7: Top Networks according to IPA.

	Top Tox Lists	Ratio
Downregulated miRNA	Decreases Transmembrane Potential of Mitochondria and Mitochondrial Membrane	1/117
Upregulated miRNA	Decreases Transmembrane Potential of Mitochondria and Mitochondrial Membrane	1/117
Hypomethylated DNA	VDR/RXR Activation	2/77
	Hepatic Fibrosis	2/95
	Liver Proliferation	2/212
	Biogenesis of Mitochondria	1/20
	Cardiac Hypertrophy	2/365
Hypermethylated DNA	Decreases Transmembrane Potential of Mitochondria and Mitochondrial Membrane	1/117
	Renal Necrosis/ Cell Death	1/464

Table 8: Top Tox List according to IPA.

in this review are 17 miRNAs and 10 genes with changes in methylation status. None of the studies included in the final review reported modifications in histone acetylation associated with preeclampsia.

All epigenetic studies of placenta, including ours, need to be evaluated with caution for several reasons. First, differences in mode of delivery and presence/absence of labor may result in modifications unrelated to preeclampsia. Second, since tissues are being collected post diagnosis, findings could already be the consequences of disease and/or treatment. Third, given that specific cell types found in the placenta may respond uniquely to the gestational environment, our findings may reflect differences in proportion of cell types rather than or in addition to the epigenetic change itself.

There are several limitations specific to our review. Articles were not homogeneous by comparison groups. Some evaluated EOPET patients, some preterm PE, some severe PE, etc. This makes quantitative comparisons impossible between the studies. This suggests a need for more studies that look at these specific comparison groups so that there is more consistent data available. Further, our study did not include a search in international databases, and since epigenetics is a relatively new field that is developing rapidly, some articles that meet our criteria may have been overlooked.

Restricting search terms to only English language is one of our review weaknesses. Also, our vigorous quality assessment excluded many articles, which might have been relevant. On the other hand, including studies from three databases with only validated results and only those that also accounted for gestational age are the major strengths of our review, which was the purpose of this systematic review.

A systematic review and meta-analysis published in 2011 identified 17 miRNA from array and profiling studies that are differentially expressed in preeclamptic placentas [27]. There were 7 miRNA in common between ours and the 2011 review. However, for these shared miRNA, four of the seven miRNAs showed inconsistent or no consensus results for the 2011 review. Out of the 17 miRNA presented in their review, nine miRNA had either inconsistent or no consensus results. This highlights the importance of validating array data. Because

we were more methodological in our requirements, we present only miRNAs that surpassed rigorous study qualifications. The significance of our review is that it spotlights the gap in knowledge concerning histone modification associated with preeclamptic placenta, emphasizes the importance of verifying the array results by other methods, and stresses the need to meticulously design future studies to include comparable samples groups.

Although the etiology remains largely unknown, preeclampsia is regarded as the 2nd leading cause for maternal mortality affecting 5-7% of women worldwide [28,29]. While the risk may seem slight, the incidence of preeclampsia has increased by 25% in the United States during the past two decades [30]. The importance of epigenetic involvement in the development in preeclampsia has been the popular subject of recent literature. The upregulation and downregulation of miRNA expression suggest a consequent regulation of target genes, which may be implicated in the pathology of preeclampsia [31]. MiRNAs work to silence genes using enzymes such as histone deacetylase, effectively modifying histone organization. While very few studies have focused on histone modifications in preeclampsia, there is evidence of such epigenetic changes occurring in the placenta [32]. DNA methylation has been demonstrated to increase in preeclamptic women as compared to normotensive patients, as well as a positive association existing between methylation levels and blood pressure found only in a preeclamptic group, further suggesting a role of epigenetics in the pathophysiology of preeclampsia [9].

We feel that this current systematic review of the epigenetic modifications that potentially play key roles in the pathogenesis of preeclampsia was necessary to condense the wide array of information available on this subject. The placenta is crucial in both the development of preeclampsia and the epigenetic changes witnessed. Moreover, in terms of clinical relevance, there have been considerable advances in the understanding of preeclampsia within the past 10 years, as well as advances in efforts to help guide early diagnostics and therapy. With epigenetic changes being reversible, epigenetic therapy is a promising field for further investigations [33,34]. We hope this review provides a fundamental cornerstone to further the growing fund of knowledge and offers a better understanding of the current literature.

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