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Preeclampsia as a parental epigenetic disease

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Summary

Objectives: Preeclampsia still remains a major cause of maternal and perinatal mortality and morbidity. The aim of this study is to provide an overview of the evidence from epigenetic regulation of preeclampsia development, with a focus on candidate imprinted genes and their roles. *Materials and Methods:* A PubMed search of the relevant literature published between 2005 and 2016 was performed to identify the preeclampsia susceptibility genes and imprinted genes. *Results:* Several susceptibility genes that have highlighted the potential role of preeclampsia development have been identified. There appears to be at least two types of genes in the placenta: the paternity-related genes appear to be evolved as the trophoblast invasion and fetal growth, while the maternity-related genes act as the defence and protective mechanism for the mother. A number of imprinting genes are essential for the biological functions such as decidualization, pregnancy maintenance, tumor suppressor, and fetal developmental processes, which include paternally expressed/maternally imprinted genes and maternally expressed/paternally imprinted genes. Some biological aspects of preeclampsia are explained from an imbalanced expression of genomic imprinting (epigenetic conflict). Although the genotypic and phenotypic extent of multilocus imprinting epimutations is poorly understood, the preeclamptic placenta showed unique epigenetic features. Changes of parental life experiences with stress or early-life conditions during pregnancy may display impaired reproductive outcome through the dynamic alterations in the patterns of the specific imprinted genes. *Conclusion:* In conclusion, preeclampsia may be recognized as a parental imprinting disease.

Key words: Preeclampsia; Imprinting; Epigenetics; Environment; Risk factor.

Introduction

Preeclampsia is a syndrome in which hypertension (≥ 140/90 mmHg) and proteinuria (≥300 mg/day) occur after 20 gestational weeks. This disease affects 5-10% of all pregnancies worldwide, but the etiology is poorly understood. Preeclampsia still remains a major cause of maternal and perinatal mortality and morbidity and is associated with long-term adverse outcomes, including future cardiovascular disease for both mother and child later in life [1]. Preeclampsia occurs as a two-stage process with shallow trophoblast invasion and poor placentation in the first half of pregnancy with an imbalance between angiogenic and anti-angiogenic factors, and then the placenta releases anti-angiogenic substances that cause generalized endothelial dysfunction in the maternal blood vessels, leading to hypertension, renal endotheliosis, and blood coagulation in the second half of pregnancy [2]. The origin of the disease may be the placenta, because the disorder can occur without a fetus as in hydatidiform mole.

Recent advances in our understanding of the genomic imprinting will unlock the black box of the mechanism that underlies the shallow trophoblast invasion, poor placentation, and then preeclampsia development. The aim of this study is to provide an overview of the evidence from epigenetic regulation of preeclampsia development, with a focus on candidate imprinted genes and their roles.

Materials and Methods

The current study aimed to summarize the preeclampsia susceptibility genes and imprinted genes. First, the authors critically reviewed the current literature regarding the preeclampsia susceptibility genes. A PubMed (http://www.ncbi.nlm.nih.gov/pubmed) search of the relevant literature published between 2005 and 2016 was performed using the following key words: 'preeclampsia', 'gene expression profiling', 'imprinting, 'paternal', and 'maternal'. English-language publication search results from PubMed and references within the relevant articles were analyzed. A list of imprinted genes, susceptibility genes, and their transcripts significantly differentially expressed in the preeclamptic placenta versus the control placenta was created. Second, the authors selected the previous studies based on a PubMed search for each known imprinted gene listed in the GeneImprint database in conjunction with the term 'preeclampsia'. Particular emphasis was given on the imprinted genes associated with preeclampsia. The genomic imprinting database is now freely accessible at http://www.geneimprint.com/site/what-is-imprinting. This data- base search identified all the existing publications on the imprinting events. In the current version, the database contains about 150 human imprinted genes, including information such as gene name, aliases, gene location, and expressed allele. The genomic imprinting database contains 90 paternally expressed and maternally imprinted genes, as well as 60 maternally expressed paternally imprinted genes. Biological functions of each imprinted gene were manually searched by PubMed. Additional information was manually collected by keyword searches of the biomedical literature databases.

To minimize selection bias, screening of the studies was inde-

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Table 1. — *Candidate imprinted genes differentially expressed in preeclampsia.*

Official symbol	Official full name	Location	Functions	Ref.	URL
Paternally expressed and maternally imprinted genes					
DIRAS3	DIRAS family, GTP-binding RAS-like 3	1p31 AS	A putative tumor suppressor gene associated with infertility, endometriosis, pregnancy loss, decidualization process, and preeclampsia.	85	http://www.ncbi.nlm.nih.gov/gene/9077
BMP8B	Bone morphogenetic protein 8b	1p35-p32 AS	Energy balance, spermatogenesis, and placentation	86	http://www.ncbi.nlm.nih.gov/gene/656
CYP1B1	Cytochrome P450, family 1, subfamily B, polypeptide 1	2p21 AS	Eye development, endometriosis, preeclampsia, and pregnancy loss	87	http://www.ncbi.nlm.nih.gov/gene/1545
VTRNA2-1	Vault RNA 2-1	5q31.1	Associated with infant neuro-behavioral development	88	http://www.ncbi.nlm.nih.gov/gene/100126299
LIN28B	Lin-28 homolog B	6q21	A puberty-associated gene associated with obesity, type 2 diabetes, and cardiovascular disease	89	http://www.ncbi.nlm.nih.gov/gene/389421
AIM1	Absent in melanoma 1	6q21	A putative tumor suppressor gene	90	http://www.ncbi.nlm.nih.gov/gene/389421
PLAGL1	PLAG1 like zinc finger 1	6q24-q25	A putative tumor suppressor gene associated with diabetes mellitus, chorioamnionitis, funisitis, placental development, and cancer	43	http://www.ncbi.nlm.nih.gov/gene/5325
PEG10	Paternally expressed 10	7q21	Pregnancy loss and preeclampsia	5	http://www.ncbi.nlm.nih.gov/gene/23089
MEST	Mesoderm specific transcript	7q32	Cell development	43	http://www.ncbi.nlm.nih.gov/gene/4232
ZFAT	zinc finger and AT hook domain containing	8q24.22 AS	Autoimmune thyroid disease, vascular remodeling, and preeclampsia	91	http://www.ncbi.nlm.nih.gov/gene/57623
IGF2AS	IGF2 antisense RNA	11p15.5	Placental development, Beckwith-Wiedemann syndrome, and Wilms' tumor	76	http://www.ncbi.nlm.nih.gov/gene/51214
MIR371A	MicroRNA 371A, also known as C19MC	19q13.42	MicroRNAs associated with gestational hypertension, fetal growth restriction, and preeclampsia	92	http://www.ncbi.nlm.nih.gov/gene/442916
MIMT1	MER1 repeat containing imprinted transcript 1	19q13.4	Abortion, fetal growth, and development	93	http://www.ncbi.nlm.nih.gov/gene/100073347
GNAS	GNAS complex locus	20q13.3	Fetal growth restriction	94	http://www.ncbi.nlm.nih.gov/gene/2778
MIR296	MicroRNA 296	20q13.32 AS	Associated with small for gestational age and myocardial infarction	3	http://www.ncbi.nlm.nih.gov/gene/407022
MIR298	MicroRNA 298	20q13.32 AS	Associated with small for gestational age and myocardial infarction	3	http://www.ncbi.nlm.nih.gov/gene/100126296
Maternally expressed and paternally imprinted genes					
DVL1	Dishevelled segment polarity protein 1	1p36 AS	Developmental pathways such as cell proliferation, migration, polarity, terminal differentiation, and the self-renewal of stem cells	95	http://www.ncbi.nlm.nih.gov/gene/1855
FGFRL1	Fibroblast growth factor receptor-like 1	4p16	Embryonic development	96	http://www.ncbi.nlm.nih.gov/gene/53834
KCNQ1DN	Potassium channel, subfamily Q, member 1 downstream neighbor	11p15.4	Wilms and other embryonal tumors	77	http://www.ncbi.nlm.nih.gov/gene/55539
PHLDA2	Pleckstrin homology like domain family A member 2	11p15.4	A putative tumor suppressor gene associated with preeclampsia	97	http://www.ncbi.nlm.nih.gov/gene/7262
KCNQ1	Potassium channel, subfamily Q, member 1	11p15.5	Diabetes susceptibility, associated with Beckwith-Wiedemann syndrome	6	http://www.ncbi.nlm.nih.gov/gene/3784
H19	H19 imprinted maternally expressed transcript (non-protein coding)	11p15.5	Functions as a tumor suppressor associated with Silver-Russell, Beckwith-Wiedemann Syndrome, and Wilms tumorigenesis.	18	http://www.ncbi.nlm.nih.gov/gene/283120
CDKN1C	Cyclin-dependent kinase inhibitor 1C (p57, Kip2)	11p15.5 AS	Functions as a tumor suppressor associated with decisualization and Beckwith-Wiedemann syndrome	4	http://www.ncbi.nlm.nih.gov/gene/1028
MEG3	Maternally expressed 3 (non-protein coding)	14q32	Down-regulated in the preeclamptic placenta and associated with trophoblast invasion	98	http://www.ncbi.nlm.nih.gov/gene/55384

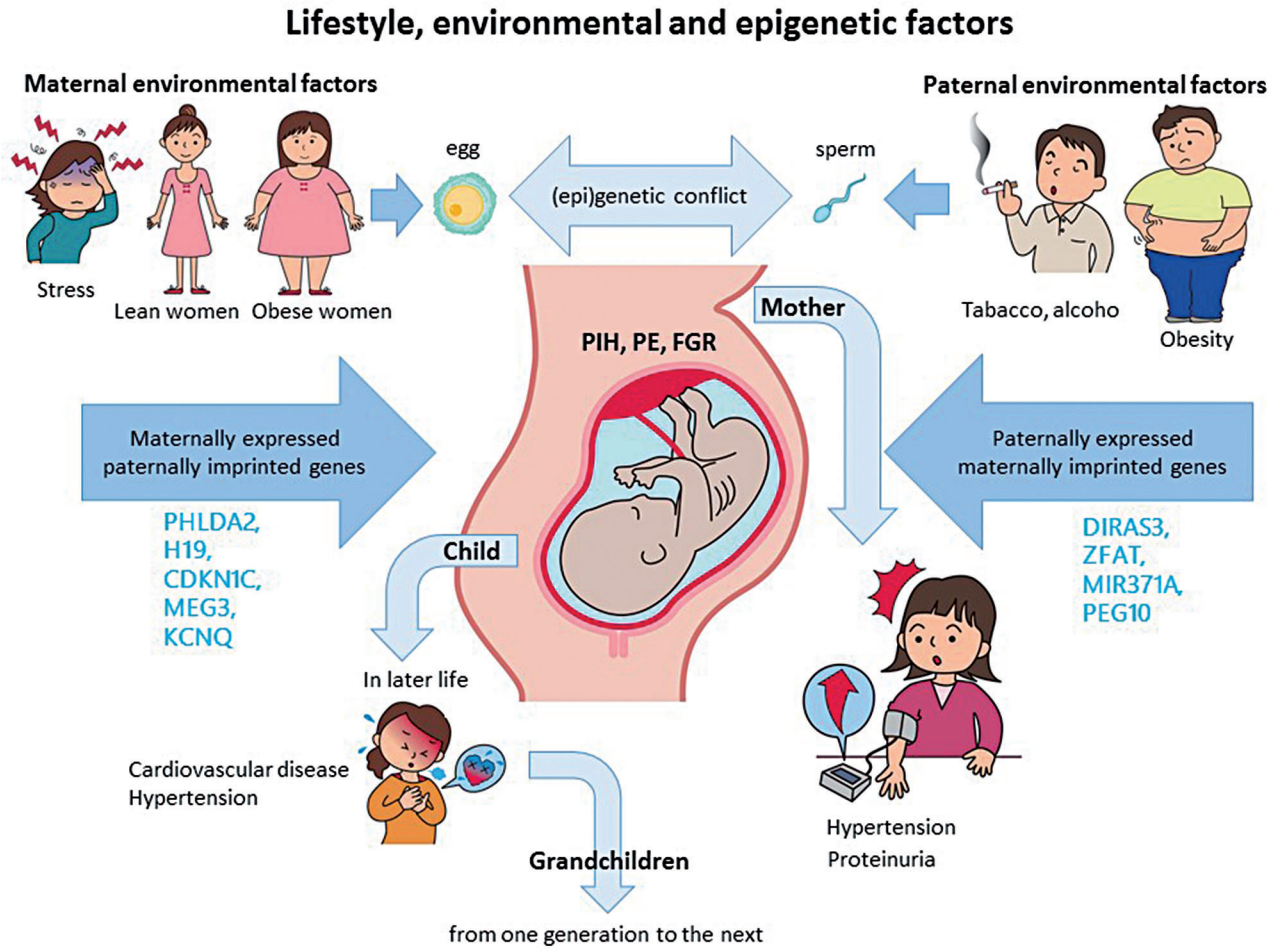

Figure 1. — Paternal lifestyle prior to conception may affect sperm epigenetic changes, offspring epigenetics and phenotypic abnormalities, pregnancy outcome, and long-term effects during the offspring lifetime, possibly through abnormal genomic imprinting. Maternal exposure to stress, famine, or obesity during pregnancy is considered to be associated with a newborn's DNA methylation at certain imprinted genes. Changes of early-life conditions during pregnancy may display impaired reproductive outcome, including preeclampsia, through the dynamic alterations in the patterns of the specific imprinting genes, which increases the risk of cardiovascular and metabolic disease in later life of her offspring. Taken together, preeclampsia may be potentially related to both the father's side (paternally expressed maternally imprinted genes) and the mother's side (maternally expressed paternally imprinted genes).

pendently performed by two of the co-authors (TT and JA) after agreeing on the selection criteria. A total of 472 articles were identified by the search; around 156 articles were potentially relevant. Among 156 articles, 68 publications available for distinguishing the preeclamptic placenta from the control placenta were chosen based on the final selection, taking into account the title and the summary analysis. The preeclampsia-related imprinting genes identified in two or more of the primary studies are listed in Table 1.

Results

Certain genetic risk factors have been suggested to cause preeclampsia. The key genetic mechanisms triggering this disease have been extensively analyzed by microarray-based gene expression profiling, single-nucleotide polymorphism (SNP) data from genome-wide association studies or other related technologies that have been widely used in identifying the susceptibility genes responsible for preeclampsia. Many genes were aberrantly expressed in the preeclamptic placentas, which includes FLT1, VEGFA, PlGF, STOX1, ERAP1 and 2, syncytin, ACVR2A, INH(B)A, CGA/CGB, LEP, CRH, EBI3, PAPPA2, CYP11A1, KRT19, PLEC, SPAG4, VIM, AQP1, PVRL4, SEMA4C, SLCO2A1, TNFSF10, RDH13, BHLHE40, PHYHIP, SASH1, TLR-4, TGF-β, Wnt, Notch, and STAT [3-23]. The major phenotypes of preeclampsia, such as hypertension and proteinuria, might be due to soluble Flt-1(sFlt-1) that neutralizes the pro-angiogenic proteins,

VEGF and PlGF. Molecular understanding of each interesting gene has been analyzed in gene ontology analysis and enriched pathways. The unique susceptibility genes include multiple pictures of gene signatures and encode enriched pathways, relating to decidualization, pregnancy maintenance, implantation, invasion, angiogenesis, vascular function, cell cycle regulation, cytokines, chemokines and (pro)inflammation, metabolism, oxidative stress, and immune modulation [19-22]. The enriched pathways of the differentially expressed genes were assigned to two main categories: the defects of decidualization/placentation process and poor trophoblast invasion. First, decidualization/placentation is a maternal process to support pregnancy. Preeclampsia placenta exhibited decreased expression of maternity-related genes known to be activated during the decidualization process [12]. The overlapping genetic signatures between preeclampsia development and poor decidualization process suggest that insufficient decidualization may be a main cause of subsequent preeclampsia [22]. Second, the shallow trophoblast invasion is also likely to be relatively a common cause of preeclampsia. These paternity-related genes and their enriched pathways are highly involved in poor trophoblast invasion and dysregulation of host defence mechanisms against trophoblast invasion. Collectively, there seems to exist a genomic imbalance between paternity (to maximize fetal growth)- and maternity (to limit conceptus growth)-related genes in preeclampsia placentas, possibly through placental maternal-fetal (paternal) genetic conflict [24-26]. Qualitative interpretation of studies involved in paternity- and maternity-related genes is summarized in references 12 and 22.

Epigenetic changes to the genome modifies gene expression without affecting the DNA sequence. Genomic imprinting is a rapidly evolving phenomenon [27]. Imprinted genes are expressed in a parent-of-origin dependent manner, which results in monoallelic expression of transcripts, and display complementary dosage-dependent effects during pregnancy [28]. Genomic imprinting undergoes epigenetic programming during spermatogenesis, organogenesis, neuronal development, early placental and fetal development through regulation of parental physical and behavioral resource allocation [29]. Paternally expressed maternally imprinted genes such as insulin-like growth factor (IGF)-2 play an important role in the control of placental size and birth weight by maximizing fetal resource acquisition from the mother, while maternally expressed paternally imprinted genes such as the H19 locus limit fetal growth [24, 30]. The placental epigenetic regulation serves as the interface between genes and the environment. The parental conflict hypothesis support the idea that imprinted genes regulate the ability of a fetus to manipulate the maternal provision of nutrients [31]. Some pregnancy-related disorders, such as transient neonatal diabetes mellitus, Silver–Russell syndrome, Beckwith–Wiedemann syndrome, Angelman syndrome, and Prader–Willi syndrome, can be caused by epigenetic alterations in the imprinted cluster [32].

Imprinted genes are regulated by DNA methylation, histone modifications, long non-coding RNA (lncRNA), and CCCTC binding factor (CTCF)-mediated boundaries [28]. At the most simple level, genomic imprinting is associated with a process of silencing genes through covalent modification of DNA by methylation and post-transcriptional histone modifications. The following findings support a role of imprinting in reproductive biology. First, the maternally expressed H19 gene is expressed in the normal placenta: biallelic expression at the early stage of normal placenta, but monoallelic expression near ten weeks of gestation through the dynamic alterations in the patterns of the specific imprinted genes. Temporal alternations in the patterns of the H19 gene imprinting may be essential for the maintenance of normal pregnancy [13]. Second, promoters of developmental genes are highly hypomethylated in sperm cells when compared with those of the somatic cells. Animal studies have already supported the link between specific epigenetic changes in sperm and paternal phenotypic abnormalities [33]. The DNA hypomethylation at the H19 gene locus in sperm was associated with oligozoospermia and azoospermia [34]. Abnormal DNA methylation at imprinted genes may be associated with defective human sperm, spermatogenesis failure, male factor infertility, and transgenerational effects. Finally, a covalent histone modification profile changes the DNA-binding capacity of histones and thereby alters gene expression. Histones are modified by numerous histone marks, including histone acetylation, methylation, phosphorylation, sumoylation, ADP-ribosylation, ubiquitination, deiminiation/citrullination, proline isomerisation, and O-GlcNAcylation [35]. Differential histone acetylation is related to the reduced expression of H19 and strong activation of IGF2, suggesting important clinical ramifications on fertility potential and embryo outcome [36].

Dynamic properties of the placental imprinted genes are responsive to environmental factors, including maternal diet, smoking, endocrine disruptors, heavy metals, and stress, by varying their epigenetic status [31]. A number of studies have shown an influence of prenatal environment in determining the methylation pattern of imprinted loci and a key regulator of pregnancy outcome [37-39]. Numerous epidemiological and experimental studies suggest the impact of early life events such as an adverse intrauterine environment, infection, or inflammation on later life disease susceptibility (hypertension, cardiovascular disease, endometriosis, and cancer) [10, 12, 40-43]. For example, maternal exposure to famine or maternal obesity during pregnancy was considered to be associated with a newborn's DNA methylation at certain imprinted genes such as IGF2, peroxisome proliferator-activated receptor (PPAR)γ, and estrogen receptor (ER)α, which increases the risk of

cardiovascular and metabolic disease in later life [44, 45]. In addition to maternal diet and health, the initial gestational exposure to maternal stress including depression was also considered to be associated with DNA methylation of imprinted genes IGF2 and GNASXL [37, 46]. These data imply that the prenatal environment can influence the epigenetic regulation in utero, which has been associated with an individual's health, adverse pregnancy outcomes, and disease susceptibility in later life [47]. This suggests that the maternal epigenetic marks is sensitive to environmental influence (Figure 1, maternal environmental factors).

Epidemiological and experimental studies in which risk factors for fetal developmental disorders have been examined mostly have focused on maternal "exposures" during pregnancy. Paternal "exposures" are difficult to examine during pregnancy. Father is only able to communicate via germ cells, and do not interact directly with his baby during pregnancy. Epigenetic alterations induced by father's lifestyle and environmental factors (diet, certain foods, reproductive toxicants, smoking, alcohol consumption, drug exposures, and radiation) may have substantial effects on the sperm function and epigenetic alterations. For example, paternal exposure to alcohol or olfactory fear induces DNA hypomethylation of the brain derived neurotrophic factor (BDNF) or Olfr151 gene, respectively, in mice sperm [48, 49]. Newborn offspring of high fat diet fathers had reduced body weight [50]. The unique methylation of sperm DNA appear to influence not only the spermatogenesis but also embryogenesis. Germ cells is vulnerable to environmental influences. DNA methylation defects of imprinted H19 induce abnormal human spermatogenesis and infertility [51]. Assisted reproductive technology (ART) may be associated with imprinting methylation errors during gametogenesis, fertilization, and early embryonic development, and late onset diseases (obesity, hypertension, diabetes, etc.) in the adult life [52]. Paternal lifestyle prior to conception could affect sperm epigenetic changes, offspring epigenetic and phenotypic abnormalities, pregnancy outcome, outcome of ART protocols, and long-term effects during the offspring lifetime, possibly through abnormal genomic imprinting [53]. These findings suggest that father can influence offspring phenotypes and transgenerational outcomes through the sperm epigenome and environment interaction (Figure 1, paternal environmental factors).

Plants possess the ability to maintain a memory of stress exposure such as limited nutrient supply and temperatures, alter the morphological and architectural phenotypes, and then provide an environmental memory heritable through mitosis [54]. Epigenetic changes can be induced by starvation and temperature [54]. Transcription of genes encoding DNA methylases is modulated by a certain type of starvation such as low phosphate availability [55]. Changes in these transcriptional genes are associated with the global changes in DNA methylation [55]. Furthermore, in plants an epigenetic memory of the temperature conditions allows rapid adaptation to changing environment. The majority of differentially expressed genes among the temperature-dependent regulators was also related to DNA and histone methylation [56]. What is a crosstalk between thermal variation and genomic regulation? External temperature can change the biophysical behavior of epigenetic marks on DNA methylation and histone H2A status through changes of nuclear ionic environment [57]. Climate could be involved in local variation in DNA methylation levels Plants rapidly acclimate to a multitude of stressful conditions and fortify their defences through epigenetic changes and genomic imprinting, which may offer greater opportunities for regulation of phenotypic plasticity [58].

In general, molecular epigenetics are involved in DNA methylation, histone modification, small RNAs, and transposable element (TE) or transposon modulation. Genomes of higher eukaryotes, including plants, animals, and humans, contain numerous endogenous TEs or DNA transposons, which are able to move around the genome [59]. In humans, about four million TEs represent almost 50% of the entire genome. DNA methylation is an important epigenetic process that protects against transposon proliferation and impacts genomic imprinting. Environmental effects were often limited to transposons, where methylation was regulated by temperature [60]. The epigenetic regulation of transposons affects the activation of nearby target genes.

It has been proposed that in humans and animals, fetal programming, including maternal caloric restriction and paternal high-fat diet, is a risk factor for the development of metabolic diseases during adulthood [61]. Environmental factors such as maternal nutrition and paternal lifestyle have strong impact on the genomic imprinting. Imprinted genes are also found in plants and closely linked to TE silencing and play an important role in reprogramming gene expression, such as plant seed development in response to environmental cues [55]. The inheritance of epigenetic characters and genomic imprinting shares common biological features between plants and animals. A recent study showed that the aberrant expression of preeclampsia-associated genes tend to occur in or near some specific genes, several of which have known involvement in the genomic imprinting [12, 22]. However, there is as yet no evidence of direct incorporation and activation of transposons into the human genome in preeclamptic placenta. Plant epigenetics provides a useful model for understanding how the onset of pregnancy complications such as preeclampsia is regulated by the parental epigenetic marks or genomic imprinting.

There are epidemiological and clinical risk factors for preeclampsia, including nulliparity, multiple pregnancies, a male fetus, previous preeclampsia, family history of preeclampsia, antiphospholipid antibody syndrome, chronic kidney disease, preexisting hypertension, preges-

tational diabetes, pre-pregnancy BMI >30, and use of ART [23, 62]. The important factors associated with an increased risk of preeclampsia are the first birth, conception with a new male partner (new paternity), and the conception occurring very shortly after the beginning of their sexual relationship [23]. Women with a history of recurrent spontaneous abortion with the same partner reduced the risk of preeclampsia. In contrast, women who had had a prior unexplained consecutive miscarriages but changed partner were associated with no reduction in the risk of preeclampsia. Thus, prolonged exposure to paternal antigens may protect against preeclampsia in a pregnancy with the same father. A change of paternity remained an elevated risk of preeclampsia, but was associated with a reduced risk among women who had had preeclampsia during their first birth [63, 64]. These clinical observations suggest that events linked to the father's side rather than the mother's side in early pregnancy are associated with the pathogenesis of preeclampsia, suggesting that paternity, rather than gravidity, is probably the leading cause of preeclampsia [65, 66].

This study mainly focus on current epigenetic researches, including imprinted genes on the pathogenesis of preeclampsia. Cohort studies have identified paternal SNPs with strong associations with preeclampsia [67]. Several researchers have identified parent-of-origin-specific imprinted genes that may be associated with preeclampsia development. The present authors explored if preeclampsia may be related to the father's side (paternity) or the mother's side (gravidity)

Similar to the preeclampsia susceptibility genes, there appears to be at least two types of imprinted genes in the placenta; paternally expressed maternally imprinted genes, including IGF2 (insulin like growth factor 2), are evolved for the benefit of the fetal development, while maternally expressed paternally imprinted genes, including CDKN1C (cyclin dependent kinase inhibitor 1C, also known as p57Kip2), are evolved as the defence and protective mechanism for the mother [68]. Normal placental function and fetal growth depend on the balance between paternal and maternal imprinted genes. Like plants, parental epigenetic contribution may be critical to understand the fundamental processes involved in preeclampsia development. There is accumulating evidence linking the dynamic changes of parental imprinted genes with the development of preeclampsia. Recent study has elucidated that, among the differentially expressed genes, 21.4% of which were evolved for the protection of the mother (maternity-related genes), approximately three times less than the number of genes, evolved for the benefit of the fetus (paternity-related genes; 78.6%) in preeclampsia placenta versus normal placenta [22]. Furthermore, a majority of the down-regulated genes appeared to be evolved as the defence and protective mechanism for the mother, namely maternity-related genes, including decidualization/placentation-related genes, suggesting that epigenetic inactivation of the maternal alleles may be a major contributor to the development of preeclampsia [12]. More recently, paternal genome involved in the MMP-related trophoblast invasion and placentation were also dysregulated in preeclamptic placenta [69]. A majority (~82%) of the paternity-related genes were negatively correlated with trophoblast invasion and fetal growth [69]. The reduced expression in paternity-related genes may be associated with shallow trophoblast invasion and poor placentation. Collectively, these findings reveal that preeclampsia may be associated with an imbalance in the maternal-paternal (fetal) epigenetic conflict [12].

This imbalance can be mediated by dysregulating genomic imprinting, because half of the down-regulated genes in the preeclamptic placenta are located within and in close proximity to known imprinted genes [12]. The major functions of the 150 imprinted genes are associated with in utero fetal and placental development, early postnatal growth and development, and tumor growth [40, 53]. Aberrant epigenetic regulation of specific imprinted genes may contribute to reproductive biology such as fetal growth restriction [70-73], preeclampsia [4-6, 13, 17, 18], endometriosis [40-42, 74, 75], and tumor predisposition [76, 77]. For example, deficiency in CDKN1C (p57Kip2, maternally expressed and paternal imprinted gene) expression induces preeclampsia-like symptoms in mice [4]. CDKN1C, a potent inhibitor of cyclin/cyclin dependent kinase (CDK) complexes, plays a role in the normal blastocyst formation and decidualization process [78]. It has been postulated that mutations and deficiency in this gene could be responsible for sporadic cancers, Beckwith-Wiedemann syndrome, and some cases of preeclampsia [4]. However, previous studies have not yet provided convincing evidence for any susceptibility imprinting genes of preeclampsia in humans. Although no clear cause-effect relationship was identified, animal models support a concept that preeclampsia is a disease associated with not only a genetic disease but also an epigenetic disorder [12, 47].

Recent studies have explored an imprinting gene expression profile in the preeclampsia placenta [12, 79]. In this study using the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) and GeneImprint database (http://www.geneimprint.com/site/genes-by-species), the present authors searched imprinted gene functions and their roles in biological processes, and identified the parentally imprinted genes that are reported to be involved in the reproductive process. Among the 150 imprinted genes, a total of 24 candidate imprinted genes have been selected, which includes 16 paternally expressed maternally imprinted genes, and eight maternally expressed paternally imprinted genes (Table 1). Biological functions of these imprinted genes include cellular proliferation and growth, tumor suppression, protein synthesis and degradation, metabolic processes, nutrient and ion transport, behavior and inflammation, and immune system [80]. The present authors speculate that

dysregulation of specific imprinted genes related to decidualization and placentation (DIRAS3, BMP8B, IGF2AS, and CDKN1C) and trophoblast invasion and fetal growth (PLAGL1, MIMT1, GNAS, DVL1, FGFRL1, and MEG3) may appear critical to the development of preeclampsia (Table 1 and Figure 1) The kinship theory in genomic imprinting and epigenetic features predicts differences in inclusive fitness between mothers and fathers, namely, the conflict over resource allocation during pregnancy [25].

Are paternal or maternal epigenetic marks in preeclampsia unequivocally confirmed by genomic imprinting? Preeclampsia may be associated with down-regulated expression of the susceptibility genes located in close proximity to known imprinted genes on specific chromosomes such as 1p31 and 11p15 [12, 22] (Table 1). Genomic inactivation in preeclampsia is not a random process. These data support that the imbalance of parental imprinted gene expression explains the risk of preeclampsia. There are some data so far when and how the disruption of such epigenetic changes occurs but with limited data to describe the pathogenesis of preeclampsia. The loss of the H19 gene imprinting may be associated with severe hypertension [13, 18, 81]. Preeclampsia may be caused by epigenetic hypomethylation of IGF2 loci, which is paternally expressed in the placenta [82]. Animal experiments showed that genetic factors contributed by the male is important for maternal hypertension during pregnancy [83]. The epigenetic modifications in father's lifestyle can also induce alterations of spermatogenesis leading to impairment of male fertility. These data suggest that not only the early stage of normal pregnancy, but also the control of paternal/maternal lifestyle prior to conception may have consequences on individual reproduction outcomes throughout the life cycle as well as in the next generation (Figure 1).

Discussion

In this study, the authors explored and summarized the recent literature that supports a direct or indirect relationship between the previously reported preeclampsia susceptibility genes and the candidate imprinted genes [3-23]. Among the 150 human imprinted genes, 24 imprinted genes related to tumor suppressor, infertility, pregnancy loss, and decidualization, may appear critical to the development of preeclampsia (Table 1). According to evolutionary genetic conflict hypothesis, placentation may occur as an epigenetic consequence of antagonistic coevolution between maternal and fetal genes [24, 25]. Animal experiment showed that complex epigenomic alterations of the imprinted gene CDKN1C may be responsible for the preeclampsia phenotype [4]. The irreversible programming of epigenetics may cause insufficient trophoblast invasion and poor decidualization, which in turn results in adverse pregnancy outcome such as preeclampsia.

Preeclampsia occurs as a two-stage process: the initial wave of poor uteroplacental circulation by defective trophoblast invasion would be followed by the second large wave of inadequate remodelling of the spiral arteries, which results in maternal endothelial dysfunction in the second half of pregnancy [84]. Recent advances allow (epi)genome-scale approaches to preeclampsia-directed imprinted gene discovery, supporting the epigenetic hypothesis [4]. Epigenetic changes are induced by various environmental stressors including a range of maternal and paternal nutrition, physical, and lifestyle features. Epigenetic differences in maternal oocyte or paternal sperm may also contribute to preeclampsia risk in mother and offspring. Epigenetic mechanisms allow an embryo to respond to the environment through changes in gene expression. Epidemiological analyses support a parental origin for development of preeclampsia, with more effect of paternal factors [65]. Interestingly, several of the preeclampsia susceptibility genes may be clustered in the close proximity to the candidate imprinted regions [12]. No attempt has been made to ascertain whether any of these imprinted genes have a "driver" role or have a role of merely a by-stander in the development of preeclampsia. The quest for and the catalogue of driver imprinted genes open new avenues to better understand the mechanisms of preeclampsia development. No convincing evidence has been provided to suggest that these candidate imprinted genes would control the preeclampsia susceptibility genes, but some indirect indications are available. The extent to which environmental factors provoke epigenetic responses in preeclampsia represents an exciting area of future research.

Conclusion

In conclusion, this study supports the possibility that aberrant epigenetic dysregulation of specific imprinted genes may contribute to preeclampsia predisposition. Preeclampsia is considered to be a parental epigenetic disease. Further investigations are needed to provide biological evidence for the direct association between the candidate imprinted genes and the previously reported preeclampsia susceptibility genes. Further study will warrant special attention that genetic, epigenetic, environmental, and lifestyle risk factors contributed by father or mother may be important for preeclampsia development. Preeclampsia may be recognized as a parental imprinting disease.

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