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Could circRNA be a new biomarker for pre-eclampsia?

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Abstract

Pre-eclampsia is a devastating complication of pregnancy which is characterized by hypertension and proteinuria in pregnant women. Pre-eclampsia is important as it is the leading cause of death. Moreover, untreated pre-eclampsia might lead to other lethal complications, for both fetus and mother. Pre-eclampsia can also affect the quality of life in affected women. Despite a large number of risk factors for pre-eclampsia, these risk factors are able to detect just 30% of women who are susceptible to pre-eclampsia. Heterogeneous manifestations of pre-eclampsia necessitate the discovery of potential biomarkers required for its early detection. Circular RNAs (circRNAs) are a type of RNA which are more abundant, specific, and highly organized compared with other types of RNA. Accordingly, circRNAs have been suggested as one of the potential biomarkers for different diseases. Recently, researchers have shown interest in the effects of circRNAs in pre-eclampsia, although the current evidence is limited. The majority of obstetricians are probably not aware of circRNAs as a useful biomarker. Here, we aimed to summarize recent supporting evidence and assess the mechanisms by which circRNAs are involved in pre-eclampsia.

KEYWORDS
circRNA, diagnosis, prediction, pre-eclampsia, pregnancy

1 | INTRODUCTION

Pre-eclampsia is a pregnancy complication which affects about 3–5% of pregnancies. It is characterized by the occurrence of hypertension and proteinuria in pregnant women (Mol et al., 2016). Hypertension in pre-eclampsia is defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg occurred after 20 weeks of gestation (Damian, Njau, Lisasi, Msuya, & Boulle, 2019). This disease leads to 70,000–80,000 maternal and 500,000 perinatal mortality per year worldwide (Hutcheon, Lisonkova, & Joseph, 2011). This pregnancy-related syndrome is a major cause of neonatal, fetal, and maternal death (Saleem et al., 2014). Untreated pre-eclampsia might have other lethal consequences, including stroke, renal failure, liver rupture, and pulmonary edema as well as fetal growth retardation and preterm birth (Souza et al., 2013). Preterm birth caused by pre-eclampsia may result in bronchopulmonary dysplasia in children (Hansen, Barnés, Folkman, & McElrath, 2010). In addition, pre-eclampsia increases the risk of postpartum depression and reduces the quality of life in women (Blom et al., 2010; Prick et al., 2015). In developing countries, pre-eclampsia is the leading cause of maternal mortality, while in developed countries, enhanced diagnostic methods and earlier detection make pre-eclampsia less devastating (Ngoc et al., 2006).

There is no approved preventive method for pre-eclampsia, though screening and early detection of high-risk women may improve its management. The major screening is the assessment of clinical risk factors, including age, body mass index (BMI) and family history, especially in the first half of the pregnancy (Hyde & Thornton, 2013). Delivery is the only treatment that is thought to be effective for this disorder. Identifying the exact cause of pre-eclampsia is likely to result in a significant decrease in maternal and perinatal morbidity and mortality. However, since its etiology

remains unknown, acting effectively for preventing its development (primary prevention) is not possible. Several factors such as genetic changes have been suggested to play a key role in the pathogenesis of pre-eclampsia. Several gene variants which are involved in some metabolic processes such as inflammation, thrombophilia, rennin–angiothensin system, and oxidative stress have been associated with pre-eclampsia (Jebbink et al., 2012; Rana, Karumanchi, & Lindheimer, 2014). The common symptoms of pre-eclampsia include headache, epigastric pain, visual impairments, nausea, and vomiting as well as some neurological, hepatic, renal, and cardiovascular complications such as the ischemic neurological deficit, liver dysfunction, acute renal disease, myocardial ischemia, and pulmonary edema. Moreover, severe pre-eclampsia may lead to fetal complications, including growth retardation, neonatal death, stillbirth, and prematurity (Mol et al., 2016).

Pre-eclampsia risk factors include history of pre-eclampsia in previous pregnancy, chronic kidney diseases, high blood pressure, diabetes, autoimmune disorders such as systematic lupus erythromatosus, first pre-eclampsia, age over 40 years, pregnancy interval of more than 10 years, BMI >35 kg/m^2, polycystic ovarian syndrome, and multiple gestation (National Collaborating Center for Women's and Children's Health, 2010). However, these risk factors are able to detect just 30% of women who are prone to pre-eclampsia (Saleem et al., 2014). Due to heterogeneous manifestations of pre-eclampsia, potential biomarkers are required for its early detection.

Current evidence shows the relationship between noncoding RNAs (ncRNAs) and pre-eclampsia (Ji et al., 2013). One of the well-known types of ncRNAs is long noncoding RNAs (lncRNAs), which consist of more than 200 nucleotides. LncRNAs have many biological functions including DNA methylation, imprinting regulation, apoptosis, cell-cycle regulation, and angiogenesis (Wilusz, Sunwoo, & Spector, 2009). Genome-wide lncRNAs expression patterns indicate numerous lncRNAs extensively expressed in pre-eclampsia. Previous studies have reported that different expression of lncRNAs in pre-eclampsia is related to multiple pathways, including trophoblast invasion (Long et al., 2016), autophagy (Gao et al., 2011, 2012), apoptosis (Song et al., 2017; Xu et al., 2018; Zou & Sun, 2015), proliferation (Cao et al., 2017; Li et al., 2018; Xu et al., 2017), migration, and angiogenesis (Chen et al., 2015; Yu et al., 2018; Zhang et al., 2015). Circular RNAs (circRNAs), as one type of ncRNAs, have been demonstrated to function as a potential regulator of other RNAs transcription like microRNAs (miRNAs). MiRNAs affect almost all cellular processes from developmental pathways to oncogenesis. Indeed, miRNAs are able to regulate the expression of the majority of human proteins (Bartel, 2004). Thus, circRNAs can be involved in a wide range of pathways in the body through regulating miRNA expression. CircRNAs as one type of ncRNAs function as a potential regulator of other RNAs transcription like miRNAs. CircRNAs are single-stranded RNAs which are produced via different posttranscriptional processes and then become circular (Ojha, Nandani, Chatterjee, & Prajapati, 2018). Previously, circRNAs were believed to be produced by errors in alternative splicing and were considered as genetic accidents (Cocquerelle, Mascrez, Hétuin, & Bailleul, 1993). Recently, by advancement in RNA sequencing and bioinformatics methods, potential biological activities of circRNAs have been approved (Danan, Schwartz, Edelheit, & Sorek, 2012). circRNAs have a regulatory role in gene expression as well as a pivotal role in biological development mechanisms, including regulating miRNA expression, endogenous RNAs, and act as a biomarker in the diagnosis of different diseases (Liu, Pan, Mao, Liu, & Chen, 2019). For instance, a large number of circRNAs have been shown to be involved in many normal processes including development of embryos, and sperm as well as pathological conditions like myocardial infarction, Alzheimer's disease, diabetes, and carcinomas such as ovarian, breast, and endometrial tumors (Greene et al., 2017; Liu et al., 2019; Szabo et al., 2015; Vausort et al., 2016; Zheng et al., 2016).

CircRNAs do not have 3′ and 5′ ends and are protected against RNA exonucleases. This unique structure has produced a highly stable marker in nature. CircRNAs have many miRNA binding sites which help them to act as a miRNA sponge leading to a reduction in the inhibitory effect of miRNAs on target genes and thereby enhancing the expression of these genes (Memczak et al., 2013). CircRNAs are more abundant, more specific, and highly organized compared with other RNAs. Accordingly, researchers have suggested that circRNAs could be strong biomarkers for different diseases; however, the exact mechanisms of circRNAs function are not clear. Recent evidence has indicated that these molecules may play important roles in various diseases from cardiovascular and neurological disorders to multiple neoplasms (Qu et al., 2015). Recently, researchers have shown interest in the role of circRNAs in pre-eclampsia and several studies have been conducted herein. However, most obstetricians are probably not aware of circRNAs. Here, we aimed to summarize recent supporting evidence and evaluate the mechanisms by which circRNAs are involved in pre-eclampsia.

2 | CircRNAs BIOGENESIS

During the alternative splicing process, some sequences which are named noncoding introns, are removed from pre-mRNA to form the mature linear RNA (Wang et al., 2008). CircRNAs are produced during a noncanonical form of alternative splicing, although its detailed mechanism has not been understood yet. Based on recent findings, back splicing could be the possible mechanism for circularization of RNA (Liu et al., 2017). Back splicing leads to the formation of exonic circRNAs (EcircRNAs), circular intronic RNAs (ciRNAs), and exon–intron circRNAs (EIcircRNAs; Li et al., 2015; Zhang et al., 2013). CircRNA is produced by special alternative splicing through exon circularization and intron circularization. There are two models for circRNA formation via exon circularization, including intron-pairing-driven circularization and lariat-driven circularization (Jeck et al., 2013). In the lariat-driven circularization, a covalent splice is formed from the 3′ end of the splice donor to the 5′ end of the splice recipient, resulting in a lariat structure which then is circularized to form an exonic circle. The intron-pairing-driven

depends on the pairing of complementary motifs existing in the transcriptome (Ye, Chen, Liu, Zhu, & Fan, 2015).

The formation process of intronic circRNA is completely different from EcircRNA. GU-rich sequences near the 5′ splice site and the C-rich sequences adjacent to the branch point bind together to form a circle structure followed by the function of spliceosome which cuts out the intronic and exonic sequences. Recent investigations have indicated that back splicing is regulated by splicing factors and *cis*-elements (Wang & Wang, 2015). Eventually, introns bind together to produce ciRNAs (Talhouarne & Gall, 2014). Extracellular vesicles transport circRNAs same as ncRNAs to the extracellular space. Moreover, other cells take up extracellular vesicles showing that circRNAs enhance cell–cell communication (Lasda & Parker, 2016). By the progression of gestation in each pregnancy, the levels of extracellular vesicles increase in the maternal plasma (Adam et al., 2017). These extracellular vesicles contain several proteins, including messenger RNAs (mRNAs) and miRNAs which have various biological functions and some of them are involved in pre-eclampsia (Salomon, Yee, Mitchell, & Rice, 2014). Recently, the role of circRNAs and extracellular vesicles in the pathogenesis of pre-eclampsia has been attractive for researchers (Figure 1).

3 | THE PATHOPHYSIOLOGY OF PRE-ECLAMPSIA

There are many investigations in terms of the pathophysiology of pre-eclampsia, though the certain mechanisms remain unclear. The pathophysiology of pre-eclampsia seems to be multifactorial and heterogeneous. The common feature of pre-eclampsia is abnormal placentation. Normally, during pregnancy the villous cytotrophoblasts occupy the inner layer of the myometrium, while maternal spiral arteries lose their endothelium and muscle fibers with subsequent conversion into low resistance vessels. The invasion of cytotrophoblast cells into the maternal spiral arteries is not similar in pre-eclampsia. Currently, there are three theories for the etiology of pre-eclampsia; one theory emphasizes the role of ischemia-reperfusion which leads to oxidative stress and vascular disorders. Hypoperfusion of the fetoplacental unit with subsequent hypoxia leads to increased production of oxygen species and inflammatory cytokines by the placenta resulting in inflammation and endothelial dysfunction as well as the expression of clinical features of the disease, especially in the third trimester.

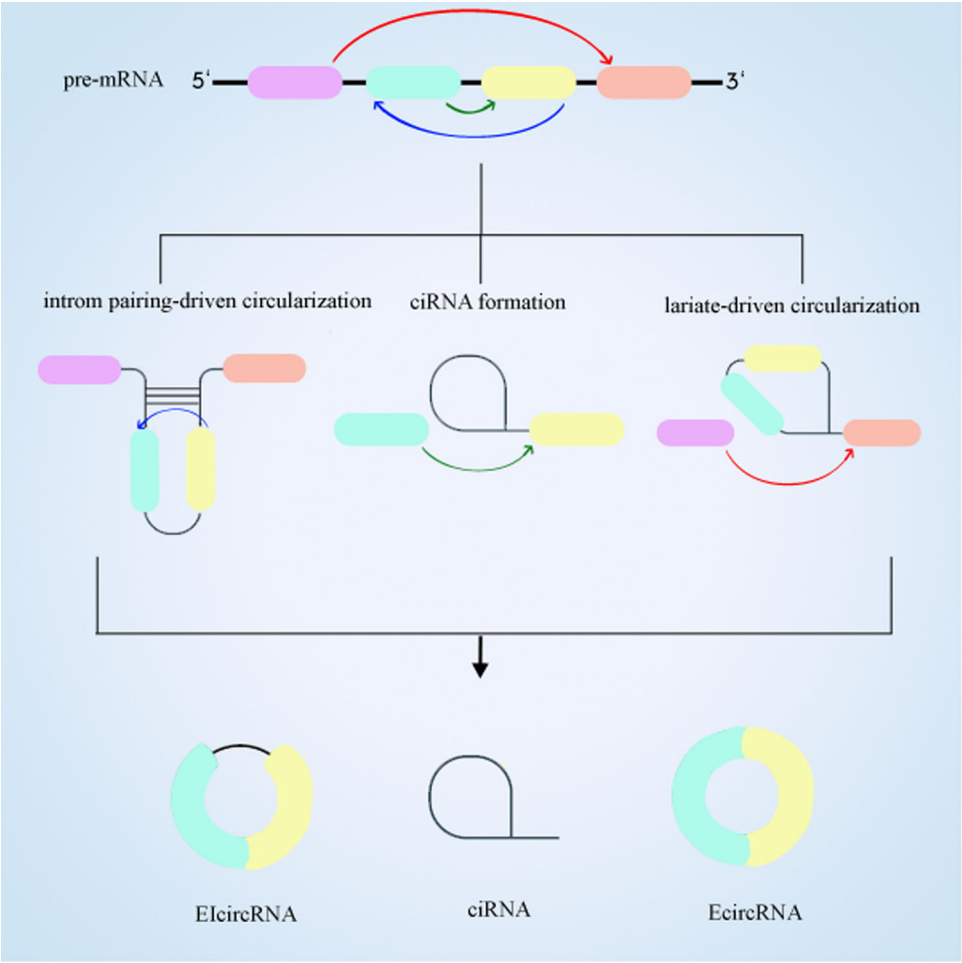

FIGURE 1 CircRNA formation. CircRNA, circular RNA; ciRNA, circular intronic RNA; EcircRNA, exonic circRNA; EIcircRNA, exon–intron circRNA; mRNA, messenger RNA [Color figure can beviewed at wileyonlinelibrary.com]

Endothelial dysfunction is the most frequent pathological feature of pre-eclampsia presents as increased endothelial cell permeability and aggregation of platelet (Wang, Gu, Zhang, & Lewis, 2004). Endothelial dysfunction lowers the production and activation of prostaglandins and nitric oxide which are the two famous vasodilators. Subsequently, decreased production of vasodilators (prostaglandins and nitric oxide) may enhance the activation of platelets on the inner lining of spiral arteries. Endothelial dysfunction and platelet aggregation may lead to increased production of thrombin and fibrin especially in utero–placental circulation (Redman, 1990). On the other hand, the suppression of nitric oxide synthesis in the mother leads to the prevention of embryo implantation (Durán-Reyes et al., 1999). Additionally, disruption of endothelial integrity impairs sodium volume homeostasis and consequently many cardiovascular parameters such as elevated cardiac output and intravascular volume. Moreover, alterations in circulating angiogenic and anti-angiogenic factors have been reported including increased levels of soluble endoglin and soluble fms-likely tyrosine kinase-1 as anti-angiogenic factors, besides reduced levels of vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) as proangiogenic factors (Nilsson, Salonen Ros, Cnattingius, & Lichtenstein, 2004).

The second theory is immune system alterations. Although immune system changes are associated with the origin of pre-eclampsia, other factors, including proinflammatory cytokines, neutrophil activation, and endothelial dysfunction, are also related to the pathophysiology of this syndrome. Increased generation of immune cells leads to the production of tumor necrosis factor-α (TNF-α) which stimulates apoptosis in the extravillous cytotrophoblasts (Genbacev, DiFederico, McMaster, & Fisher, 1999). Furthermore, the human leukocyte antigen (HLA) is involved in the invasion of the spiral arteries. In normal gestation, these cells interact with the trophoblast due to the production of VEGF and PIGF by natural-killer cells. In pre-eclampsia, these factors are elevated while other HLAs such as HLA-G and HLA-E have been reduced (Colbern, Chiang, & Main, 1994). Moreover, recent evidence has demonstrated that heme oxygenase-1 and its metabolite, carbon monoxide, have a protective role in pregnancy which are identified as appropriate targets for the treatment of pre-eclampsia (Ahmed, 2011). Furthermore, immunologists believe that pre-eclampsia is a maternal–fetal immune maladaptation. Fetal or maternal immune maladaptation leads to the induction of apoptosis as well as increasing of various cytokines such as interleukin-2 (IL-2), interferon-γ (IFN-γ), TNF-α, and FAS ligand which are famous mediators of apoptosis (Mor, Straszewski, & Kamsteeg, 2002).

In the pathogenesis of pre-eclampsia, increased placental apoptotic debris may play an important role through deteriorating inflammatory and immune responses. Also, syncytiotrophoblast microparticles can attract monocytes and neutrophiles which lead to increased levels of TNF, IL-12, and superoxide radicals (Aly et al., 2004; Sacks, Redman, & Sargent, 2003). In addition, increased apoptosis leads to the activation of macrophages (Mor et al., 2002). IL-12 which is derived from macrophages or monocytes has the main role in promoting T-helper-1 reactions during pre-eclampsia. IL-12 can significantly stimulate IFN-γ production from natural-killer cells and naive T cells. Interestingly, IFN-γ induces monocytes to more release of IL-12 which leads to rapid decadence in severe pre-eclampsia (Sacks et al., 2003). Taken together, maternal–fetal immune maladaptation may increase the risk of pre-eclampsia by triggering a systematic inflammatory response in mothers. The third theory is the genetic theory which suggests multiple susceptible genes which might affect cardiovascular and hemostatic systems and inflammation. These genes including HLA-G, the angiotensin-converting enzyme (I/D) and Type 1 angiotensin II receptor (AGTR1 A1166C) are also associated with several other genes such as angiotensinogen and endothelial nitric oxide synthase (Mütze, Rudnik-Schoneborn, Zerres, & Rath, 2008; Nilsson et al., 2004). Polymorphism in some genes such as inflammatory regulators leads to altered transcription of cytokines or some antiangiogenic agents (Story & Chappell, 2017). Altogether, pre-eclampsia is a multifactorial disease in which a wide range of factors are involved from genetics to inflammatory and immune responses.

4 | CircRNAs AND PRE-ECLAMPSIA: LATEST EVIDENCE

Zhang, Yang, Long, & Li (2016) investigated the expression of circRNAs in the blood of 82 pregnant women who were between 8 and 20 gestation weeks with the aim of identifying the role of circRNAs in early diagnosis of pre-eclampsia. Pre-eclampsia was detected in 41 subjects while other 41 individuals had a healthy pregnancy. Human circRNA microarray was used to analyze the samples. In addition to circRNA, protein factor endoglin concentration was also measured. The results showed that the blood concentration of circ_101222 in patients with pre-eclampsia was remarkably greater than healthy pregnant women. Circ_101222 in combination with endoglin had the sensitivity of 0.7073 and the specificity of 0.8049 for prediction of pre-eclampsia. This study introduced a novel method for prediction of pre-eclampsia, using a specific circRNA and a protein factor.

Another recent study was conducted with the same purpose using the placental tissues of pregnant women with pre-eclampsia (Qian et al., 2016). The results of microarray analysis detected three circRNAs which were highly upregulated in pre-eclampsia, including hsa_circRNA_100782, hsa_circRNA_102682, and hsa_circRNA_104820. This study suggested that circRNAs might take part in the pathogenesis of pre-eclampsia through activating miRNA sponges (Qian et al., 2016). Indeed, identified circRNAs have several binding sites for miRNA-17 suggesting that these circRNAs are able to regulate the expression of miRNA-17 in human placental tissues. miRNA-17 has been introduced as an angiogenesis-related miRNA, which is expressed highly in pre-eclampsia (Wang et al., 2012). A previous study indicated that increased expression of miRNA-17 in the placenta enhanced developing pre-eclampsia through contributing to trophoblast invasion (Chen & Wang, 2013). Thus, differential expression of circRNAs in the placenta may

lead to upregulation of miRNA-17 via activating miRNA sponge method, thereby enhancing the pathogenesis of pre-eclampsia (Qian et al., 2016). Bai et al. (2018) investigated the profile of circRNAs in placental tissues of pre-eclampsic women, also examined the potential effects of circRNAs dysregulation on the progression of pre-eclampsia. They identified 300 circRNAs differently expressed between women with pre-eclampsia and healthy pregnant women. The results of real-time quantitative polymerase chain reaction showed that in all patients with pre-eclampsia, hg38_circ_0014736 and hsa_circ_0015382 were highly upregulated and hsa_circ_0007121 was downregulated. Data revealed that these three circRNAs are significantly associated with the regulation of transcription, proliferation, response to hypoxia, and protein binding. This study introduced hsa_circ_0007121 as the circRNA which was expressed differently between pre-eclampsia and normal pregnancy before 20 gestation weeks. So, hsa_circ_0007121 could be an appropriate noninvasive biomarker for the prediction of pre-eclampsia.

In another analysis, Zhou et al. (2018) found that 49 circRNAs differently expressed in placental tissues of women with pre-eclampsia, compared to healthy pregnant women. Two of them were upregulated and others downregulated in pre-eclampsic cases. These three circRNAs, including circRNA_3286, circRNA_5593, and circRNA_3800, participated in several cellular functions in pre-eclampsia through activating miRNA sponge (Zhou et al., 2018). In the latest related investigation, the expression of several mRNAs, ncRNAs, and circRNAs was profiled in women with pre-eclampsia and healthy pregnant women to determine a potential prediction marker for pre-eclampsia. Among all of the detected markers, hsa_circ_0036877 was observed to be a potent blood biomarker for pre-eclampsia (Hu et al., 2018). Recently, a bioinformatic analysis reported hsa_circ_0004904 and hsa_circ_0001855 as the two biomarkers involved in the pathogenesis of pre-eclampsia, through activating miRNA sponges which directly target pregnancy-associated plasma protein-A (PAPP-A). According to previous evidence, low levels of PAPP-A have been documented in the serum of pre-eclampsic women (Jiang et al., 2018). There are evidence demonstrating the existence of PAPP-A in the serum of pre-eclampsic women (Jiang et al., 2018). Taken together, the above data indicates that circRNAs are differently expressed in pre-eclampsia which provides new insight into the novel biomarkers for the prediction of pre-eclampsia. Currently, the exact reason why circRNAs levels change during pre-eclampsia is not completely understood. One of the main functions of circRNAs is the activation of miRNA sponge which is involved in the pathogenesis of several diseases. On the other hand, some studies have suggested that circRNAs might play an important role in the pathogenesis of pre-eclampsia through activating miRNA sponge method (Jiang et al., 2018; Qian et al., 2016; Zhou et al., 2018). Thus, we hypothesize that alterations in the levels of circRNAs may be involved in the pathogenesis of pre-eclampsia and associated with its incidence. However, further investigations are required to evaluate possible pathways in pre-eclampsia related to circRNAs (Table 1; Figure 2).

5 | CONCLUSIONS

Pre-eclampsia is a serious complication of pregnancy which is one of the main causes of neonatal, fetal, and maternal death. Untreated pre-eclampsia can develop many other lethal complications such as fetal growth retardation and preterm birth. However, several risk factors have been determined for this disease, which might help with its diagnosis

Still, its early diagnosis and prediction is the main issue for obstetricians. In recent years, circRNAs have attracted more attention for the prediction of diseases and also several studies have conducted to evaluate their roles in pre-eclampsia. Researchers could successfully identify several circRNAs, which are differently expressed during pre-eclampsia. These data revealed that circRNAs could be promising biomarkers in the prediction and diagnosis of

TABLE 1 Experimental studies that investigated the role of circRNAs in pre-eclampsia

CircRNA	Week of gestation	Upregulated/downregulated in pre-eclampsia	Publication year	Ref
circ_101222	Between 8 and 20 weeks	Upregulated	2016	Zhang et al. (2016)
hsa_circRNA_100782	Between 30 and 34 weeks	Upregulated	2016	Qian et al. (2016)
hsa_circRNA_104820	Between 30 and 34 weeks	Upregulated	2016	Qian et al. (2016)
hsa_circRNA_102682	Between 30 and 34 weeks	Upregulated	2016	Qian et al. (2016)
hg38_circ_0014736	Before 20 weeks	Upregulated	2018	Bai et al. (2018)
hsa_circ_0015382	Before 20 weeks	Upregulated	2018	Bai et al. (2018)
hsa_circ_0007121	Before 20 weeks	Downregulated	2018	Bai et al. (2018)
circRNA_3286	Undergone cesarean section	Downregulated	2018	Zhou et al. (2018)
circRNA_5593	Undergone cesarean section	Downregulated	2018	Zhou et al. (2018)
circRNA_3800	Undergone cesarean section	Downregulated	2018	Zhou et al. (2018)
hsa_circ_0036877	24 weeks	Downregulated	2018	Hu et al. (2018)
hsa_circ_0004904	Before 20 weeks	Upregulated	2018	Jiang et al. (2018)
hsa_circ_0001855	Before 20 weeks	Upregulated	2018	Jiang et al. (2018)

Abbreviation: circRNA, circular RNA.

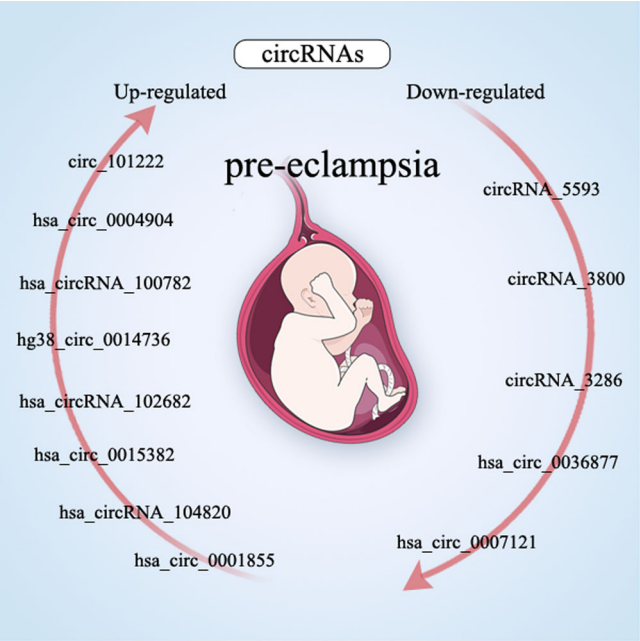

FIGURE 2 Factors related to circRNAs and their impact on the development of pre-eclampsia. CircRNA, circular RNA. [Color figure can beviewed at wileyonlinelibrary.com]

pre-eclampsia. However, further studies are necessary to elucidate certain mechanisms of action for circRNAs in pre-eclampsia.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Z. A. contributed to the conception, design, and drafting of the manuscript. R. S., S. C., and B. M. contributed in reviewing the relevant literature. N. M. was involved in drafting and editing the revised version. All authors approved the final version for submission. Z. M. was involved in the revised version. Z. A. oversaw the study.

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