REVIEW ARTICLE

The Involvement of Long Non-coding RNAs, MicroRNAs and Circular RNA in the Prediction of Cardiovascular Disease in Hypertensive Disorder of Pregnancy- A Scoping Review

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ABSTRACT

Hypertensive disorders of pregnancy (HDP) is a common condition in pregnant women affecting 5% to 10% of pregnancies worldwide. Women who have had HDP are at a higher risk of developing cardiovascular diseases (CVD) earlier in life compared to those who remained normotensive during pregnancy. HDP is associated with a significant increased risk of early-onset of CVD particularly hypertension and stroke, and this can lead to maternal mortality. Non-coding RNAs (ncRNAs) have been linked to HDP, particularly the long non-coding RNA (lncRNA), microRNA (miRNA), and circular RNA (circRNA). This scoping review identifies the most significant ncRNAs involved in predicting CVD in HDP. The protocol by Arksey and O'Malley was used in this scoping review. The steps were carried out in a systematic manner, including the identification of research questions, identification and selection of relevant studies, data charting and collating, summarizing the data, and reporting the findings. Multiple databases were searched for data collection, including Semantic Scholar, Scopus, PubMed Central, and Science Direct. In all thirty-one relevant studies were explored in this review. This review demonstrates the types, models, methodologies, and descriptions of non-coding RNAs associated with HDP. This review highlights that non-coding RNAs play a key role in predicting heart disease linked to high blood pressure in pregnancy by influencing blood vessels, inflammation, and stress, thus emphasizing their potential as early markers and the need for further study.

Keywords:
long non-coding RNA (lncRNA); microRNA (miRNA); Hypertensive disorders of Pregnancy (HDP); cardiovascular disease (CVD)

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INTRODUCTION

During a normal pregnancy, the mean arterial pressure (MAP) drops in the first trimester due to reduced vascular resistance, then gradually rises as blood volume and cardiac output increases, stabilizing by the third trimester. Hypertensive disorders of pregnancy (HDP) affect 5% to 10% of pregnancies and is rising due to increasing cardiometabolic diseases in younger women. Hypertension is defined as SBP≥130 mmHg or DBP ≥80 mmHg in non-pregnant adults, while in pregnancy, it includes chronic hypertension (BP≥140/90 mmHg before 20 weeks), gestational hypertension (BP≥140/90 mmHg after 20 weeks without proteinuria), and preeclampsia (BP≥140/90 mmHg after 20 weeks with proteinuria or end-organ dysfunction).[1]

HDP results from the failure of the maternal cardiovascular system to adapt to hemodynamic changes in pregnancy, involving the placental, vascular, and systemic factors. Inadequate trophoblast invasion leads to high-resistance, ischemic placental vessels, triggering hypoxia and antiangiogenic factors (sFlt-1, soluble endoglin) that impair endothelial function by reducing VEGF and PlGF. This in turn, causes vasoconstriction, increased vascular permeability, inflammation, and oxidative stress, worsening vascular damage. HDP is also linked to abnormal blood volume regulation, immune dysfunction, and genetic factors, including dysregulated non-coding RNAs.

HDP is strongly associated with an increased risk of maternal cardiovascular disease (CVD) later in life, including chronic hypertension, coronary artery diseases, heart failure, and stroke. Persistent endothelial dysfunction from HDP-induced vascular damage can lead to chronic inflammation, impaired vascular repair, and increased arterial stiffness, all of which elevate long-term cardiovascular risk.[1]

HDP are common pregnancy complications that significantly contribute to maternal morbidity and mortality while increasing the risk of early-onset CVD, particularly hypertension and stroke, within 1 to 10 years postpartum. HDP shares key risk factors with CVD, including obesity, insulin resistance, and dyslipidaemia, and serves as an early marker of these conditions. Women with a history of gestational hypertension or preeclampsia face a higher likelihood of developing chronic hypertension, a major driver of CVD.

Molecular and epigenetic mechanisms, such as the dysregulation of non-coding RNAs (lncRNAs, miRNAs, circRNAs), link HDP to cardiovascular complications by influencing inflammation, oxidative stress, and endothelial dysfunction. These vascular and systemic dysfunctions create a pathophysiological connection between HDP and CVD. Given this association, long-term cardiovascular monitoring and preventive care, including regular screening and lifestyle modifications, are essential for women with a history of HDP.[2]

Further research into the molecular pathways connecting HDP and CVD may lead to novel diagnostic tools and targeted interventions. HDP is not just a pregnancy-related condition but a key predictor of future cardiovascular health, highlighting the need for early recognition and proactive management to reduce long-term complications.[2]

NONCODING RNA IN HYPERTENSIVE DISORDERS OF PREGNANCY

Noncoding RNAs (ncRNAs) does not encode or translate into protein. There are more than 75% of human genome transcripted into noncoding RNAs (ncRNAs) that include microRNA (miRNA), long noncoding RNA (lncRNA) and circular RNA (circRNA).[3] miRNA is a small ncRNA with less than 200 nucleotides and plays important roles in regulating gene expression. lncRNAs are transcripts of more than 200 nucleotides without known protein-coding function and less abundant and far less conserved compared with protein coding genes.

They are implicated in epigenetic processes in the nucleus such as chromatin modification, transcription modulation, alternative splicing regulation and also regulates gene expression by activating or suppressing gene expression and translation.[4] circRNA endogenous ncRNA which have circular structure that function as transcriptional regulator. Numerous previous studies have demonstrated the involvement of noncoding RNAs (ncRNAs) in pathophysiological processes in humans including HDP. Therefore, ncRNAs may contribute as novel biomarkers in the diagnosis of HDP.[3]

METHODOLOGY

A scoping review was conducted following the Arksey and O'Malley's protocol. The review identified key studies on ncRNA involvement in HDP, with stages including research question identification, study selection, data charting, and synthesis. A comprehensive literature search was performed using databases such as Semantic Scholar, Scopus, PubMed Central, and Science Direct, focusing on articles published between 2012 and 2022. The following five stages were used to conduct the review:

Stage 1 Identifying the research question
Stage 2 Identifying relevant studies
Stage 3 Study selection
Stage 4 Charting the data
Stage 5 Collating, summarizing, and reporting the results

Stage 1 : Identifying the research question

Research questions are significant in providing guidelines for the studies conducted. Thus, they are important in preparing strategies for scoping review. The research question was: "What are the noncoding RNA involve in Hypertensive disorders of pregnancy (HDP)?"

Stage 2 : Identifying relevant studies

A comprehensive literature search was performed using databases such as Semantic Scholar, Scopus, PubMed Central, and Science Direct. Keywords were derived from Medical Subject Headings (MeSH), focusing on "Hypertensive Disorders of Pregnancy" and "noncoding RNA," with studies published between 2012 and 2022.

Stage 3 : Study selection

Study selection process involved several steps, as shown in *Figure 1*. Firstly, duplicate studies, conference papers, and review articles were excluded during the initial screening. The remaining studies were then evaluated based on their titles and abstracts according to the inclusion and exclusion criteria specified in *Table 1*. Articles that were incomplete or lacked full text were also excluded from the review.

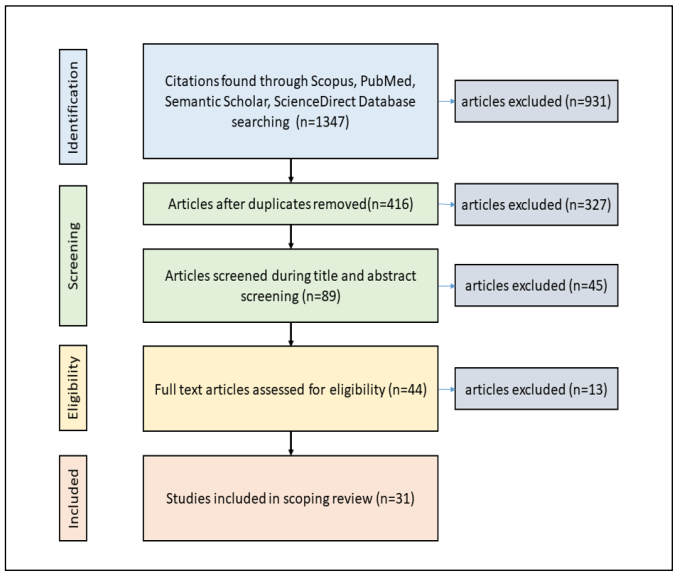

Figure 1 The flow of identification and screening process

Stage 4 : Charting the data

Data extraction involved collecting key information from each study, including the author(s), year of publication, titles of the articles, methodology used, research models, results, and discussions. This data was systematically charted to ensure a comprehensive overview of the relevant studies, allowing for the identification of significant findings related to noncoding RNAs in HDP.

Table I Inclusion and exclusion criteria

Criteria	Inclusion criteria	Exclusion criteria
Types and characteristic of sample	• Pregnancy related human or animal sample which involve in hypertension disease.	• Not hypertension related disease.
Methodology	• *In vivo* studies which produce qualitative and quantitative results.	• In silico studies.
Source of literatures	• Original research article available in English language. • Full text articles published from 2013 to 2023.	• Review articles, conference articles, npublished article which not available in English language. • Articles before stated time frame.

Stage 5 : Collating, summarizing and reporting the results

The remaining selected articles were analyzed to categorize significant noncoding RNAs (ncRNAs) and summarize their involvement in HDP.]

RESULTS

Literature search

Initially, 1347 articles were identified from the four databases. After removing 931 duplicates, conference papers, and review articles, 416 articles remained that met the inclusion and exclusion criteria. These articles were then screened based on their titles and abstracts, leading to the exclusion of 327 irrelevant studies. The remaining articles underwent full-text screening, ultimately resulting in the final selection of 31 studies, as summarized in Table 2.

Study characteristics

Among the 31 articles included in this review, the studies varied in their focus on different types of non-coding RNAs (ncRNAs) and their association with HDP. Specifically, 9 studies examined the involvement of long non-coding RNAs (lncRNAs), 21 studies investigated the role of microRNAs (miRNAs), and 1 study focused on circular RNAs (circRNAs). Each of these studies clearly identified the specific type of ncRNA studied and assessed its expression levels. The findings revealed that the expression levels of these ncRNAs correlated with the

pathogenesis of HDP, highlighting their potential as biomarkers for diagnosing the disease.

Majority of the studies involved human subjects, although a few researchers utilized animal models. The studies were conducted in several countries, namely China, Egypt, the Netherlands, Iran, Hungary, the Czech Republic, Istanbul, Korea, and Bahrain. All the studies included control groups, consisting of either normotensive pregnant women or normotensive female rats

Their research designs followed a consistent and structured approach, starting with the determination of subjects and sample preparation, followed by analysis of gene expression. The gene expression was predominantly measured using real-time PCR techniques, and all studies adhered to the protocol of the manufacturers. This methodology ensured that data collection was standardized and results were reliable across all the studies.

Table II. Summary of involvement of noncoding RNA in hypertensive disorders of pregnancy.

Study No.	Authors	Title	Country	Model	Methodology	Key Findings	Conclusions
1	Abd El Gayed, Eman Masoud, Abo Shady, Heba Maged, Elhelbawy, Mohammed, El Deen Arafat, Eman S. (2022)	Study the relationship between long non-coding RNA (CCAT1) expression and CDK4 expression levels in Egyptian patients with preeclampsia	Egypt	Human	RNA expression analysis	CCAT1 expression was significantly higher in preeclampsia patients	CCAT1 may be a potential biomarker for preeclampsia
2	El Gayed, Eman Masoud Abd, Zaid, Ibrahim Fathi, El Gayed, Alaa Masoud Abd, Zaki, Aziza Mahmoud Mohamed, Fouda, Eman Abd allah Mahmoud	Biochemical study on long non coding RNA gene expression in women having preeclampsia	Egypt	Human	RNA expression study	Altered expression of lncRNAs in preeclampsia cases	lncRNA expression profiles can be used to predict preeclampsia
3	Wang, Qiuhong, Lu, Xun, Li, Chunyan, Zhang, Wen, Lv, Yan, Wang, Luyao, Wu, Lan, Meng, Li, Fan, Yuru, Ding, Hongjuan, Long, Wei, Lv, Mingming (2019)	Down-regulated long non-coding RNA PVT1 contributes to gestational diabetes mellitus and preeclampsia via regulation of human trophoblast cells	China	Human	RNA analysis, trophoblast cell study	PVT1 expression was down-regulated in preeclampsia and gestational diabetes	PVT1 may serve as a therapeutic target for these conditions
4	Lei, Di, Fang, Congcong, Deng, Na, Yao, Baozhen, Fan, Cuifang (2021)	Long noncoding RNA expression profiling identifies MIR210HG as a novel molecule in severe preeclampsia	China	Human	RNA profiling	MIR210HG is significantly overexpressed in severe preeclampsia	MIR210HG could be a potential biomarker for severe preeclampsia
5	Lip, Simone V., Boekschoten, Mark V., Hooiveld, Guido J., van Pampus, Mariëlle G., Scherjon, Sicco A., Plösch, Torsten, Faas, Marijke M. (2020)	Early-onset preeclampsia, plasma microRNAs, and endothelial cell function	Netherlands	Human	Plasma microRNA profiling	Specific microRNAs are altered in early-onset preeclampsia	Plasma microRNAs could serve as early biomarkers for preeclampsia
6	Adel, Sherihan, Mansour, Amal, Louka, Manal, F, Elmekkawi S, Swelam, Nahed (2017)	Evaluation of MicroRNA-210 and Protein tyrosine phosphatase, non receptor type 2 in Preeclampsia	Egypt	Human	MicroRNA and protein analysis	MicroRNA-210 is significantly altered in preeclampsia	MicroRNA-210 could be a potential diagnostic marker
7	Nejad, Reza Mola Ali, Saeidi, Kolsoum, Gharbi, Sedigheh, Salari, Zohreh, Saleh-Gohari, Nasrollah	Quantification of circulating miR-517c-3p and miR-210-3p levels in preeclampsia	Iran	Human	Circulating miRNA quantification	miR-517c-3p and miR-210-3p levels are significantly altered in preeclampsia	These miRNAs could be used as biomarkers for preeclampsia diagnosis
8.	Wang, Yonghong, Cheng, Keyan, Zhou, Wenli, Liu, Huiqiang, Yang, Taotao, Hou, Peiqin, Li, Xiaowei (2019)	miR-141-5p regulate ATF2 via effecting MAPK1/ERK2 signaling to promote preeclampsia	China	Human	miRNA regulation study	miR-141-5p regulates ATF2 and MAPK1/ERK2 signaling in preeclampsia	miR-141-5p may be involved in preeclampsia pathogenesis

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Study No.	Authors	Title	Country	Model	Methodology	Key Findings	Conclusions
9	Zheng, Dongying, Hou, Yue, Li, Yuanyuan, Bian, Yue, Khan, Muhanmmad, Li, Fan, Huang, Ling, Qiao, Chong (2020)	Long Non-coding RNA Gas5 Is Associated With Preeclampsia and Regulates Biological Behaviors of Trophoblast via MicroRNA-21	China	Human	RNA interaction study	Gas5 lncRNA interacts with miR-21 to affect trophoblast functions	Gas5 could be a therapeutic target for preeclampsia
10	Ghafari, Ali, Lessan Peze shki, Mahboob, Saffari, Mojtaba (2020)	MICRO RNA 155, 210, 494, 29B AND 34A EXPRESSION PROFILE IN PREECL AMPSIA AND NORMAL PREGNANCIES	Iran	Human	miRNA expression profiling	Expression of miR-155, miR-210, miR-494, miR-29B, and miR-34A is altered in preeclampsia	miRNA expression profiles can differentiate preeclampsia from normal pregnancies
11	Abdelaleem, Omayma, Mahmoud, Rania, Shaker, Olfat, Hemeda, Nada, Ahmed, Naglaa (2018)	LNC RNA HULC AS A NOVEL DIAGNOSTIC AND THERAPEUTIC TARGET IN PREECLAMPSIA	Egypt	Human	lncRNA analysis	LncRNA HULC is significantly upregulated in preeclampsia	LncRNA HULC could be used for early detection and therapy
12	Chen, Dan, He, Biwei, Zheng, Panchan, Wang, Shuying, Zhao, Xueya, Liu, Jinyu, Yang, Xingyu, Cheng, Weiwei (2021)	Identification of mRNA-, circRNA- and lncRNA-Associated ceRNA Networks and Potential Biomarkers for Preeclampsia From Umbilical Vein Endothelial Cells	China	Human	ceRNA network analysis	Identified key mRNA, circRNA, and lncRNA in preeclampsia	These molecules could be potential biomarkers for preeclampsia diagnosis
13	Lázár, Levente, Nagy, Bálint, Molvarec, Attila, Szarka, András, Rigó, János (2012)	Role of hsa-miR-325 in the etiopathology of preeclampsia	Hungary	Human	miRNA profiling	miR-325 is significantly altered in preeclampsia	miR-325 could be a novel marker for preeclampsia
14	Zhou, Dexia, Qu, Bin, Zhang, Xuan (2022)	Diagnostic value of serum miR-25-3p in hypertensive disorders in pregnancy	China	Human	miRNA profiling	miR-25-3p is upregulated in hypertensive disorders of pregnancy	miR-25-3p could be a diagnostic marker for hypertensive pregnancy disorders
15	He, Xin, Ding, Dan Ni (2022)	Expression and clinical significance of miR-204 in patients with hypertensive disorder complicating pregnancy	China	Human	miRNA expression study	miR-204 expression is altered in hypertensive disorders of pregnancy	miR-204 could serve as a diagnostic marker for hypertensive pregnancy disorders
16	He, Xin, Ding, Danni (2022)	High miR-200a-3p expression has high diagnostic values for hypertensive disorders complicating pregnancy and predicts adverse pregnancy outcomes	China	Human	miRNA profiling	miR-200a-3p is elevated in hypertensive disorders of pregnancy	miR-200a-3p may predict adverse pregnancy outcomes
17	Yang, Hai Yan, Jiang, Ling (2022)	The involvement of long noncoding RNA APOA1-AS in the pathogenesis of preeclampsia	China	Human	lncRNA study	APOA1-AS is involved in the pathogenesis of preeclampsia	APOA1-AS may be a therapeutic target for preeclampsia
18	Tang, Qiuqin, Gui, Jing, Wu, Xian, Wu, Wei (2019)	Downregulation of miR-424 in placenta is associated with severe preeclampsia	China	Human	miRNA expression analysis	miR-424 is downregulated in severe preeclampsia	miR-424 could be used as a diagnostic marker for severe preeclampsia
19	Huang, Jin, Qian, Yating, Cheng, Qing, Yang, Jing, Ding, Hongjuan, Jia, Ruizhe (2020)	Overexpression of Long Noncoding RNA Uc.187 Induces Preeclampsia-Like Symptoms in Pregnancy Rats	China	Human	lncRNA overexpression study	Uc.187 overexpression induces preeclampsia-like symptoms	Uc.187 could be a target for preeclampsia therapy
20	Hromadnikova, Ilona, Kotlabova, Katerina, Dvorakova, Lenka, Krofta, Ladislav (2019)	Postpartum profiling of microRNAs involved in pathogenesis of cardiovascular/cerebrovascular diseases in women exposed to pregnancy-related complications	Czech Republic	Human	Postpartum miRNA profiling	MiRNAs related to cardiovascular diseases are altered postpartum	Postpartum miRNA profiling could be used for predicting long-term health outcomes
21	Biró, Orsolya, Alasztics, Bálint, Molvarec, Attila, Joó, József, Nagy, Bálint, Rigó, János (2017)	Various levels of circulating exosomal total-miRNA and miR-210 hypoxamiR in different forms of pregnancy hypertension	Hungary	Human	Exosomal miRNA profiling	Circulating exosomal miRNA levels vary across different types of pregnancy hypertension	miRNA profiling could aid in the diagnosis of pregnancy hypertension
22	Gao, Zheng, Wang, Li, Wang, Jinyun, Yang, Fengyong, Qu, Jin (2017)	Molecular mechanism of miR-181b in heart disease due to pregnancy-induced hypertension syndrome	China	Rats	miRNA mechanism study	miR-181b regulates heart disease caused by pregnancy-induced hypertension	miR-181b could be a target for therapeutic intervention in heart disease during pregnancy
23	Gunel, Tuba, Hosseini, Mohammad Kazem, Gumusoglu, Ece, Kisakesen, Halil Ibrahim, Benian, Ali, Aydinli, Kilic (2017)	Expression profiling of maternal plasma and placenta microRNAs in preeclamptic pregnancies by microarray technology	Istanbul	Human	miRNA profiling	Maternal plasma and placenta miRNAs are differentially expressed in preeclampsia	miRNA profiling could help diagnose preeclampsia

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Study No.	Authors	Title	Country	Model	Methodology	Key Findings	Conclusions
24	Wu, Gui Mei, Jin, Yan, Cao, Yan Min, Li, Ji Yun (2020)	The diagnostic value and regulatory mechanism of miR-200a targeting ZEB1 in pregnancy-induced hypertension	China	Human	miRNA target study	miR-200a targets ZEB1 in pregnancy -induced hypertension	miR-200a could be a diagnostic biomarker and therapeutic target
25	Jairajpuri, Deeba S., Malalla, Zainab H., Mahmood, Naeema, Almawi, Wassim Y. (2017)	Circulating microRNA expression as predictor of preeclampsia and its severity	Bahrain	Human	miRNA profiling	Specific microRNAs are predictive of preeclampsia and its severity	Circulating miRNAs could be used as biomarkers for preeclampsia
26	Liu, D.-F, Li, S.-M, Zhu, Q.-X, Jiang, W (2018)	The involvement of miR-155 in blood pressure regulation in pregnant hypertension rat via targeting FOXO3a	China	Rats	miRNA mechanism study	miR-155 regulates blood pressure during pregnancy by targeting FOXO3a	miR-155 could be a potential therapeutic target in hypertensive pregnancies
27	Kim, Suji, Park, Minsik, Kim, Ji Yoon, Kim, Taesam, Hwang, Jong Yun, Ha, Kwon Soo, Won, Moo Ho, Ryoo, Sungwoo, Kwon, Young Guen, Kim, Young Myeong (2020)	Circulating miRNAs Associated with Dysregulated Vascular and Trophoblast Function as Target-Based Diagnostic Biomarkers for Preeclampsia	Korea	Human	miRNA analysis	Dysregulated miRNAs in circulation are associated with vascular and trophoblast dysfunction	These miRNAs could be biomarkers for preeclampsia diagnosis
28	Hromadnikova, Ilona, Kotlabova, Katerina, Ondrackova, Marketa, Kestlerova, Andrea, Novotna, Veronika, Hympanova, Lucie, Doucha, Jindrich, Krofta, Ladislav (2013)	Circulating C19MC MicroRNAs in preeclampsia, gestational hypertension, and fetal growth restriction	Czech Republic	Human	MicroRNA profiling	C19MC microRNAs are differentially expressed in preeclampsia and related conditions	C19MC microRNAs could serve as biomarkers for pregnancy-related complications
29	Fan, Xufei, Lou, Jianyi, Zheng, et al. (2021)	Interference with lncRNA NEAT1 promotes the proliferation, migration, and invasion of trophoblasts by upregulating miR-411-5p and inhibiting PTEN expression	China	Human	lncRNA interference study	NEAT1 upregulates miR-411-5p and promotes trophoblast cell activity	NEAT1 may be a therapeutic target for trophoblast dysfunction
30	Hromadnikova, Ilona, Kotlabova, Katerina, Hympanova, Lucie, Krofta, Ladislav (2016)	Gestational hypertension, preeclampsia and intrauterine growth restriction induce dysregulation of cardiovascular and cerebrovascular disease associated microRNAs in maternal whole peripheral blood	Czech Republic	Human	miRNA profiling	Pregnancy complications lead to dysregulation of miRNAs associated with cardiovascular diseases	Maternal blood miRNAs could predict long-term health risks
31	Hany, Ayman M, Nasser, Yasser H, Ahmed, Hanan H, Rashed, Laila A, Mostafa, Mostafa M, Ibrahim, Walaa, Sanad, Salah A (2019)	Expression of Micro RNAs 206 and 133b and serum IL-17 levels in preeclamptic females	Egypt	Human	miRNA and IL-17 expression study	miR-206 and miR-133b levels are altered in preeclampsia	miR-206 and miR-133b could serve as biomarkers for preeclampsia

DISCUSSION

This scoping review highlights the significant roles of long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs) in predicting cardiovascular diseases (CVD) associated with hypertensive disorders of pregnancy (HDP). By systematically reviewing 31 studies, we identified substantial evidence supporting the involvement of these non-coding RNA species in the pathogenesis and potential diagnosis of HDP-related cardiovascular complications.

Functions and Mechanisms of Long Non-Coding RNAs in HDP

Among the nine studies focusing on lncRNAs, a common theme is their regulatory role in gene expression, articularly in pathways relevant to HDP pathophysiology. LncRNAs influence endothelial function, inflammation, oxidative stress, and vascular remodeling, all of which are pivotal in HDP development and its long-term cardiovascular consequences. Elevated or reduced expression levels of specific lncRNAs were consistently associated with key biomarkers of HDP and its progression to CVD. These findings suggest that lncRNAs may serve as early predictors of CVD, allowing for timely intervention to mitigate cardiovascular risk. The reviewed studies highlighted the diverse regulatory functions of lncRNAs.

Many lncRNAs interact with chromatin-modifying proteins, DNA, or histones to influence gene expression epigenetically. They can recruit chromatin modifiers, such

as histone methyltransferases or demethylases, to specific genomic loci, resulting in chromatin remodeling and subsequent activation or repression of target genes. Additionally, some lncRNAs act as transcriptional regulators by interacting with transcription factors or other DNA-binding proteins. They can act as molecular scaffolds, guiding the formation of transcriptional complexes or acting as decoys by sequestering transcriptional regulators away from their target sites.[6]

Some lncRNAs participate in the regulation of RNA processing, including alternative splicing, RNA editing, and RNA stability. They can interact with splicing factors, RNA-binding proteins, or small nuclear ribonucleoprotein particles (snRNPs), influencing the processing and maturation of various RNA species. Some lncRNAs function as molecular scaffolds that facilitate the assembly of ribonucleoprotein complexes. By interacting with proteins and RNA molecules simultaneously, lncRNAs can bring together multiple components to form functional complexes involved in diverse cellular processes. lncRNAs can localize to specific subcellular compartments, such as the nucleus, cytoplasm, or specific organelles. Their subcellular localization plays a role in their functional specificity and regulatory roles.[7]

Long non-coding RNAs are a diverse group of RNA molecules characterized by their extended nucleotide sequences and lack of protein-coding potential. While early genomics research primarily focused on protein-coding genes, the realization that a substantial portion of the genome is transcribed into non-coding RNAs, including lncRNAs, has stepped up new avenues of investigation.

Long non-coding RNAs (lncRNAs) have emerged as versatile players involved in a diverse array of vital biological processes. To enhance our understanding of their functionality and delve deeper into the wealth of transcribed sequences, it is advantageous to categorize lncRNAs into distinct groups. In this review, we present a summary of classification methods for lncRNAs based on four major features: their genomic location and context, the effects they exert on DNA sequences, the mechanisms through which they function, and their targeting mechanisms.

By combining these classification criteria with existing functional annotations, we aim to uncover potential connections between different categories and provide a comprehensive analysis of the biological characteristics exhibited by lncRNAs within each category. This systematic approach not only aids in simplifying the interpretation of lncRNA functionality but also promotes in-depth exploration of their roles in various biological processes.

The above classifications facilitate the identification of commonalities and distinctions among lncRNAs, which can be crucial in formulating new hypotheses based on their unique features and understanding the intricate mechanisms underlying lncRNA functionality.[8]
The precise mechanisms through which lncRNAs influence gene expression is not fully comprehended. Some lncRNAs serve as scaffolds or guides for protein complexes, while others regulate gene expression by binding to DNA or RNA molecules. However, the exact workings of many lncRNAs are yet to be uncovered. Furthermore, lncRNA expression is often highly specific to certain tissues and cell types, posing a challenge to the study of their functions and regulatory mechanisms in a broader context.

Functions and Mechanisms of MicroRNAs in HDP

MicroRNAs (miRNAs) are major regulators of endothelial dysfunction, angiogenesis, and inflammation, major causes of HDP and CVD. Among the 21 studies reviewed, miRNAs such as miR-21 and miR-126 control vascular integrity, nitric oxide bioavailability, and inflammatory signaling, making them valuable diagnostic biomarkers for HDP-associated cardiovascular risks.

MiRNAs regulate gene expression post-transcription by inhibiting protein synthesis or triggering mRNA degradation, modulating cell proliferation, differentiation, apoptosis, and homeostasis. Their dysregulation plays a role in cancer, neurodegenerative disorders, and CVD, making them as potential therapeutic targets.[9]

In hypertension and endothelial dysfunction, miR-21 and miR-155 contribute to inflammation, oxidative stress, and reduced nitric oxide (NO) availability-features of vascular dysfunction. Angiogenesis and vascular repair are regulated by miR-126 and miR-155, while miR-29 and miR-143/145 regulate the renin-angiotensin-aldosterone system (RAAS), affecting vascular tone and fluid balance. Owing to their tissue-restricted expression, miRNAs are very specific biomarkers yet hard to detect and analyze functionally. The role of miRNAs in endothelial function defines therapeutic approaches directed to miRNA pathway blockade for the prevention of hypertension and reduction of cardiovascular risks. Continued investigation unraveled miRNA-mediated regulatory pathways, promising new cardiovascular interventions.[10]

Functions and Mechanisms of Circular RNAs in HDP

Circular RNAs (circRNAs) play roles in gene regulation and have been put forward as biomarkers in and essential hypertension. Despite the paucity of research into circRNAs in HDP, their stability and function as microRNA (miRNA) sponges suggest that they may modulate pathways significant in oxidative stress and endothelial dysfunction. Their resistance to degradation and tissue-specific expression patterns makes them perfect candidates for diagnostic and prognostic research in HDP-related cardiovascular disease.

CircRNAs regulate gene expression post-transcriptionally by sequestering miRNAs, preventing them from downregulating target mRNAs, and interacting with RNA-binding proteins. They influence cell proliferation, differentiation, apoptosis, immune responses, and are implicated in various diseases, including cancer and neurological disorders. Their stable circular structure enhances their potential as reliable biomarkers.[11]

In primary hypertension, circRNAs are involved in inflammation, oxidative stress, and endothelial dysfunction. They have been proposed to have diagnostic potential in studies, circRNA_15698, which was significantly upregulated in hypertensive patients. Their clinical utility, however, awaits confirmation and standardization of detection methods.

Despite the relative stability of circRNAs, degradation mechanisms are not known. They are expressed at low levels with high tissue specificity, and their quantitation and detection are challenging. Inspite of these limitations, circRNA research continues to expand, yielding novel information on gene regulation and disease mechanisms. Their potential involvement in the early diagnosis and therapy of hypertension indicates the need for further investigation to establish their application in the clinical setting.

LIMITATION

This scoping review examines the role of non-coding RNAs (ncRNAs) in Hypertensive Disorders of Pregnancy (HDP). However, several limitations specific to the topic must be considered. One key challenge is the variability of ncRNA biomarkers across different populations, as the studies reviewed included diverse sample types, such as human and animal models, which may impact the generalizability of the findings. Moreover, the available data on ncRNAs in HDP remains limited, with many studies focusing on individual ncRNAs rather than offering a comprehensive understanding of their overall role. Additionally, there is no consensus on the most reliable and validated ncRNA biomarkers for predicting cardiovascular outcomes in HDP, which complicates their clinical application. Lastly, the use of varying methodologies and techniques for ncRNA detection and analysis across studies may contribute to inconsistencies in the results, hindering the ability to draw definitive conclusions.

CONCLUSION

This scoping review underscores the pivotal roles of non-coding RNAs (lncRNAs, miRNAs, and circRNAs) in predicting cardiovascular diseases (CVD) linked to hypertensive disorders of pregnancy (HDP). LncRNAs are crucial in regulating endothelial function, inflammation, oxidative stress, and vascular remodelling, positioning them as potential early biomarkers for cardiovascular risk in HDP. MiRNAs are key regulators of endothelial dysfunction, angiogenesis, and inflammation, offering promise as non-invasive diagnostic tools for HDP-related cardiovascular complications.

Although circRNAs are less studied, their stability and ability to modulate miRNA activity highlight their potential for further exploration in the diagnosis of HDP and CVD. These findings emphasize the need for more focused research, particularly on circRNAs, to fully understand their mechanisms and clinical applications. Advancing the knowledge of ncRNAs and their diagnostic and prognostic roles could lead to earlier identification and intervention for individuals at-risk, ultimately improving maternal cardiovascular health outcomes.

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