v. 5, n. 5, 2025

International Journal of Health Science

Acceptance date: 15/01/2025

THE ROLE OF MICRORNAS AS BIOMARKERS IN THE PREDICTION, MONITORING AND DIAGNOSIS OF FETAL GROWTH RESTRICTION

Giselle Vaz Dos Reis Semedo
Universidade Federal do Mato Grosso Do Sul (UFMS), Campo Grande - MS
https://orcid.org/0009-0006-4469-7665

Vanessa de Oliveira Medeiros
Universidade Federal Fluminense (UFF)
Niterói - RJ
https://orcid.org/0009-0001-8615-8049

Wilcéia Aparecida Souza da Silva
Universidade Federal do Paraná (UFPR)
Curitiba - PR
https://orcid.org/0009-0001-5150-5047

Lívia Gontijo Silva
Faculdade Atenas Passos (UniAtenas)
Passos - MG
https://orcid.org/0009-0002-0749-0279

Luiza Nunes Levado
Universidade Metropolitana de Santos (UNIMES), Santos - SP
https://orcid.org/0009-0009-5488-4706

Gleice Mara Alves Nunes
Universidade de Mogi das Cruzes (UMC)
Mogi das Cruzes - SP
https://orcid.org/0009-0005-7487-2578

Mariana Estella Conti Nicoletti
Universidade do Oeste Paulista (UNOESTE)
Jaú-SP
https://orcid.org/0009-0006-7709-6540

Alceste Pomar Schiochet
Centro Universitário CEUNI (FAMETRO)
Manaus- AM
https://orcid.org/0000-0002-4320-7007

Hilda Cristiane Costa Cruz Ogura
Universidade do Oeste Paulista (UNOESTE)
Jaú-SP
https://orcid.org/0009-0006-7664-1914

Giovanna Vieira Picoloto
Universidade de Taubaté (UNITAU)
Taubaté - SP
https://orcid.org/0009-0003-1089-5450

Juliana Zeferino Reinaldo
Universidade Federal de Santa Catarina (UFSC)
Florianópolis - SC
https://orcid.org/0009-0005-3389-8771

Abstract: Objective: This study aims to investigate the role of microRNAs (miRNAs) as biomarkers in the early diagnosis, monitoring and prognosis of fetal growth restriction (FGR). **Method**: A literature review was carried out following the PVO (Population, Variables and Outcome) strategy. The search took place on the PubMed database, using the keywords "microRNA", "fetal growth restriction" and "diagnosis", combined with Boolean operators. After initial screening of 91 articles, 23 were selected based on inclusion and exclusion criteria. **Discussion**: miRNAs play an essential role in regulating fetal growth, influencing processes such as angiogenesis, apoptosis and cell metabolism. Specific profiles, including miR-16-5p, miR-27b-3p, miR-206 and miR-185-5p, have been associated with placental function and response to hypoxia, suggesting their potential as diagnostic and prognostic biomarkers. However, there are differences between the studies, especially regarding the specificity and sensitivity of these markers, as well as limitations such as small sample sizes and lack of methodological standardization. **Final considerations:** miRNAs show significant potential as diagnostic tools in CRF, offering a promising approach for early detection and clinical follow-up. However, additional robust studies are needed to validate the profiles identified and explore their interactions with other molecular factors. Standardization of methodologies and the development of clear clinical protocols are essential to enable their practical incorporation into the management of CRF, providing more accurate diagnoses and personalized interventions.

Keywords: Microrna, Fetal Growth Restriction, Diagnosis, Biomarkers, Angiogenesis, Gene Expression.

INTRODUCTION

MicroRNAs (miRNAs), small non-coding RNA molecules, play crucial roles in gene regulation and in mediating fundamental biological processes such as proliferation, cell differentiation and angiogenesis. These mechanisms are particularly relevant in pregnancy, where placental functionality and fetal development depend on balanced molecular regulation. Recent studies have highlighted the association of miRNAs with fetal growth restriction (FGR), a condition characterized by impaired intrauterine development, with a significant impact on neonatal and lifelong health (Kennedy *et al*., 2023; Jin *et al.*, 2024).

According to the literature, the differential expression of miRNAs in placental samples and in the maternal circulation has been linked to various obstetric complications, including pre-eclampsia, preterm birth and small for gestational age (Ali *et al*., 2021; Tsai *et al.*, 2017). These changes not only reflect placental dysfunction, but also suggest a potential for miRNAs to act as biomarkers in the early diagnosis and monitoring of these conditions. Specifically, exosomal miRNAs, due to their stability and presence in the maternal circulation, are emerging as a promising tool for non-invasive clinical applications (Jin *et al*., 2024; Wen *et al*., 2017).

Despite advances in the identification of miRNAs associated with CRF, gaps remain in the understanding of their underlying molecular mechanisms and in the integration of these biomarkers into clinical protocols. Studies indicate that miRNAs regulate essential signaling pathways such as TGF-β and IGF/IGFR, directly influencing angiogenesis and nutrient transport across the placenta (Chiofalo *et al*., 2017; Tsai *et al.*, 2017). However, the heterogeneity of miRNA expression profiles in different populations and clinical conditions limits their universal validation as biomarkers.

This study aims to evaluate the role of miRNAs as biomarkers in the early diagnosis, monitoring and prognosis of CRF. The aim is to understand how these small regulators can contribute to the identification of fetuses at risk, improve the assessment of placental function and elucidate the molecular mechanisms of the pathophysiology of CRF, with a view to advancing the clinical management of this condition.

METHOD

This study consists of a literature review based on the PVO (Population, Variables and Outcome) strategy. The guiding question formulated was: *"How can microRNAs (miRNAs) act as effective biomarkers in the early diagnosis, monitoring and prognosis of fetal growth restriction (FGR), contributing to the identification of fetuses at risk, assessment of placental function and understanding of the molecular mechanisms involved in the pathophysiology of FGR?"* In this context, the population or problem of the study refers to patients with fetal growth restriction (FGR), focusing on the expression of microRNAs as biomarkers for the identification of fetuses at risk, evaluation of placental function and understanding of the molecular mechanisms of the pathophysiology of FGR.

The searches were carried out in the PubMed Central (PMC) database using descriptors combined with the Boolean operator "AND". The search strategy included the terms: ("microrna s"[All Fields] OR "micrornas"[MeSH Terms] OR "microrna"[All Fields]) AND ("diagnosis"[MeSH Terms] OR "diagnosing"[All Fields]) AND ("fetal growth retardation"[MeSH Terms] OR "fetal growth restriction"[All Fields]). The initial search resulted in 91 articles, which were submitted to the selection criteria. The inclusion criteria were: articles in English, published between 2014 and 2024, which directly addressed the

proposed theme, including reviews and meta-analyses, and which were available in full. On the other hand, the exclusion criteria included: duplicate articles, publications available only in the form of abstracts and studies that did not directly address the proposed theme or that did not meet the defined criteria.

After applying the inclusion and exclusion criteria, 23 articles were selected to make up the body of evidence for this study. This methodology was designed to ensure the quality and relevance of the studies included, enabling an in-depth analysis of the role of miRNAs as biomarkers in the early diagnosis, monitoring and prognosis of fetal growth restriction (FGR), as well as in understanding the molecular mechanisms involved in the pathogenesis of this condition.

DISCUSSION

THE IMPORTANCE OF MICRORNAS IN THE PATHOPHYSIOLOGY AND DIAGNOSIS OF FETAL GROWTH RESTRICTION

MicroRNAs (miRNAs) play a central role in gene regulation during pregnancy, influencing fundamental processes such as angiogenesis, vascular remodeling and placental signaling. Studies show that the differential expression of miRNAs is directly related to placental dysfunction, one of the main determinants of fetal growth restriction (FGR). MiRNAs such as miR-210-5p (Awamleh and Han, 2020) and miR-141-3p (Saha *et al*., 2017) have been identified as critical regulators of pathways associated with placental hypoxia, negatively affecting trophoblast invasion and nutrient transport to the fetus.

MicroRNAs, such as miR-28-5p and miR-301a-3p (Baker *et al*., 2021), also show significant relevance in regulating molecular mechanisms associated with fetal growth restriction (FGR). These miRNAs not only act as mediators in cell communication, but also have potential as therapeutic targets in conditions of placental hypoxia. Furthermore, the identification of miRNAs in maternal circulation, such as miR-127-3p (Gusar *et al*., 2017), allows for a direct correlation between placental molecular alterations and fetal pathophysiological status, highlighting their relevance as non-invasive diagnostic biomarkers. These findings reinforce the potential of miRNAs to elucidate mechanisms underlying FGR and advance early diagnosis, enabling more precise and effective medical interventions.

MiRNAs AS BIOMARKERS AND THERAPEUTIC TARGETS IN GESTATIONAL COMPLICATIONS

The use of miRNAs as biomarkers has emerged as a promising tool for the management of gestational complications. MiRNAs such as miR-206 (Li and Liu, 2020) and miR-132 (Morales-Roselló *et al*., 2022a) have shown high predictive accuracy for complications such as pre-eclampsia and late FGR, especially when combined with clinical parameters such as the cerebroplacental ratio (CPR).

The expression of miRNAs such as miR-210 (Chen *et al*., 2021) also reinforces their potential as a biomarker in complications such as pre-eclampsia and placental insufficiency, due to their direct impact on trophoblast invasion and placental angiogenesis. In addition, the therapeutic potential of miRNAs has been explored in conditions of placental insufficiency. MiRNAs such as miR-25-3p (Gusar *et al*., 2017), which regulates placental redox state, offer new prospects for molecular interventions that can restore cellular homeostasis and mitigate the effects of intrauterine hypoxia. However, the challenge lies in the effective and safe delivery of these miRNAs as targeted therapies.

The development of technologies to deliver miRNAs as therapeutic agents has also shown significant progress. The use of lipid nanoparticles to stabilize miRNAs and deliver them locally can overcome the limitations of toxicity and specificity. This reflects significant potential for the future of personalized medicine in obstetric complications.

CLINICAL POTENTIAL OF miRNAs IN PREDICTING AND MONITORING FETAL GROWTH

miRNAs have great potential as clinical tools for predicting and monitoring CRF. Studies such as that by Tagliaferri *et al*. (2021) show that miRNAs such as miR-16-5p can be detected in maternal plasma before clinical signs appear, allowing for early interventions. Similarly, miR-185-5p was associated with brain redistribution in fetuses with late-onset FGR, reflecting adaptations to fetal hypoxia (Morales-Roselló *et al*., 2022).

Studies such as that by Hromadnikova, Kotlabova and Krofta (2022), identify miRNAs associated with cardiovascular diseases as promising tools for predicting adverse outcomes, including CHR. These miRNAs have demonstrated a significant relationship with placental functionality, allowing for more refined monitoring throughout pregnancy. Despite this, challenges remain in the broad clinical validation of miRNAs as biomarkers (Hromadnikova; Kotlabova; Krofta, 2022). Heterogeneity in collection and analysis protocols, as well as population differences, limit the generalizability of results (Rahman et al., 2018). Thus, the integration of miRNAs into biomarker panels, combined with imaging techniques and genetic testing, represents the future of personalized management of CRF (Pinson *et al*., 2023).

THE ROLE OF miRNAs IN MATERNAL-FETAL INTERACTION AND EPIGENETIC PROGRAMMING

Maternal-fetal interaction, mediated by miRNAs, plays a crucial role in the adaptation of the fetus to adverse intrauterine conditions. MiRNAs such as miR-148b-3p (Morales-Roselló *et al*., 2020) are associated with the epigenetic regulation of genes related to neurodevelopment and metabolism. In addition, studies in animal models have shown that miRNAs such as miR-449a influence critical hormonal axes, such as the hypothalamic-pituitary-adrenal axis, affecting growth and stress axis programming (Nemoto; Kakinuma; Shibasaki, 2015).

This evidence highlights that altered expression of miRNAs during pregnancy not only influences immediate fetal development, but also impacts long-term health, with the potential to predispose to chronic diseases in adulthood (Hromadnikova *et al*., 2017; Morales-Roselló *et al*., 2020). Future studies should explore the possibility of miRNA-based interventions to prevent or mitigate these programmatic effects (Nemoto; Kakinuma; Shibasaki, 2015). The integration of technological advances to analyze miRNA regulatory networks and their interaction with the maternal-fetal epigenome could open up new therapeutic perspectives in the field of fetal medicine.

FINAL CONSIDERATIONS

The review highlighted the relevance of microRNAs (miRNAs) in fetal growth restriction (FGR), highlighting their role as diagnostic biomarkers and potential therapeutic targets. MiRNAs such as miR-210-5p, miR-132 and miR-206 were identified as crucial regulators of placental processes, broadening the understanding of the pathophysiology of FGR and consolidating them as promising tools in fetal medicine. Despite these advances, the review highlighted gaps in the field, such as

the need for large-scale clinical validation and the standardization of miRNA detection methods. In addition, there are challenges related to population heterogeneity and biomarker specificity, which limit the broad application of miRNAs in clinical contexts. The clinical implications of these findings are significant, including the possibility of early diagnosis and targeted interventions to mitigate the effects of CRF. The integration of miRNAs with diagnostic technologies such as imaging techniques and multibiomarker panels could improve diagnostic and therapeutic accuracy. It is recommended that future research prioritize longitudinal studies that explore the interaction between miRNAs and epigenetic networks, as well as clinical trials to evaluate the therapeutic use of modified miRNAs. These studies will be essential for translating scientific advances into effective clinical solutions, promoting substantial improvements in maternal and fetal outcomes. Finally, the consolidation of miRNAs as biomarkers and therapeutic targets reinforces their relevance in the management of CRF and highlights their role in the personalization of fetal medicine, promoting significant advances in diagnosis and treatment.

REFERENCES

ALI, Asghar *et al.* MicroRNA–mRNA networks in pregnancy complications: A comprehensive downstream analysis of potential biomarkers. **International journal of molecular sciences,** v. 22, n. 5, p. 2313, 2021.

AWAMLEH, Zain; HAN, Victor KM. Identification of miR-210-5p in human placentae from pregnancies complicated by preeclampsia and intrauterine growth restriction, and its potential role in the pregnancy complications. **Pregnancy hypertension**, v. 19, p. 159-168, 2020.

BAKER, Bernadette C. *et al*. Sexually dimorphic patterns in maternal circulating microRNAs in pregnancies complicated by fetal growth restriction. **Biology of sex Differences**, v. 12, n. 1, p. 61, 2021.

CHEN, Ailing, *et al*. Recent Advances of MicroRNAs, Long Non-coding RNAs, and Circular RNAs in Preeclampsia. **Frontiers in Physiology**, v. 12, 2021.

CHIOFALO, Benito *et a*l. Do miRNAs play a role in fetal growth restriction? A fresh look to a busy corner. **BioMed research international**, v. 2017, n. 1, p. 6073167, 2017.

GUSAR, Vladislava A. *et al*. Interrelation between miRNAs expression associated with redox state fluctuations, immune and inflammatory response activation, and neonatal outcomes in complicated pregnancy, accompanied by placental insufficiency. **Antioxidants**, v. 12, n. 1, p. 6, 2022.

HROMADNIKOVA, Ilona *et al*. First trimester screening of circulating C19MC microRNAs and the evaluation of their potential to predict the onset of preeclampsia and IUGR. **Plos One**, v. 12, n. 2, p. e0171756, 2017.

HROMADNIKOVA, Ilona; KOTLABOVA, Katerina; KROFTA, Ladislav. First-trimester screening for fetal growth restriction and small-for-gestational-age pregnancies without preeclampsia using cardiovascular disease-associated microRNA biomarkers. **Biomedicines**, v. 10, n. 3, p. 718, 2022.

HROMADNIKOVA, Ilona; KOTLABOVA, Katerina; KROFTA, Ladislav. First Trimester Prediction of Preterm Delivery in the Absence of Other Pregnancy-Related Complications Using Cardiovascular-Disease Associated MicroRNA Biomarkers. **International Journal of Molecular Sciences**, v. 23, n. 7, p. 3951, 2022.

JIN, Keqin *et al*. Exosomal miRNAs in prenatal diagnosis: Recent advances. **Medicine**, v. 103, n. 28, p. e38717, 2024.

KENNEDY, Elizabeth M. *et al*. Placental microRNAs relate to early childhood growth trajectories. **Pediatric research**, v. 94, n. 1, p. 341-348, 2023.

Li, Ying; Liu, Jiaqian. MicroRNA-206 predicts raised fetal growth retardation risk through the interaction with vascular endothelial growth factor in pregnancies. **Medicine**, v. 99, n. 7, p. e18897, 2020.

MORALES-ROSELLÓ, José *et al*. MicroRNA-148b-3p and MicroRNA-25-3p Are Overexpressed in Fetuses with Late-Onset Fetal Growth Restriction. **Fetal Diagnosis and Therapy**, v. 47, n. 9, p. 665-674, 2020.

MORALES-ROSELLÓ, José *et al*. MicroRNA-185-5p: a marker of brain-sparing in foetuses with late-onset growth restriction. **Epigenetics**, v. 17, n. 11, p. 1345-1356, 2022.

MORALES-ROSELLÓ, José *et al*. MicroRNA-132 is overexpressed in fetuses with late-onset fetal growth restriction. **Health Science Reports**, v. 5, n. 2, p. e558, 2022.

NEMOTO, Takahiro; KAKINUMA, Yoshihiko; SHIBASAKI, Tamotsu. Impaired miR449a-induced downregulation of Crhr1 expression in low-birth-weight rats. **J Endocrinol**, v. 224, n. 2, p. 195-203, 2015.

PINSON, Marisa R. *et al*. Maternal circulating miRNAs contribute to negative pregnancy outcomes by altering placental transcriptome and fetal vascular dynamics. **Plos one**, v. 18, n. 11, p. e0290720, 2023.

RAHMAN, Mohammad L. *et al*. Regulation of birthweight by placenta-derived miRNAs: evidence from an arsenic-exposed birth cohort in Bangladesh. **Epigenetics**, v. 13, n. 6, p. 573-590, 2018.

SAHA, Sarbani *et al*. MicroRNA regulation of transthyretin in trophoblast differentiation and intra-uterine growth restriction. **Scientific Reports**, v. 7, n. 1, p. 16548, 2017.

TAGLIAFERRI, Salvatore *et al*. miR-16-5p, miR-103-3p, and miR-27b-3p as early peripheral biomarkers of fetal growth restriction. **Frontiers in Pediatrics**, v. 9, p. 611112, 2021.

TSAI, Pei-Yin *et al*. Differential miR-346 and miR-582-3p expression in association with selected maternal and fetal complications. **International Journal of Molecular Sciences**, v. 18, n. 7, p. 1570, 2017.

WEN, Hong *et al*. MicroRNA expression profiles and networks in placentas complicated with selective intrauterine growth restriction. **Molecular medicine reports**, v. 16, n. 5, p. 6650-6673, 2017.