Epigenetic and clinical characterization of preeclampsia in oocyte donation pregnancies: insights into immune dysregulation and microRNA-mediated pathways

Lops G [1,2], Di Giminiani M [2], Saulle I [1,3], Biasin M [1,3], Greppi D [1,2], Manfredonia F [1,2], Savasi V [1,2]

[1] Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy; [2] Department of Woman, Mother and Neonate Buzzi Children's Hospital, and Sacco Hospital, ASST Fatebenefratelli-Sacco, Milan, Italy; [3] Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

Introduction

PreEclampsia (PE) is a severe hypertensive disorder of pregnancy that significantly impacts maternal and fetal health. It is characterized by the new onset of hypertension (≥140/90 mmHg) and proteinuria (≥300 mg/day) or other signs of organ system complications that develop after 20 weeks of gestation. Globally, the incidence of PE ranges from 2% to 8%, making it one of the leading causes of maternal and neonatal morbidity and mortality [1]. While the exact cause remains unclear, immune system dysfunction at the maternal-fetal interface is increasingly recognized as a key factor. The incidence of PE is notably higher in pregnancies following Oocyte Donation (OD), potentially due to the significant HLA mismatch between the fetus and the mother. In Natural Conception (NC) pregnancies, partial maternal-fetal HLA compatibility supports immune tolerance. However, in OD pregnancies, the fetus's genome is completely allogeneic, leading to heightened maternal immune activation and an increased risk of PE, suggesting that inadequate immune adaptation may be a key contributor to disease development [2]. Hormonal imbalances, such as the use of exogenous estrogen and the absence of a corpus luteum, may also contribute. Recent research has highlighted the growing role of microRNAs (miRNAs) in placental development, immune modulation, and endothelial function. miRNAs are small, non-coding RNAs that regulate gene expression at the post-transcriptional level by targeting mRNAs for degradation or translation repression. Several placenta-related miRNAs have been shown to regulate maternal immune tolerance, modulate the function of Natural Killer (NK) cells, activate Dendritic Cells (DCs), and regulate T-cell responses, thereby helping to establish the immune environment necessary for a successful pregnancy [3]. Disruptions in miRNA regulatory networks may lead to maternal immune activation, systemic inflammation, and impaired placentation, contributing to PE. Furthermore, circulating miRNAs have been proposed as potential biomarkers for diagnosing the progression of normal or pathological pregnancies due to their stability in maternal blood and ability to reflect placental dysfunction [4].

Objectives

The study aims to identify potential miRNA biomarkers associated with preeclampsia in OD and spontaneous pregnancies. This profiling may offer valuable insights into the role of miRNAs in the pathogenesis of PE, immune regulation in OD pregnancies, and the underlying disease mechanisms. Additionally, it may help facilitate the development of targeted therapeutic strategies to modulate immune responses and improve maternal-fetal outcomes.

Results

The study examined the expression of 10 miRNAs in maternal plasma, placental tissue, and umbilical cord plasma across four groups of pregnant women: Normotensive Oocyte Recipients (NOR), Preeclamptic Oocyte Recipients (POR), Normotensive Spontaneous Pregnant (NSP), and Preeclamptic Spontaneous Pregnant (PSP).

In maternal plasma, miR-17 was upregulated in PORs compared to all other groups, particularly NSPs and PSPs. miR-30 was downregulated in PORs, especially compared to NSPs and PSPs. Anti-inflammatory miRNAs miR-223 and miR-155 were upregulated in PORs compared to the other groups, with miR-223 showing higher expression compared to NSPs and PSPs, and miR-155 more expressed in PORs compared to NORs and PSPs. miR-let-7c was reduced in NSPs compared to both PSPs and PORs. No significant differences were found for other preeclampsia-associated miRNAs (miR-150, miR-140, miR-146, miR-181a, miR-210).

In placental tissue, the expression patterns were similar to those in maternal plasma, with significant differences observed in the POR group. miR-17 and miR-223 were upregulated in PORs compared to PSPs and NORs, while miR-155 was more highly expressed in PORs compared to NSPs and PSPs. miR-30 showed downregulation in PORs and NSPs compared to NORs and PSPs, and miR-let-7c was reduced in PORs compared to NORs. These trends reinforce the potential of these miRNAs as biomarkers for preeclampsia.

In umbilical cord plasma, miR-30, which was downregulated in maternal plasma of PORs, was upregulated compared to NSPs and PSPs, while miR-17 was downregulated in umbilical cord plasma of PORs compared to NSPs and PSPs. miR-223 and miR-let-7c were significantly reduced in umbilical cord plasma of PORs compared to PSPs, Additionally, miR-223, miR-155, and miR-let-7c were more highly expressed in PSPs compared to NSPs.

Conclusions

Overall, these findings suggest that miRNAs such as miR-17, miR-223, miR-155, miR-30, and Let-7c, which show differential expression across maternal plasma, placental tissue, and umbilical cord plasma, could serve as potential biomarkers for preeclampsia. The distinct miRNA expression patterns observed in the maternal and fetal compartments indicate specific dynamics of miRNA regulation during pregnancy, which could offer new insights into the early detection and monitoring of preeclampsia and other pregnancy-related complications. The upregulation of anti-inflammatory miRNAs in PORs may play a role in modulating immune responses, suggesting a protective function in preeclampsia. These miRNAs may offer valuable tools for diagnosing and monitoring pregnancy complications.

Bibliography

1 *Poon LC, Shennan A, Hyett JA, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet. 2019;145 Suppl 1(Suppl 1):1-33 [published correction appears in Int J Gynaecol Obstet. 2019;146(3):390-1].*

2 *van 't Hof LJ, Schotvanger N, Haasnoot GW, et al. Maternal-fetal HLA compatibility in uncomplicated and preeclamptic naturally conceived pregnancies. Front Immunol. 2021;12:673131.*

3 *Chen A, Yu R, Jiang S, et al. Recent advances of microRNAs, long non-coding RNAs, and circular RNAs in preeclampsia. Front Physiol. 2021;12:659638.*

4 *Kim SH, MacIntyre DA, Binkhamis R, et al. Maternal plasma miRNAs as potential biomarkers for detecting risk of small-for-gestational-age births. EBioMedicine. 2020;62:103145.*