Journal of Pre-Clinical and Clinical Research 2020, Vol 14, No 4, 174-177
www.jpccr.eu

REVIEW ARTICLE

Blood serum microRNA profiles of pregnant women as biomarkers of pre-eclampsia evaluation

Adrianna Kondracka[1,A-F], Ilona Jaszczuk[2,A-F], Dorota Koczkodaj[2,D], Agata Filip[2,E], Anna Kwaśniewska[1,E]

[1] *Department of Obstetrics and Pathology of Pregnancy, Independent Public Teaching Hospital No. 1, Lublin, Poland*
[2] *Department of Cancer Genetics with Cytogenetic Laboratory, Lublin, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

Kondracka A, Jaszczuk I, Koczkodaj D, Filip A, Kwaśniewska A. Blood serum microRNA profiles of pregnant women as biomarkers of preeclampsia evaluation. J Pre-Clin Clin Res. 2020; 14(4): 174–177. doi: 10.26444/jpccr/131597

Abstract

Introduction. pre-eclampsia is a pregnancy-related syndrome characterized by hypertension and proteinuria that makes its appearance after 20 weeks of gestation. It develops approximately in 2–10% of all pregnancies. Pre-eclampsia, as a severe complication during pregnancy, is a major cause of maternal and perinatal morbidity and mortality.

Objectives. The aim of the study was to assess the possibility of utilizing selected microRNAs at the earliest possible stage as safe biomarkers of severe complications of pregnancy, such as pre-eclampsia.

State of konowledge. Nowadays, there are many trials aimed at finding effective methods for pre-eclampsia prediction at the early stage of pregnancy, before the onset of clinical signs. Although the precise pathophysiology of pre-eclampsia remains unknown, early prediction of the syndrome would allow the initiation of proper preventive therapy to savethe mother and future child. Current strategies for pre-eclampsia prediction are assessments of combinations of maternal risk factors, ultrasound parameters and different biomarkers (proteins, circulating cell free DNA and microRNAs). Studies of microRNAs in particular offer great potential for diagnosis and therapy in pregnancy-related disorders. The fraction of specific placenta-related circulating microRNAs in the serum of pregnant women who present symptoms of pre-eclampsia after 20 weeks of gestation, and show the strongest changes in the level, can play an important role in the development of placenta-related complications.

Conclusion. Further research into the level of microRNAs in the blood serum of pregnant women with pre-eclampsia will allow a practical way of utilizing selected microRNAs at the earliest possible stage as safe biomarkers of severe complications of pregnancy.

Key words

pre-eclampsia, micro-RNA, biomarkers

INTRODUCTION

Pre-eclampsia is a pregnancy-related syndrome characterized by hypertension and proteinuria that makes its appearance after 20 weeks of gestation. It develops in approximately 2–10% of all pregnancies. Pre-eclampsia, as a severe complication during pregnancy, is a major cause of maternal and perinatal morbidity and mortality. Nowadays, there are many trials aimed at finding effective methods for pre-eclampsia prediction at an early stage of pregnancy, before the onset of clinical signs. Although the precise pathophysiology of pre-eclampsia remains unknown, early prediction of the syndrome would allow initiation of proper preventive therapy to save the mother and future child. Current strategies for pre-eclampsia prediction are assessments of combinations of maternal risk factors, ultrasound parameters and different biomarkers (proteins, circulating cell free DNA and microRNAs). Studies of microRNAs, in particular, offer great potential for diagnosis and therapy in pregnancy-related disorders.

Address for correspondence: Adrianna Kondracka, Department of Obstetrics and Pathology of Pregnancy, (SPSK) No.1, Staszica 16, 20-081 Lublin, Poland
E-mail: adriannakondracka@wp.pl

Received: 22.09.2020; accepted: 09.12.2020; first published: 28.12.2020

OBJECTIVES

The aim of further analysis is to ascertain the effectiveness of following certain pre-eclampsia development prognostic factors during the first trimester of the pregnancy. The approach being accessed is the utilization of estimations of microRNA profiles in the serum of pregnant women. The intention is to identify an effective and non-invasive method for predicting pre-eclampsia development at an early stage of pregnancy (< 20 hbd). The study, therefore, is an attempt to discover the role of microRNAs in pre-eclampsia development by determining their target genes.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Pre-eclampsia is a severe complication of pregnancy, the clinical signs of which develop during the second trimester. Pre-eclampsia is defined as co-occurrence of hypertension (blood pressure >140/90 mmHg) and proteinuria (>0.3 g of protein in the 24-hour collection of urine) after 20 weeks of gestation in a previously normotensive woman [1]. Because of the possible course leading to severe complications, such as convulsions (eclampsia), hypertension and proteinuria, pre-eclampsia

is an important factor increasing the risk of morbidity and mortality among pregnant women and foetuses or neonates [2–6]. Pre-eclampsia is a disease clinically recognized only during the second half of pregnancy, but the processes leading to its development start at the moment blastocysts nest in the uterine. The basis cause of the onset of pre-eclampsia symptoms is defective placentation. This elicits an abnormal uterus and placenta blood perfusion and the clinical effects result from this ischemia. Placental development during each pregnancy is connected with intensive placental remodeling [7] through cell proliferation, angiogenesis and simultaneous apoptosis [2]. Extracellular foetal and placental nucleic acids arising during these processes are packed into trophoblast-derived apoptotic bodies or syncytiotrophoblast microparticles, detected in the mother's blood. The trophoblastic debris and the microparticles show pro-inflammatory activity, which is exaggerated in pre-eclampsia [3, 7].

The initial 'latent' period of the disease, until 20 weeks of gestation, is now intensively studied. The key to success in pre-eclampsia prevention is to find an effective way to select-out women who are at risk of developing a severe form of pre-eclampsia. The ultrasound markers and biochemical factors of maternal blood uterine activity, including specific proteins, circulating cell free DNA, circulating microRNAs, are the prognostic factors that are being assessed [1]. Factors of interest in this pursuit are the specific microRNAs belonging to a class of non-coding RNAs (ncRNAs). MicroRNAs (miRNAs) are short, single-stranded 19–25 nucleotides-length RNAs. The current 22.1 release of miRNA database miRBase includes 38,589 mature miRNA sequences [8–10].

MicroRNAs play an important role in post-transcriptional regulation of gene expression. More than 60% of all human genes are negatively regulated by microRNAs, in the way called 'silencing' of genes expression. MicroRNAs are found to be implicated in many physiological processes, including: cell proliferation, cell differentiation, programmed death or pregnancy development, and in many pathological processes, such as: tumorigenesis, myocardial infarction, reaction during infections and inflammation, as well as development of chronic diseases [11]. Authors' own research conducted in the Department of Cancer Genetics with Cytogenetic Laboratory of the Medical University in Lublin, Poland, revealed the important role of specific circulating microRNAs in pathogenesis and the development of chronic lymphoblastic leukemia (CLL) in adults [12]. Recent studies also indicate the role of microRNAs in cell-to-cell communication [13].

MicroRNAs may be assessed within cells or tissues (cellular miRNAs) or even easier in different body fluids (circulating miRNAs) [14]. The circulating fraction of microRNAs appears resistant to endogenous ribonuclease activity and may be freely circulating or associated with extracellular structures such as exosomes. Two features of microRNAs: stability and circulation in most extracellular body fluids (particularly in whole blood and serum) make them ideal biological markers (biomarkers) [15–17].

MicroRNAs are also proven regulators of processes that take place during pregnancy, including pregnancy-related complications such as pre-eclampsia [2–6]. The profile of serum microRNAs of pregnant women differs from the profile of non-pregnant women. MicroRNAs associated with pregnancy and with the placenta can be distinguished by comparing the profile of serum microRNAs of pregnant and non-pregnant women, or before and after labour [18]. The developing of the trophoblast, growth of its mass and volume quantitatively and qualitatively change the microRNA profile in the serum of pregnant women. Recent results presume a potential role for microRNAs in the regulation of apoptosis (programmed cell death) and cell migration in pre-eclampsia [7]. According to the latest studies on the pathogenesis of development of complications during pregnancy that are associated with the presence of trophoblast (PIRCs – placental insufficiency-related complications) [], microRNAs can be placed within four groups: placenta-specific, placenta-associated, placenta-derived, circulating and uterine (Fig. 1.) [2–6,16].

The fraction of specific placenta-derived circulating microRNAs can be analyzed in whole blood and also in the blood serum of pregnant women [16]. MicroRNAs profiling from pregnant women serum gives the opportunity to correlate changes in their level with the development of gestational complications. MicroRNAs associated with trophoblast presence are detected in serum during the pregnancy and disappear from the serum after parturition [18]. Hence, statistic differences in pregnant women serum microRNAs expression levels with pre-eclampsia and pregnant women with healthy pregnancy, will allow specific, selected microRNAs to serve as safe clinical biomarkers of severe complications during pregnancy. The literature data indicate the possibility of the qualitative differences in microRNAs profile from representatives of various populations [16] and such studies have not carried out so far on the large populations.

Knowledge of molecular targets for specific microRNAs will also enable understanding of their role in pre-eclampsia and further help to protect women or to find new effective therapeutic methods to mitigate pre-eclampsia (Tab. 1) [19–20].

CONCLUSIONS

The key to pre-eclampsia prevention is to identify the prognostic factors that develop during the first trimester of pregnancy. The role of selected microRNAs in the pathomechanism of pre-eclampsia development is very important. Estimation of the expression and microRNA profile associated with the presence of the trophoblast in the population of pregnant women that research determined carries great diagnostic value. The fraction of specific placenta-related circulating microRNAs in the serum of

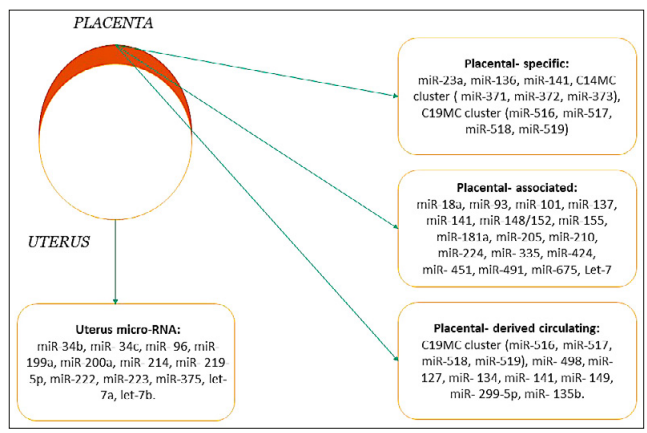

Figure 1. Four groups of microRNAs associated with pregnacy [12]

Table 1. Examples of miRNAs involved in the development of preeclamsia with target genes and the role in immune system response (4)

microRNA	Target Genes	Role of immune system response
miR-516b-5p	*CCR2*	Binds monocyte chemoattractant protein-1 involved in monocyte infiltration during inflammation
	CD109	Encodes GPI-linked glycoprotein that negatively regulates signaling of TGF-β
	CD1A	Encodes glycoproteins structurally related to MHC proteins mediating the presentation of lipid and glycolipid antigens
	DNAJC25	A molecular chaperone protein protecting against cellular stress
	FLT1	A member of vascular endothelial growth factor receptor (VEGFR) playing an important role in angiogenesis and vasculogenesis
	IL17RE	Participation in MAPK pathway
	IRAK1	Responsible for IL-1 induced upregulation of the transcription factor NF-kappa B
	LILRB5	An inhibitory cell-surface receptor expressed on immune cells
	PDCD6IP	Protects against cell death
	SOCS2	A negative regulator of JAK/STAT cytokine signaling pathway
miR-517-5p	*FAS*	Plays a central role in regulation of programmed cell death
	IL6ST	A signal transducer shared by IL-6, LIF, and oncostatin M
	IL9R	Mediates IL-9 effects like stimulation of cell proliferation and prevention of apoptosis
	IRAK3	Functions as a negative regulator of Toll-like receptor signaling
	LILRA2	An activatory cell-surface receptor expressed on monocytes, B cells, dendritic, and NK cells
	MTDH	Involvement in HIF-1 alpha mediated angiogenesis and RNA-induced silencing complex and miRNA functions
	PAPPA	Involvement in local proliferative processes, such as wound healing
miR-520a-5p	*ACVR2B*	Activins belong to the TGF- superfamily
	AHSA2	Hsp90 is an inducible molecular chaperone protecting stressed cells
	ATRN	Involvement in initial immune cell clustering during inflammatory responses that may regulate the chemotactic activity of chemokines
	CD2	A surface antigen of thymocytes, T, and NK cells
	CD300LB	A non-classical activating receptor of the Ig superfamily expressed on myeloid cells
	CD46	Has co-factor activity for inactivation of complement components C3b and C4b by serum factor I
	CD93	Involvement in intercellular adhesion and in the clearance of apoptotic cells
	HSF5	A transcriptional activator of heat shock genes
	IGF1R	Anti-apoptotic agent enhancing cell survival
	IL10RA	Involvement in inhibition of the synthesis of pro-inflammatory cytokines
	MMD2	Modulates Ras signaling
	PPARA	Affects the expression of genes involved in cell proliferation, cell differentiation, and in immune and inflammation responses
	TLR7	Plays a fundamental role in activation of innate immunity
	VSIG4	A negative regulator of T-cell responses structurally related to the B7 family of immune regulatory proteins
miR-525a-5p	*TOX*	Highly expressed in thymus, the site of development of T cells
miR-526a	*BCAP29,*	Involvement in CASP8-mediated apoptosis
	CD24	Encodes a sialoglycoprotein expressed on mature granulocytes and B cells
	CD302	A C-type lectin receptor involved in cell adhesion, migration, endocytosis, and phagocytosis
	CFLAR	Regulator of apoptosis, structurally similar to caspase-8
	DNAJC21	A molecular chaperone protein protecting against cellular stress
	HSP90AA1	An inducible molecular chaperone protecting stressed cells
	IGFBP1	Prolongs the half-time of IGFs in plasma that regulate cell growth and development
	TLR2	Plays a fundamental role in activation of innate immunity, stimulates NF-kappa B
	TNFRSF19	Interacts with TRAF family members, induces apoptosis by a caspase-independent mechanism
	TNFSF15	A cytokine induced by TNF and IL-1 alpha activating NF-kappa B and MAP kinases inducing apoptosis in endothelial cells
	TRAF6	Functions as a signal transducer in the NF-kappa B pathway, activates Ikappa B kinase in response to proinflammatory cytokines

pregnant women who present symptoms of pre-eclampsia after 20 weeks of gestation, and show the strongest changes in the level, can play an important role in the development of placenta-related complications. Further research into the level of microRNAs in the blood serum of pregnant women with pre-eclampsia will allow a practical way of utilizing selected microRNAs at the earliest possible stage as a safe biomarker of severe complications of pregnancy. By using available databases, the search of target genes for the afore-mentioned microRNAs can be carried out in order to understand the association between changes in gene expression and the molecular base of pre-eclampsia development [8–10]. The conducted studies will serve to elaborate an effective and noninvasive method for diagnosing at an early stage of the pregnancy.

REFERENCES

1. Park H, Shim S, Cha D. Combined Screening for Early Detection of Pre-Eclampsia. Int J Mol Sci. 2015; 16(8): 17952–17974. doi: 10.3390/ijms160817952
2. Hromadnikova I, Kotlabova K, Doucha J, et al. Absolute and related quantification of placenta – specific microRNAs in maternal circulation with placental insufficiency – related complications. JMD. March 2012; 14(2): 160–167. doi: 10.1016/j.moldx.2011.11.003
3. Hromadnikova I, Kotlabova K, Ondrackova M, et al. Circulating C19MC MicroRNAs in Pre-eclampsia, Gestational Hypertension, and Fetal Growth Restriction. Mediators of Inflammation. 2013. vol. 2013, article ID186041; 12 pages. http://dx.doi.org/10.1155/2013/186041
4. Hromadnikova I, Kotlabova K, Hympanova L, et al. First Trimester Screening of Circulating C19MC microRNAs Can Predict Subsequent Onset of Gestational Hypertension. PloS ONE 2014; 9(12): 113735. doi: 10.1371/journal.pone.0113735
5. Hromadnikova I, Kotlabova K, Ondrackova M, et al. Expression Profile of C19MC microRNAs in Placental Tissue in Pregnancy-Related Complications. DNA AND CELL BIOLOGY, 2015; 34(6): 437–457. doi: 10.1089/dna.2014.2687
6. Hromadnikova I, Kotlabova K, Ivankova K, et al. First trimester screening of circulating C19MC microRNAs and the evaluation of their potential to predict the onset of pre-eclampsia and IUGR. PLoS ONE 2017; 12(2): 0171756. doi: 10.1371/journal.pone.0171756
7. Zhao G, Zhou X, Chen S, et al. Differential expression of microRNAs in decidua – derived mesenchymal stem cells from patients with pre-eclampsia. Journal of Biomedical Science. 2014; 21: 81. http://www.jbiomedsci.com/content/21/1/81
8. miRBase Release 22.1: www.mirbase.org (access: 2020.09.22).
9. miRTarBase Release 7: http://mirtarbase.mbc.nctu.edu.tw/php/index.php (access: 2020.09.22).
10. TargetScanHuman Release 7.1: http://www.targetscan.org/vert_72/ (access: 2020.09.22).
11. Zhang Z, Yang T, Xiao J. Circular RNAs: Promising Biomarkers for Human Diseases. EBioMedicine. 2018. https://doi.org/10.1016/j.ebiom.2018.07.036
12. Filip A, Grenda A, Popek S, et al. Expression of circulating miRNAs associated with lymphocyte differentiation and activation in CLL – another piece in the puzzle. Ann Hematol. 2017 Jan; 96(1): 33–50. doi: 10.1007/s00277-016-2840-6. Epub 2016 Oct 12.
13. Chen X, Liang H, Zhang J, et al. Horizontal transfer of microRNAs: molecular mechanisms and clinical applications. Protein Cell. 2012; 3(1): 28–37. doi: 10.1007/s13238-012-2003-z
14. Cretoiu D, Xu J, Xiao J, et al. Circulating microRNAs as potential molecular biomarkers in pathophysiological evolution of pregnancy. Disease Markers. Volume 2016, Article ID 3851054, 7 pages. http://dx.doi.org/10.1155/2016/3851054
15. Betoni JS, Derr K, Pahl MC, et al. MicroRNA analysis in placentas from patients with pre-eclampsia: comparison of new and published results. Hypertens Pregnancy. 2013; 32(4): 321–339. doi: 10.3109/10641955.2013.807819
16. Cai M, Kolluru GK, Asif A. Small molecule, big prospects: microRNA in pregnancy and its complications. Journal of Pregnancy. 2017, Article ID 6972732, 15 pages. doi: 10.1155/2017/6972732
17. Bounds KR, Chiasson VL, Pan LJ, et al. MicroRNAs: New Players in the Pathobiology of Preclampsia. Front Cardiovasc Med. 2017; 4: 60. doi: 10.3389/fcvm.2017.00060
18. Pan M, Ge Q, Li H, et al. Sequencing the microRNAs in maternal plasma from women before and after parturition. J. Nanosci. Nanotechnol. 2012; 12(5): 4035–4043. doi: 10.1166/jnn.2012.6196
19. Liu Z, Zhao X, Shan HY, et al. MicroRNA-520c-3p suppresses NLRP3 inflammasome activation and inflammatory cascade in pre-eclampsia by downregulating NLRP3. Inflammation Research. https://doi.org/10.1007//s00011-019-01246-8
20. Sandrim VC, Luizon MR, Palei AC, et al. Circulating microRNA expression profiles in pre-eclampsia: evidence of increased miR-885–5p levels. BJOG. 2016; 123: 2120–2128. doi: 10.1111/1471-0528.13903