degradation. A large number of miRNAs have been identified and/or predicted, and in humans evidence indicate to a key regulatory function for microRNAs (miRNAs) in gene expression regulation. Further investigation of microRNA target genes may manifest the molecular pathogenesis of these diseases as well as identify potential therapeutic targets and diagnostic biomarkers. About 30% of human genes are regulated by miRNAs (14). More than 1500 human microRNAs have been identified experimentally or by bioinformatics (15). As a member of nonprotein coding short RNAs family miRNAs through binding to the 3′ untranslated region of specific target genes regulate their expression through translational regression. Important molecules involved in miRNA biogenesis, such as Drosha, Exportin 5, Dicer, Argonaute 2 (Ago 2) and DP103, have also been known in trophoblast cells (16) confirming that the miRNA biogenesis pathway is active in human placenta. MiRNA expression in the placenta is regulated by environment factors (17), sinaling pathways and epigenetic modification (18).

MicroRNAs regulate mRNA, which encodes proteins that modulate cellular functions, therefore, miRNAs play key roles in physiological homeostasis in health and pathophysiological states in disease. MicroRNAs are known to have function in pathological process and prognosis of diseases such as diabetes (19), neurodegenerative diseases (20), preeclampsia (21), cancer and its resistance against chemotherapy (22). It has been also believed that the presence of single nucleotide polymorphism (SNP) in the processing machinery and target binding sites genes of miRNA affects cancer risk, treatment efficacy and prognosis of some diseases.

The first study that linked miRNA and PE was done by Pineles et al (23). The study was conducted to determine whether PE and small-for-gestational age (SGA) are associated with aberrations in placental miRNA expression. Thus they evaluated placental miRNAs' expression from patients with PE, SGA, PE + SGA along with a control group (Table 1).

They found that seven miRNAs (miR-210, miR-155, miR-181b, miR-182∗, miR-200b, miR-154∗, and miR-183) had higher expression between PE + SGA and the control group. The expression of miR-182 and miR-210 was significantly higher in PE than in the control group.

Some studies have reported the expression of a number of miRNAs in placentas and fetal membranes with altered expression in these tissues affected by preeclampsia (10,11). The association between PE and altered miRNA expression indicates the possibility of a functional role for miRNA in this disease (13). MicroRNAs produced by human trophoblast cells could be secreted into maternal plasma or serum via an exosome-mediated pathway and have the potential to be used as biomarkers (24). Detection of miRNAs in the maternal circulation consider the possibility of using miRNAs as biomarkers to monitor the progression of normal pregnancy and gestational diseases such as preeclampsia. Aberrant expression of miRNAs in placenta from compromised pregnancies also discuss the potential of using miRNAs as therapeutic targets.

Placental Specific miRNAs

Many miRNAs are expressed in human placenta and some of them, such as the C19MC and C14MC clusters, are specifically or preferentially expressed in the placenta (25). The three most fomous clusters are the chromosome 19 miRNA cluster (C19MC), C14MC and miR-371-3 cluster, which is also localized on chromosome 19. MiRNA members of these clusters are not only detected in the placenta, but also in other compartments, e.g. in serum where they have the potential to become novel biomarkers of pregnancy disorders. Antagonism of some of these miRNAs or their targets may lead to novel therapeutic points for the development of new drug classes in pregnancy disorders (26). The C19MC, located in chromosome 19q13.41, is the largest miRNA cluster identified to date and is encoded by paternally imprinted genes. This cluster 46 pre-miRNAs transcribed from a non protein coding host gene and expressed only in the placenta (27).

The C19MC is primate specific and expressed from the paternal harbors allele (28). On the other hand, the C14MC cluster, containing 46 miRNAs in 14q32, is also highly expressed in the human placenta but is encoded by maternally imprinted genes (29). MicroRNAs 518b belongs to C19MC.

MiR-154* is located on 14q32.31 and has predominant expression pattern from placenta tissue. It is one of the pregnancy-associated

miRNAs and showed major decreased concentrations in maternal plasma after pregnancy (30).

Luo *et al.* 2008 found that miRNAs are exported from the human placental syncytiotrophoblast into maternal circulation, where they could target maternal tissues (24). Miura *et al* (2010) showed that as the pregnancy progressed into the third trimester, the plasma concentrations of cell-free chromosome 19–derived miRNAs (has-miR-515-3p, has-miR-517a, has-miR-517c, has-miR-518b, andhas-miR-526b) enhanced significantly, whereas that of cell-free has-miR- 323-3p on chromosome 14q32.31 showed no change (31).

Hromadnikova *et al*. (2012) showed that both quantification approaches revealed significant up regulation in extracellular placenta–specific miRNA levels over time in women with normally progressing pregnancies; however, they did not had the capacity to differentiate between normally progressing and complicated pregnancies at the time of preeclampsia and/or IUGR onset. Also, significant elevation of extracellular miRNA levels was observed during early gestation (ie, within the 12th to 16th weeks) in women who later developed preeclampsia and/or IUGR (32). In Kotlabova *et al*. study (2011) seven microRNAs (miR-516-5p, miR-517*, miR-518b, miR-520a*, miR-520h, miR-525 and miR-526a) were identified as new pregnancy associated microRNAs with diagnostic potential but they mentioned only miR-518b had all criteria for selection as microRNA marker with diagnostic and or prognostic potential because of: 1) detection rate of 100% in full-term placentas, (2) detection rate of ≥67% in maternal plasma throughout gestation (at least four positive wells out of six tested wells) and (3) not detectable in blood and plasma samples of nonpregnant women(33). A quantitative real-time RT-PCR analysis of the expression of eight placenta- specific miRNAs in trophoblast cells with different proliferative activities by WANG *et al*. (2012) indicated that the expression levels of two miRNAs (miR-517b and miR-1283) were increased and miR-519a was decreased in trophoblast cells with lower proliferative activities (34).

Table 1. Expression of some microRNAs in placenta

miR name	Sample	Expression	References
210, 155, 181b, 182, 200b, 154, 183,493,372,34c,195	Placenta	High Expression	Pineles *et al.* 2007 Enquobahrie *et al.*2010 Mayor-Lynn *et al.* 2010 Hu *et al.* 2009
16, 29b, 195, 26b, 181a, 335, 222,181a, 584, 30a-3p, 210, 152, 517, 518b, 519e, 638, 296, 362 ,512-3p	severe PE placenta	High Expression	Hu *et al.* 2009 Zhu *et al.* 2009 Mayor *et al*. 2011
328, 584, 139-5p, 500, 1247, 340-5p, 1, 15b, 181a, 210, 483-5p ,154*,34c-5p	Placenta	Low Expression	Enquobahrie *et al.* 2010 Mayor-Lynn *et al.* 2010 Zhu *et al*.2009 Daniel *et al*.2011
101, 10b, 218, 590, 204, 32, 126,18a, 19a, 411, 377, 154, 625, 144, 195, 150, 1, 18b, 363, 342-3p, 450, 223, 374	severe PE placenta	Low Expression	Zhu *et al.* 2009

Conclusion:

MicroRNAs (miRNAs) are expressed in the human placenta and could be detected in maternal plasma. Specific miRNA profiles have been explained for the placenta, maternal plasma and pregnancy disorders such as PE. It has been observed that numerous miRNAs, which are predominantly or exclusively expressed during pregnancy in placenta, are clustered in chromosomal regions, may be controlled by the same promoters, may have similar seed regions and targets, and work synergistically. MiRNA members of these clusters are not only detected in the placenta, but also in serum where they have the potential to become novel biomarkers for early detection of pregnancy disorders. Antagonism of selected miRNAs or their targets may lead to novel targets for the development of new drug classes in pregnancy disorders such as PE.

References:

1. Zhang Y, Fei M, Xue G, Zhou Q, Jia Y, Li L, et al. Elevated levels of hypoxia-inducible microRNA-210 in pre-eclampsia: new insights into molecular mechanisms for the disease. Journal of cellular and molecular medicine. 2012;16(2):249-59.
2. Sibai BM, Lindheimer M, Hauth J, Caritis S, VanDorsten P, Klebanoff M, et al. Risk factors for preeclampsia, abruptio placentae, and adverse neonatal outcomes among women with chronic hypertension. New England Journal of Medicine. 1998;339(10):667-71.
3. Choudhury M ,Friedman JE. Epigenetics and microRNAs in preeclampsia. Clinical and experimental hypertension. 2012;34(5):334-41.
4. Nejatizadeh A, Stobdan T, Malhotra N, Pasha MQ. The genetic aspects of pre-eclampsia: achievements and limitations .Biochemical genetics. 2008;46(7-8):451-79.
5. Mutter WP, Karumanchi SA. Molecular mechanisms of preeclampsia. Microvascular research. 2008;75(1):1-8.
6. Goldman-Wohl D, Yagel S. Regulation of trophoblast invasion: from normal implantation to pre-eclampsia. Molecular and cellular endocrinology. 2002;187(1):233-8.
7. Burton G, Woods A, Jauniaux E. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta. 2009;30(6):473-82.
8. Dechanet C, Fort A, Barbero-Camps E, Dechaud H, Richard S, Virsolvy A. Endothelin-dependent vasoconstriction in human uterine artery: application to preeclampsia. PloS one. 2011;6(1):e16540.
9. R Garzon, GA Calin, CM Croce. MicroRNAs in cancer. Annual review of medicine, 2009
10. Pan Q, Chegini N, editors. MicroRNA signature and regulatory functions in the endometrium during normal and disease states. Seminars in reproductive medicine; 2008: NIH Public Access.
11. Wang Y, Fan H, Zhao G, Liu D, Du L, Wang Z, et al. miR-16 inhibits the proliferation and angiogenesis-regulating potential of mesenchymal stem cells in severe pre-eclampsia. FEBS Journal. 2012;279(24):4510-24.
12. Carty DM, Delles C, Dominiczak AF. Novel biomarkers for predicting preeclampsia. Trends in cardiovascular medicine. 2008;18(5-24):186.
13. Hu Y, Li P, Hao S, Liu L, Zhao J, Hou Y. Differential expression of microRNAs in the placentae of Chinese patients with severe pre-eclampsia. Clinical Chemistry and Laboratory Medicine. 2009;47(8):923-9.
14. Morales Prieto DM, Markert UR. MicroRNAs in pregnancy. Journal of reproductive immunology. 2011;88(2):106-11.
15. Li Y, Kowdley KV. Method for microRNA isolation from clinical serum samples. Analytical Biochemistry. 2012.
16. Forbes K, Farrokhnia F, Aplin J, Westwood M. Dicer-dependent miRNAs provide an endogenous restraint on cytotrophoblast proliferation. Placenta. 2012.
17. Donker RB, Mouillet J-F, Nelson DM, Sadovsky Y. The expression of Argonaute2

and related microRNA biogenesis proteins in normal and hypoxic trophoblasts†. Molecular human reproduction. 2007;13(4):273-9.

18. Ji L, Brkić J, Liu M, Fu G, Peng C, Wang Y-L. Placental trophoblast cell differentiation: Physiological regulation and pathological relevance to preeclampsia. Molecular aspects of medicine. 2012.
19. Poy MN, Eliasson L, Krutzfeldt J, Kuwajima S, Ma X, MacDonald PE, et al. A pancreatic islet-specific microRNA regulates insulin secretion. Nature. 2004;432(7014):226-30.
20. Jin P, Alisch RS, Warren ST. RNA and microRNAs in fragile X mental retardation. Nature Cell Biology. 2004;6(11):1048-53.
21. Chen D-b, Wang W. Human Placental MicroRNAs and Preeclampsia .Biology of Reproduction. 2013.
22. Garofalo M, Croce CM. microRNAs: Master regulators as potential therapeutics in cancer. Annual review of pharmacology and toxicology. 2011;51:25-43.
23. BL Pineles, R Romero, D Montenegro, AL Tarca. Distinct subsets of microRNAs are expressed differentially in the human placentas of patients with preeclampsia. American Journal of Obstetrics and Gynecology.Volume 196, Issue 3, March 2007, Pages 261.e1–261.e6.
24. Luo S-S, Ishibashi O, Ishikawa G, Ishikawa T, Katayama A, Mishima T, et al. Human villous trophoblasts express and secrete placenta-specific microRNAs into maternal circulation via exosomes. Biology of reproduction. 2009;81(4):717-29.
25. Donker R, Mouillet J, Chu T, Hubel C, Stolz D, Morelli A, et al. The expression profile of C19MC microRNAs in primary human trophoblast cells and exosomes. Molecular human reproduction. 2012;24-417:(8);18.
26. Morales-Prieto DM, Ospina-Prieto S , Chaiwangyen W, Schoenleben M, Markert UR. Pregnancy-associated miRNA-clusters. Journal of reproductive immunology. 2013;97(1):51-61.
27. Bortolin-Cavaillé M-L, Dance M, Weber M, Cavaillé J. C19MC microRNAs are processed from introns of large Pol-II, non-protein-coding transcripts. Nucleic acids research. 2009;37(10):3464-73.
28. Noguer-Dance M, Abu-Amero S, Al-Khtib M, Lefèvre A, Coullin P, Moore GE, et al. The primate-specific microRNA gene cluster (C19MC) is imprinted in the placenta. Human molecular genetics. 2010;19(18):3566-82.
29. Seitz H, Royo H, Bortolin M-L, Lin S-P, Ferguson-Smith AC, Cavaillé J. A large imprinted microRNA gene cluster at the mouse Dlk1-Gtl2 domain. Genome research. 2004;14(9):1741-8.
30. Miura K, Miura S, Yamasaki K, Higashijima A, Kinoshita A, Yoshiura K-i, et al. Identification of pregnancy-associated microRNAs in maternal plasma. Clinical chemistry. 2010;56(11):1767-71.
31. Kiyonori Miura,1* Shoko Miura,1 Kentaro Yamasaki. Identification of Pregnancy-Associated MicroRNAs in Maternal Plasma. Clinical Chemistry 2010.56:11 1767–1771.
32. I Hromadnikova, K Kotlabova, J Doucha.. Absolute and Relative Quantification of Placenta-Specific MicroRNAs in Maternal Circulation with Placental Insufficiency–Related Complications. The Journal of Molecular Diagnostics.Volume 14, Issue 2, March–April 2012, Pages 160–167.
33. K Kotlabova, J Doucha, I Hromadnikova. Placental-specific microRNA in maternal circulation – identification of appropriate pregnancy-associated microRNAs with diagnostic potential. Journal of Reproductive Immunology.Volume 89, Issue 2, May 2011, Pages 185–191.
34. Dan WANG, Weiwei SONG and Quan NA. The emerging roles of placenta-specific microRNAs in regulating trophoblast proliferation during the first trimester. Australian and New Zealand Journal of Obstetrics and Gynaecology 2012; 52: 565–570.