

First trimester screening of pregnancy-related complications

Novel predictive models for GH, PE, HELLP, FGR, SGA, preterm birth, GDM and pregnancy loss

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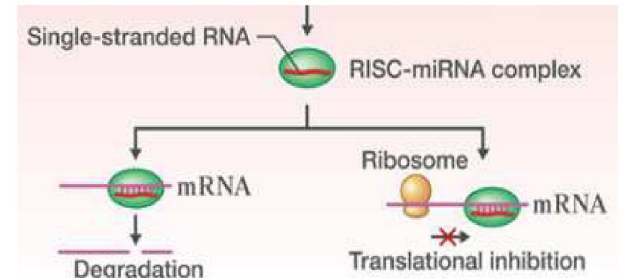
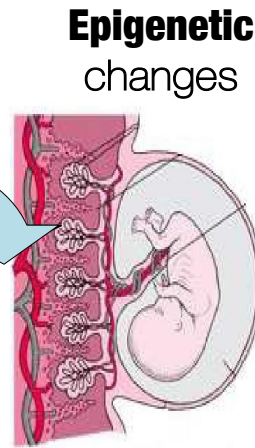
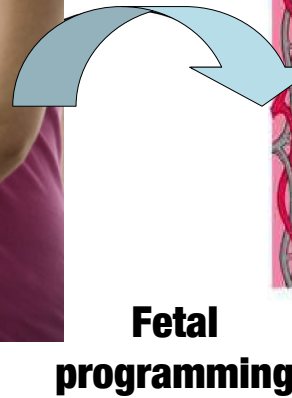
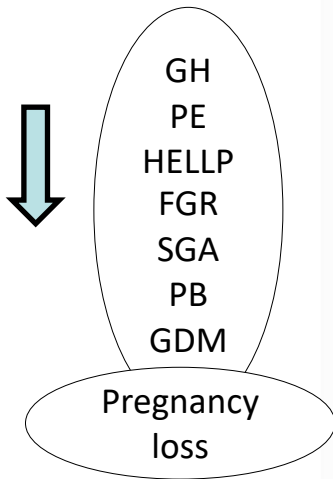
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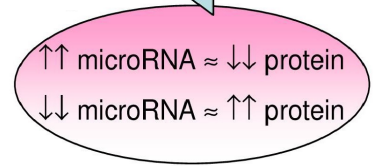
Overview

First trimester screening

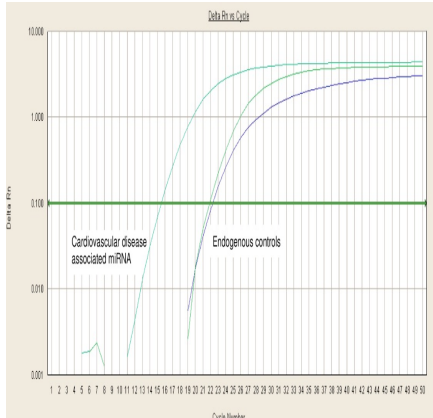


Cardiovascular risk

microRNA
gene expression analysis



Early stratification of risky groups



Implementation of primary prevention strategies (National Cardiovascular Plan 2023 - 2033)

Key issues during research phase



Early Diagnosis – I. trimester – Identification of pregnancies at risk

Real-time RT-PCR, 2 ml peripheral blood

2 working days

miRNA gene expression

pathogenesis of cardiovascular diseases



The highest achievable detection rate

Prediction models: miRNA and maternal clinical data

	miR-1-3p	miR-16-5p	miR-17-5p	miR-20a-5p	miR-20b-5p	miR-21-5p	miR-23a-3p	miR-24-3p	miR-26a-5p	miR-100-5p	miR-125b-5p	miR-126-3p	miR-130b-3p	miR-133a-3p	miR-143-3p	miR-145-5p	miR-146a-3p	miR-155-5p	miR-181a-5p	miR-195-5p	miR-210-3p	miR-342-3p	miR-499a-5p	miR-574-3p
Homeostasis of the cardiovascular system						+																		
Angiogenesis																	+							
Cardiac development			+																					
Cardiac regeneration																							+	
Adipogenic differentiation			+																					
Obesity							+											+	+			+		
Insulin resistance					+	+																		
Gestational diabetes mellitus		+	+	+							+	+	+			+		+		+		+		
Diabetes mellitus (T1DM, T2DM) and its complications	+	+	+	+	+	+		+	+	+	+	+	+	+		+	+	+	+	+		+		+
Hypercholesterolemia								+					+					+						
Metabolic syndrome																			+					
Hypertension						+				+						+		+	+					
Atherosclerosis																	+	+	+		+			
Myocardial infarction	+	+	+			+			+		+	+			+	+	+		+		+		+	+
Cerebral ischemic events		+	+				+				+		+		+	+	+		+				+	+
Coronary heart disease		+	+				+	+	+					+	+		+	+	+	+	+	+		+
Pulmonary hypertension				+					+						+									
Heart failure		+			+	+	+		+	+				+						+				

miRNA biomarkers – pilot results monocentric study – screening variants I and II

	GH	PE	FGR	SGA	GDM		PPROM PTB No other complications	HELLP	Pregnancy loss		
					On diet	On therapy			Early MA <13. week	Late MA 13.-20. week	Stillbirth >20. week
Variant I <i>Identification of risky pregnancy</i>	1	4	5	4	3	1	2	3	4	4	6
Variant II <i>Identification of risky pregnancy</i>	+0	+2	+2	+0	+5	+2	+5	+3	+3	+2	+0
Patent protection	1	8	10	8	8	3	12	6	7	6	11
miR-181a-5p	⁺	⁺	⁺	⁺				⁺	⁺	⁺	⁺
miR-20a-5p		⁺	⁺	⁺	⁺	⁺					⁺
miR-146a-5p		⁺	⁺	⁺			+	⁺	⁺	⁺	⁺
miR-574-3p		⁺	⁺		⁺						⁺
miR-1-3p				⁺	⁺			⁺	⁺	⁺	⁺
miR-16-5p			⁺				⁺		⁺	⁺	⁺
miR-145-5p		⁺	⁺				+				+
miR-20b-5p				+	⁺	⁺	+				
miR-21-5p		+					⁺				
miR-23a-3p											
miR-24-3p							⁺				
miR-100-5p			+		⁺						

miRNA biomarkers– pilot results monocentric study – screening variants I and II

	GH	PE	FGR	SGA	GDM		PPROM PTB No other complications	HELLP	Pregnancy loss		
					On diet	On therapy			Early MA <13. week	Late MA 13.-20. weeks	Stillbirth >20. wek
miR-125b-5p					+						
miR-126-3p		+		+							
miR-133a-3p							+				
miR-143-3p		+	+					+			
miR-155-5p							+				
miR-195-5p			+		+	+			+		
miR-210-3p							+				+
miR-342-3p			+				+				+
miR-499a-5p				+	+			+			
miR-17-5p								+	+	+	+
miR-26a-5p							+				
miR-130b-3p				+					+	+	+
miR-92a-3p							+				

Identification of Clinical Risk Factors for the Development of Pregnancy-Related Complications

10-13 gestational weeks Personal and family anamnesis	GH	PE	HELLP	FGR	SGA	PPROM PTB	GDM	Late MA
Total number in prediction model	5 7	6 8	6 7	7 9	3 5	5 7	3 7	8 9
Maternal age	+	+	+	+	+	+	+	+
Maternal BMI	+	+	+	+	+	+	+	+
Primiparity	+	+		+				
Any kind of autoimmune disease in anamnesis	+	+	+	+		+		+
Chronic hypertension in anamnesis				+				
Family history of diabetes mellitus (first-degree relatives only)							+	
Actual pregnancy resulting from assisted reproductive technology	+	+	+	+	+	+	+	+
Thrombophilic gene mutations in anamnesis			+				+	+

GH, gestational hypertension; **PE**, preeclampsia; **HELLP**, hemolysis, elevated liver enzymes, low platelets syndrome; **FGR**, fetal growth restriction; **SGA**, small for gestational age; **PPROM**, preterm prelabor rupture of membranes; **PTB**, spontaneous preterm birth; **GDM**, gestational diabetes mellitus; **MA**, miscarriage

Identification of Clinical Risk Factors for the Development of Pregnancy-Related Complications

10 -13 gestational weeks Personal and family anamnesis	GH	PE	HELLP	FGR	SGA	PPROM PTB	GDM	Late MA
History of miscarriage (spontaneous pregnancy loss <20 weeks)							+	+
History of HELLP and/or PE		+	+					
History of FGR or SGA				+				
History of spontaneous preterm birth						+		
Non-autoimmune hypothyroidism in anamnesis								+
Uterine fibroids or abnormal shaped womb								+
Screening positive for PE and/or FGR by FMF algorithm	+	+	+	+	+	+	+	+
Screening positive for spontaneous preterm birth by FMF algorithm	+	+	NA*	+	+	+	NA ^o	

NA not included in prediction model * low number of screening results ^o patients delivered in term

Pregnancy complications – Screening 10.-13. weeks – pilot results – sensitivity at 10.0 % FPR

Pregnancy complications	Actual screening (I. trimester) Improvement of identification of risky pregnancies	Screening variant I Identification of risky pregnancies (choice from 6 mutual miRNA)	Screening variant II Identification of risky pregnancies (choice from 25 miRNA)	Patent protection miRNA
GH (n=83)	No	😊 62.65%, 69.88% (1 miRNA + 5 or 7 clinical parameters)		22.89% (1 miRNA)
PE <i>Early, late, mild, severe</i> (n=66)	Yes + 2.37x / 2.50x Variant I + 2.37x / 2.55x Variant II	😊 78.79%, 83.33% (4 miRNA + 6 or 8 clinical parameters)	78.79%, 84.85% (6 miRNA + 6 or 8 clinical parameters)	53.03% (8 miRNA)
FGR <i>Early, late</i> (n=82)	Yes + 2.1x / 2.61x Variant I + 2.31x / 2.66x Variant II	😊 58.54%, 73.17% (5 miRNA + 7 or 9 clinical parameters)	64.63%, 74.39% (7 miRNA + 7 or 9 clinical parameters)	40.24% (10 miRNA)
SGA (n=37)	No	😊 70.27%, 81.08% (4 miRNA + 3 or 5 clinical parameters)		83.78% (8 miRNA)
PTB or PPROM without other complications (n=106)	Only PTB <34. weeks limited	45.28%, 51.89% (2 miRNA + 5 or 7 clinical parameters)	😊 69.81%, 71.70% (6 miRNA + 5 or 7 clinical parameters)	52.83% (12 miRNA)
GDM on diet (n=101)	Only assessment of peripheral blood glucose, dg. 3.3% GDM	51.49%, 56.44% (3 miRNA + 3 or 7 clinical parameters)	50.50%, 56.44% (8 miRNA + 3 or 7 clinical parameters)	34.65% (8 miRNA)
GDM on therapy (n=20)		😊 78.95%, 89.47% (1 miRNA + 3 or 7 clinical parameters)	78.95%, 89.47% (3 miRNA + 3 or 7 clinical parameters)	30.0% (3 miRNA)

Pregnancy complications – Screening 10.-13. weeks – pilot results – sensitivity at 10.0 % FPR

Pregnancy complications	Actual screening (I. trimester) Improvement of identification of risky pregnancies	Screening variant I Identification of risky pregnancies (choice from 6 mutual miRNA)	Screening variant II Identification of risky pregnancies (choice from 25 miRNA)	Patent protection miRNA
HELLP syndrome (n=14)	No	😊 85.71%, 92.86% (3 miRNA + 6 or 7 clinical parameters)	85.71%, 92.86% (6 miRNA + 6 or 7 clinical parameters)	78.57% (6 miRNA)
Late MA (13. - 20. weeks) (n=34)	No	😊 84.85%, 84.85% (4 miRNA + 8 or 9 clinical parameters)	93.94%, 93.94% (6 miRNA + 8 or 9 clinical parameters)	79.41% (6 miRNA)
Stillbirth (>20 weeks – 7 days after birth) (n=24)	No	😊 91.67% (6 miRNA) (2 miRNA) No necessity to use clinical parameters in prediction model		95.83% (11 miRNA)

Key issues during transfer phase

IPR issues



CUIP



Licensing and patent sale (4 patents, 1 patent application)

Cooperation on the follow-up development

Transfer to medical practice

