Thrombosis Research 137 (2016) 126–140

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Gestational hypertension, preeclampsia and intrauterine growth restriction induce dysregulation of cardiovascular and cerebrovascular disease associated microRNAs in maternal whole peripheral blood

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ARTICLE INFO

Article history:
Received 23 July 2015
Received in revised form 11 November 2015
Accepted 20 November 2015
Available online 22 November 2015

Keywords:
Cardio/cerebrovascular diseases
Gestational hypertension
Intrauterine growth restriction
MicroRNA
Preeclampsia

ABSTRACT

Aims: To demonstrate that pregnancy-related complications are associated with alterations in cardiovascular and cerebrovascular microRNA expression. Gene expression of 29 microRNAs (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-29a-3p, miR-92a-3p, miR-100-5p, miR-103a-3p, miR-122-5p, miR-125b-5p, miR-126-3p, miR-130b-3p, miR-133a-3p, miR-143-3p, miR-145-5p, miR-146a-5p, miR-181a-5p, miR-195-5p, miR-199a-5p, miR-210-3p, miR-221-3p, miR-342-3p, miR-499a-5p, and miR-574-3p) was assessed in maternal whole peripheral blood, compared between groups (39 gestational hypertension, 68 preeclampsia, 33 intrauterine growth restriction and 20 normal pregnancies) and correlated with the severity of the disease with respect to clinical signs, delivery date, and Doppler ultrasound parameters. Initially, selection and validation of endogenous controls for microRNA expression studies in patients affected by pregnancy-related complications have been carried out.
Results: The expression profile of microRNAs was different between pregnancy-related complications and controls. The down-regulation of miR-100-5p, miR-125b-5p and miR-199a-5p was a common phenomenon shared between gestational hypertension, preeclampsia, and intrauterine growth restriction. Moreover, IUGR pregnancies induced down-regulation of miR-17-5p, miR-146a-5p, miR-221-3p and miR-574-3p in maternal circulation. Irrespective of the severity of the disease, preeclampsia was associated with the dysregulation of miR-100-5p and miR-125b-5p and IUGR with dysregulation of miR-199a-5p. Preeclampsia requiring termination of gestation before 34 weeks was associated with down-regulation of miR-146a-5p, miR-199a-5p and miR-221-3p. Weak negative correlation between miR-146a-5p and miR-221-3p expression and the pulsatility index in the umbilical artery was found. Additional microRNAs (miR-103a-3p, miR-126-3p, miR-195-5p and miR-499a-5p) showed a trend to down-regulation in appropriate pregnancy-related complications.
Conclusion: Epigenetic changes are induced by pregnancy-related complications in maternal whole peripheral blood.

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1. Introduction

Preeclampsia and fetal growth restriction (FGR) are major complications affecting 2–10% of pregnancies responsible for maternal and perinatal morbidity and mortality [1,2]. Preeclampsia usually develops after 20 weeks of gestation and is characterized by chronic or gestational hypertension combined with proteinuria [3], which results from defective placentation eliciting inadequate uteroplacental blood perfusion and ischemia [4]. The causes of preeclampsia and FGR remain unknown; however, preeclampsia is thought to be an implantation disorder [5].

Hypertension in pregnancy induces long-term metabolic and vascular abnormalities that might increase the overall risk of cardiovascular, cerebrovascular, and kidney diseases, as well as diabetes mellitus, later in life [6,7]. Increasing evidence suggests an association between preeclampsia or eclampsia and the risk for latter developing hypertension, atherosclerosis, ischemic heart disease, congestive heart failure, stroke, and deep venous thrombosis, and metabolic syndrome [8–10]. Increased risk for ischemic heart disease,

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http://dx.doi.org/10.1016/j.thromres.2015.11.032
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Table 1
The clinical characteristics of normal and complicated pregnancies.

	Healthy pregnant women (n = 20)	Preeclamptic patients (n = 68)	IUGR patients (n = 33)	GH patients (n = 39)
Age (years)	30 (26.5–33)	33 (30–36)	31 (28–34.3)	31 (29–34.3)
Blood pressure (mm Hg)				
Systolic	118 (110.5–119.5)	156 (149.8–165.5)	125 (115–140)	145 (140–150)
Diastolic	72 (70–82)	100 (90.8–104.3)	80 (73–86)	92 (90–100)
Proteinuria (g/24 h)	None	1.6 (0.56–3.5)	None	None
Gestational age at delivery (weeks)	40 (38–41)	37 (32–39)	36 (31–37)	38 (37–39)
Pregnancy body mass index	26.1 (24.8–27.9)	29.4 (27.3–34.0)	29.8 (28.3–33.5)	30.2 (27.6–34.8)
Fetal birth weight (grams)	3420 (3170–3750)	2660 (1815–3330)	1925 (1047.5–2400)	3400 (3080–3620)
Mode of delivery				
Vaginal	18 (90%)	6 (8.8%)	9 (27.3%)	16 (41%)
Cesarean section	2 (10%)	62 (91.2%)	24 (72.7%)	23 (59%)
Fetal sex				
Boy	11 (55%)	34 (50%)	16 (48.5%)	24 (61.5%)
Girl	9 (45%)	34 (50%)	17 (51.5%)	15 (38.5%)
Glucose status				
Normal	19 (95%)	59 (86.8%)	31 (93.9%)	35 (89.7%)
GDM/DM	1 (5%)	9 (13.2%)	2 (6.1%)	4 (10.3%)

Data are presented as median (25–75 percentile) for continuous variables and as number (percent) for categorical variables.
Data normality was assessed within individual categories using the Shapiro–Wilk test. The test showed that our data did not follow a normal distribution (fetal birth weight: $W = 0.944$, $p < 0.001$; age of the mother: 0.982, $p < 0.001$; systolic blood pressure: $W = 0.969$, $p = 0.04$; diastolic blood pressure: $W = 0.976$, $p = 0.004$; proteinuria: $W = 0.627$, $p = 0.018$; BMI: $W = 0.905$, $p < 0.001$; gestational age at delivery: $W = 0.900$, $p = 0.004$).

myocardial infarcts, heart failure, and ischemic stroke has also been observed among women with gestational hypertension [7]. Women with a history of pregnancy complicated by intrauterine growth restriction and low infant birth weight are at a higher risk for subsequent ischemic heart disease as well [11]. Epidemiologic and experimental data strongly indicate that children born to a pregnancy complicated by preeclampsia have a unique, life time cardiovascular risk profile that is present from early life, and represent a population that may benefit from early implementation of primary prevention strategies [12]. Childhood obesity, hypertension, and diabetes are the most common intermediate and long-term health consequences of fetal undernutrition caused by placental insufficiency [6,13].

MicroRNAs belong to the family of small noncoding RNAs (18–25 nucleotides) that regulate gene expression at the posttranscriptional level by degrading or blocking translation of target messenger RNA (mRNA) [14]. MicroRNA analyses indicate that a variety of tissues display microRNA expression profiles that are significantly different from normal tissues, which may be useful for a wide range of applications in clinical diagnostics [15]. Recent studies have shown that preeclampsia and fetal growth restriction are associated with alterations in microRNA expression in the placenta [16–20].

The aim of the present study was to explore maternal whole peripheral blood expression profile of microRNAs known to be involved in the onset of diverse cardiovascular and cerebrovascular diseases (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-29a-3p, miR-92a-3p, miR-100-5p, miR-103a-3p, miR-122-5p, miR-125b-5p, miR-126-3p, miR-130b-3p, miR-133a-3p, miR-143-3p, miR-145-5p, miR-146a-5p, miR-181a-5p, miR-195-5p, miR-199a-5p, miR-210-3p, miR-221-3p, miR-342-3p, miR-499a-5p, and miR-574-3p).

We focus mainly on those microRNAs playing a role in pathogenesis of dyslipidemia [21,22], hypertension [23–25], vascular inflammation [26,27], insulin resistance and diabetes [28], atherosclerosis [29,30], angiogenesis [31,32], coronary artery disease [24,27,31,33], myocardial infarction and heart failure [23,34–37].

To our knowledge, no study on cardiovascular and cerebrovascular microRNA expression in maternal whole peripheral blood derived from gestational hypertension, preeclampsia and intrauterine growth restriction has been carried out.

2. Materials and methods

2.1. Patients

The study was retrospective. The studied cohort consisted of 160 consecutive Caucasian pregnant women involving 39 pregnancies with gestational hypertension (GH), 68 pregnancies with clinically established preeclampsia (PE), 33 pregnancies complicated by intrauterine growth restriction (IUGR), and 20 normal pregnancies. Of the 68 patients with preeclampsia, 32 had symptoms of mild preeclampsia and 36 were diagnosed with severe preeclampsia. Twenty-four preeclamptic patients required delivery before 34 weeks of gestation and 44 patients delivered after 34 weeks of gestation. Preeclampsia occurred both in previously normotensive patients (48 cases), and was superimposed on pre-existing hypertension (20 cases). Thirteen growth-retarded fetuses were delivered before 34 weeks of gestation and 20 after 34 weeks of gestation. Oligohydramnios or anhydramnios were present in 11 growth-restricted fetuses.

An examination of blood flow (Doppler ultrasonography) showed an abnormal pulsatility index (PI) in the umbilical artery (10 preeclampsia and 17 IUGR) and/or in the middle cerebral artery (8 preeclampsia and 13 IUGR). The cerebro-placental ratio (CPR), expressed as a ratio between the middle cerebral artery and the umbilical artery pulsatility indexes was below the fifth percentile in 24 cases (8 preeclampsia and 16 IUGR). Absent or reversed end-diastolic velocity waveforms in the umbilical artery occurred in 3 IUGR cases.

The clinical characteristics of normal and complicated pregnancies are presented in Table 1.

Women with normal pregnancies were defined as those without medical, obstetrical, or surgical complications at the time of the study and who subsequently delivered full term, singleton healthy infants weighing >2500 g after 37 completed weeks of gestation. Gestational hypertension was defined as high blood pressure that developed after the twentieth week of pregnancy.

Preeclampsia was defined as blood pressure > 140/90 mm Hg in two determinations 4 h apart that was associated with proteinuria >300 mg/24 h after 20 weeks of gestation [3]. Severe preeclampsia was diagnosed by the presence of one or more of the following findings: 1) a systolic blood pressure > 160 mm Hg or a diastolic blood pressure > 110 mm Hg, 2) proteinuria greater than 5 g of protein in a

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