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Serum preadipocyte factor-1 is increased in fetuses of pregnancy complicated with severe preeclampsia

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ABSTRACT

Background: Preadipocyte factor-1 (Pref-1), an inhibitor of adipocyte differentiation, is increased in fetal blood of small for gestational age (SGA) and is considered a factor involved in determining adiposity and associated with high risk of metabolic diseases in adulthood. Preeclampsia is a condition closely associated with SGA, however, the alteration of Pref-1 of in fetuses of preeclampsia remains unknown. The aims of the current investigation were to clarify the alteration of serum Pref-1 in fetuses of preeclamptic pregnancy and to explore possible role of Pref-1 in metabolic diseases in late life.

Methods: Cord blood samples were taken at birth from 45 fetuses of normal pregnancy, 16 of gestational hypertension, 29 of mild preeclampsia and 29 of severe preeclampsia. Serum Pref-1 concentrations were measured with ELISA.

Results: There were significant differences in cord blood Pref-1 and neonatal birth weight among normal pregnancy, gestational hypertension, mild and severe preeclampsia ($F = 8.557$, $P < 0.001$ for Pref-1; $F = 38.405$, $P < 0.001$ for birth weight). Serum Pref-1 was significantly higher while birth weight were lower in severe preeclampsia than normal pregnancy, gestational hypertension and mild preeclampsia respectively ($P <= 0.001$ for all). However, either serum Pref-1 or birth weight did not significantly differ among normal pregnancy, gestational hypertension and mild preeclampsia ($P > 0.05$ for all). Fetal Pref-1 concentration was significantly negatively correlated with birth weight ($R^2 = 0.175$, $P = 0.027$ for severe preeclampsia; $R^2 = 0.209$, $P < 0.001$ for preeclampsia; $R^2 = 0.25$, $P < 0.001$ for all subjects).

Conclusions: Increased serum Pref-1 was demonstrated in fetuses of preeclampsia-complicated pregnancy, and it may be proposed that Pref-1 is among the possible mediators leading to high risk of metabolic diseases in adulthood.

1. Introduction

Preeclampsia, affecting 5–7% of pregnancies, manifests maternal hypertension and proteiunira in the second half of pregnancy, and is pathologically characterized by shadow invasion of trophoblast cells into the spiral arteries of the placenta, small placenta and inadequate placental perfusion [1,2]. Small placenta, low placental perfusion and subsequently under-nutrition and inadequate oxygen supply of fetus lead to low birth weight in preeclamptic pregnancies [1,2]. Preeclampsia caused substantial preterm delivery, which subsequently leads to low birth weight [1,2]. It has been well demonstrated that low birth weight is associated with high risk of metabolic diseases including hypertension, carotid arteriosclerosis and mortality caused by coronary heart disease or stroke in adulthood [3]. On the other hand, series of investigations revealed that the offspring of preeclamptic pregnancies had significantly higher blood pressure in childhood, adolescence and adulthood as compared to those of normotensive pregnancies [4–6]. The offspring of preelamptic women have increased blood pressure during childhood and adolescence, pulmonary and systemic vascular dysfunction during adolescence, and nearly double the risk of stroke in later life [4–6]. The effect of intrauterine exposure to preeclampsia on adiposity remains controversial, but some investigations revealed that male offspring of preeclamptic pregnancy had higher BMI, waist circumference, subscapular skinfold thicknesses and body fat percentage than male offspring of normal pregnancy [7].

The mechanisms underlying this association remained unclear. Hormones may be one of the potential mediators. Very recently, Zegher et al. [8] reported that soluble preadipocyte factor 1 (Pref-1), a factor that inhibits adipocyte differentiation, was significantly increased in neonates of small for gestational age (SGA) at birth, and proposed that increased Pref-1 concentration in early life is involved in determining the adipocyte numbers, the variation of fat tissues in the later life and subsequently metabolic diseases.

Low birth weight is one of the characteristics of preeclampsia [1,2] and offspring of preeclamptic women are at high risk of metabolic

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diseases [4–6], however, the association behind remains largely unknown. We hypothesized that circulating Pref-1 concentration may be changed in fetuses of preeclamptic pregnancies. To verify our hypothesis, we determined Pref-1 concentrations in blood samples taken from neonates at birth born to preeclamptic and normal pregnancies.

2. Materials and methods

2.1. Subjects

This cross-sectional investigation was conducted in Women's Hospital, School of Medicine, Zhejiang University, with the approval from Institutional Review Board, and informed consents obtained from all participants. In the current investigation, 58 women with preeclampsia and 16 women with gestational hypertension were recruited and 45 normally pregnant women served as control. Among the preeclamptic women, 29 were diagnosed with severe preeclampsia and 29 mild. All subjects were nulliparous Chinese women.

Pregnancy was diagnosed upon positive human chorionic gonadotropin test after missed menstruation. Gestational age was calculated by menstrual dating. Ultrasound was performed to confirm pregnancy and the gestational age. Preeclampsia was diagnosed and classified according to strict criteria recommended by ACOG [9]: a systolic blood pressure of 140 mmHg or higher or a diastolic blood pressure of 90 mmHg or higher on two occasions at least six hours apart occurring after 20 weeks of gestation in a pregnant woman with previously normal blood pressure and detectable urinary protein ($\geq 1+$ by dipstick or ≥ 0.3 g/24 h). Severe preeclampsia was defined as a blood pressure $\geq 160/110$ mmHg with either a urine dipstick showing $3+$ or $4+$ in a random urine sample or ≥ 5.0 g of proteinuria over 24 h. Other evidence of severe disease included increased serum creatinine, eclampsia, pulmonary edema, oliguria (<500 ml/24 h), fetal growth restriction, oligohydramnios and symptoms suggesting significant end-organ involvement (headache, visual disturbance, or epigastric or right upper quadrant pain). Women who met criteria of preeclampsia but not severe preeclampsia were diagnosed mild preeclampsia.

Exclusion criteria were multiple gestation, diabetes mellitus, chronic hypertension, infectious diseases recognized in pregnancy, premature rupture of membrane, active labor, polyhydramnios and signs of other concurrent medical complication. The women in control group had no sign of gestational complications and fetal distress and gave birth to healthy neonates of appropriate size for gestational age. To exclude the possible effect of labor on fetal Pref-1 concentration, only women who received elective Cesareans section were included.

2.2. Sample collection and assay

Blood samples were taken from umbilical vein immediately after the delivery of baby. Blood samples were centrifuged after standing at room temperature for at least 30 min. Serum was separated and aliquoted in −80 °C until assayed. Pref-1 concentrations were measured with a commercially available human Pref-1 ELISA (R&D System, Minneapolis, MN).

2.3. Statistical analysis

Data were tested by Kolmogorov–Smirnov test for their distribution. Normally distributed data were presented in mean ± SD and compared by Student's *t* test or one-way ANOVA. Category data were compared with chi-square test and the correlation was analyzed with regression analysis. Statistic package SPSS (Statistical Analysis System, Chicago, IL) was used for data analysis. A $P < 0.05$ was considered to be statistically significant.

3. Results

Table 1 showed the clinical data. There was significant difference in maternal age among normal pregnancy, gestational hypertension, mild and severe preeclampsia ($F = 6.687$, $P = 0.002$) but there was no significant correlation between Pref-1 concentration and maternal age. As expected, there were significant differences in gestational age at delivery ($F = 72.509$, $P < 0.001$) and neonatal birth weight ($F = 45.591$, $P < 0.001$). Gestational age at delivery was significantly shorter in preeclampsia than normal pregnancy and gestational hypertension ($P < 0.001$ for both, Bonferroni test), but was not significantly different between normal pregnancy and gestational hypertension. There was no significant difference in fetal gender among three groups ($x2 = 4.442$, P = NS), however, the difference in the prevalence of SGA fetuses was significant ($x2 = 37.72$, $P < 0.001$).

As shown in Table 1, there were significant differences in neonatal birth weight among normal pregnancy, gestational hypertension, mild and severe preeclampsia ($F = 38.405$, $P < 0.001$). The birth weight was significantly lower in severe preeclampsia than normal pregnancy, gestational hypertension or mild preeclampsia respectively ($P < 0.001$ for all). However, the birth weight did not significantly differ among normal pregnancy, gestational hypertension and mild preeclampsia. There were significant differences in cord blood Pref-1 among normal pregnancy, gestational hypertension, mild and severe preeclampsia (Fig. 1) ($F = 8.557$, $P < 0.001$). Neonatal serum Pref-1 was significantly higher in severe preeclampsia than normal pregnancy, gestational hypertension and mild preeclampsia respectively ($P < = 0.001$ for all). However, the neonatal serum Pref-1 did not significantly differ among normal pregnancy, gestational hypertension and mild preeclampsia. In the four groups, there was no significant difference of the neonatal serum Pref-1 between male and female fetus. In severe preeclampsia, fetal Pref-1 concentrations did not differ between SGA (30.33 ± 11.21, n = 16) and AGA (26.48 ± 8.37, n = 13) fetuses ($t = 0.274$, P = NS). However, Pref-1 concentration was significantly negatively correlated with birth weight in severe preeclampsia ($R^2 = 0.175$, $P = 0.027$) or mild and severe preeclampsia ($R^2 = 0.209$, $P < 0.001$), even in all subjects ($R^2 = 0.25$, $P < 0.001$).

4. Discussion

Very recently, Zegher et al. [8] reported that soluble Pref-1 is abundantly present in fetal circulation, and, at birth, SGA fetuses have significantly higher serum concentrations of Pref-1 than control fetuses. These authors proposed that soluble Pref-1 is one of the mediators for

Table 1
Clinical data and fetal Pref-1.

	Normal pregnancy	Gestational hypertension	Mild preeclampsia	Severe preeclampsia		P-value
n	45	16	29	29		
Maternal age (y)	28.6 ± 3.4	31.8 ± 4.7	30.8 ± 5.0	30.3 ± 5.2	F = 6.687	0.002
Gestational age at delivery (w)	38.70 ± 1.37	38.29 ± 1.90	34.07 ± 3.29	33.03 ± 2.75	F = 72.509	<0.001
Birth weight (g)	3253 ± 370	3429 ± 641	3065 ± 792	1792 ± 773	F = 38.405	<0.001
Fetal gender (male/female)	21/24	5/11	16/13	18/11	$x^2 = 4.442$	NS
SGA fetuses	0	1	5	16	$x^2 = 37.72$	<0.001