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Preeclampsia and Adiponectin in Cord Blood

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Key Words
Preeclampsia · Cord blood · Adiponectin · Infant development

Abstract
Aims: To compare cord blood concentrations of total adiponectin in the offspring of pregnancies with and without preeclampsia. ***Methods:*** Using a Luminex analyzer, cord blood adiponectin was measured in 182 singleton pregnancies with preeclampsia and compared to adiponectin measured in 511 singleton pregnancies without preeclampsia. ***Results:*** Adiponectin levels in cord blood increased with increasing gestational age, but overall, crude levels were similar in pregnancies with and without preeclampsia. However, in pregnancies with early delivery (weeks 32–36), and in pregnancies with delivery after spontaneous contractions, adiponectin levels were higher in the preeclampsia group. ***Conclusion:*** In preterm pregnancies and in pregnancies with spontaneous contractions, adiponectin levels in cord blood were higher in the preeclampsia group than in pregnancies without preeclampsia, maybe reflecting the need to optimize energy in preeclampsia.

Introduction

Preeclampsia is clinically characterized by hypertension and proteinuria after the 20th week of pregnancy, and the condition may cause serious adverse effects for the mother and her offspring. Thus, preeclampsia often results in premature delivery, and neonates born after severe preeclampsia are typically small for gestational age (SGA). Worldwide, preeclampsia is an important cause of morbidity and mortality in mother and child [1–6].

In adults, adiponectin is a multifunctional protein regulated by IGF-I and insulin [7, 8]. It is primarily produced in adipocytes, and its main effect is to increase insulin sensitivity [9]. In pregnancy, however, adiponectin may also be produced by the placenta, and transferred to the maternal and fetal circulation [10, 11]. It has been suggested that maternal levels of adiponectin may be higher in pregnancies with preeclampsia than in pregnancies without preeclampsia [12–14].

In the developing fetus, adiponectin is expressed from mid-gestation, with gradually increasing concentrations [11]. Apart from being expressed in fetal adipocytes, adiponectin is expressed in many other fetal tissues, including striated and smooth muscle, vascular tissue, and the kidney. Adiponectin concentrations seem to be higher in cord blood than in maternal blood, and fetal concentra-

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tions appear to be independent of maternal concentrations [10]. It has been hypothesized that adiponectin is involved in optimizing energy expenditure [15–21], and there is some evidence to suggest that adiponectin may be positively associated with central adiposity in childhood [22].

Since energy supply to the fetus is challenged in preeclampsia, we hypothesized that cord blood adiponectin levels of pregnancies with preeclampsia would be higher than in pregnancies without preeclampsia. In this population study, we therefore measured adiponectin concentrations in cord blood, and compared levels in the preeclampsia group and in pregnancies without preeclampsia.

Material and Methods

This nested case-control study has previously been described in detail [23]. Briefly, the study was conducted at Stavanger University Hospital in Norway, which covers a geographical area of approximately 239,000 inhabitants. Virtually all births in the area take place in this hospital, and between 1993 and 1995, cord blood was collected from all newborns (n = 12,804).

Based on clinical charts, the diagnosis of preeclampsia was verified and checked to be in accordance with the criteria of the CLASP study [24]. Thus, preeclampsia had to be diagnosed after gestational week 20; diastolic blood pressure had to be at least 90 mm Hg at repeated measurements, and proteinuria with dipstick +1 or more should be present in at least one urine sample. Using these criteria, we identified 307 singleton cases of preeclampsia, including virtually all cases of preeclampsia in the area during the study period. For each case, we selected 2 singleton controls without preeclampsia from the population. One control was the subsequent delivery to the case, whereas the other control was matched by maternal age. The cord blood has been utilized in previous studies, and for some of the participants of the original study [23], there was not enough blood left for the present study. However, we had sufficient cord blood available for adiponectin measurements in 182 preeclampsia cases, and in 511 controls.

The umbilical cord blood was collected in heparin vacutainers immediately after birth and before separation of the placenta. The blood was centrifuged and kept at 4°C for up to 60 h, and the serum was subsequently stored at –80°C.

All mothers had an ultrasound examination at around 18 weeks of pregnancy that was the basis for calculating gestational age. Birth weight for gestational age was standardized by calculating Z-scores based on another large Scandinavian population study [25]. SGA was defined as 2 standard deviations (SDs) below the mean birth weight, adjusted for length of gestation, and large for gestational age was defined as 2 SDs above the mean. Further, children with birth weight less than or higher than 1 SD from the mean were classified as relatively small or relatively large. Ponderal index was calculated as birth weight (in kg) divided by the birth length cubed (in meters).

Total cord blood adiponectin concentrations were measured at the Stavanger University Hospital using the XY Platform of the Luminex 100 System from the Luminex Corp. (Austin, Tex., USA). A human adiponectin antibody bead kit (Linco Research, Inc., St. Charles, Mo., USA) was used in accordance with the manufacturer's instructions except that we used a higher dilution factor of the cord samples. Acquired fluorescence data were analyzed by StarStation software version 2.0 from Applied Cytometry Systems. The minimum detectable level for adiponectin was 0.145 μg/ml, and the intra- and interassay coefficients of variation were both less than 10%.

Adiponectin concentrations had a normal distribution both in the study population as a whole and in each comparison group (preeclampsia vs. normotensive). Differences in means were therefore calculated using t tests for independent samples, and Levene's test was used to assess equality of variances. The χ^2 test was used to compare and assess statistical significance between proportions. We present the results according to strata of several variables, including offspring sex, length of gestation, offspring birth size (based on Z-scores), maternal age and parity, and categories of contractions (none, induced, spontaneous). We tested for interaction between preeclampsia status and each of the covariates. p values <0.05 were considered statistically significant. The statistical analyses were done using SPSS for Windows Version 14.0 (SPSS, Inc., Chicago, Ill., USA). The study was approved by the Regional Committee for Ethics in Medical Research and by the Norwegian Data Inspectorate.

Table 1. Descriptive data of pregnancies with and without preeclampsia

	Without preeclampsia	With preeclampsia[1]	p value
Maternal age	28.2 ± 5.0	27.0 ± 4.5	0.003
Length of gestation, weeks	40.0 ± 1.6	38.3 ± 2.7	<0.001
Birth weight, kg	3.6 ± 0.5	3.2 ± 0.8	<0.001
Birth length, cm	49.9 ± 2.2	48.1 ± 3.8	<0.001
Head circumference, cm	35.1 ± 1.4	34.4 ± 2.2	<0.001
Z-score birth weight	0.0 ± 1.0	–0.3 ± 1.3	0.004
Ponderal index[2]	4.5 ± 0.6	4.0 ± 0.90	<0.001
Adiponectin, μg/ml	73.4 ± 28.3	69.2 ± 28.3	0.09

[1] Preeclampsia: mild 31%, moderate 50%, severe 20%.
[2] Ponderal index = weight/birth length cubed.

Results

Table 1 shows maternal and offspring data of pregnancies with preeclampsia and pregnancies without preeclampsia. Only 2 women in the preeclampsia group were diagnosed with gestational diabetes, and none of the women in the normotensive group had gestational diabetes. In general, the preeclampsia group had shorter length of gestation, lower birth weight, birth length. Head cir-

Table 2. Cord blood adiponectin (μg/ml) in pregnancies with and without preeclampsia

		Without preeclampsia		With preeclampsia	
		n	mean ± SD	n	mean ± SD
Offspring sex	Male	256	70.8 ± 29.3	83	67.0 ± 28.7
	Female	255	76.0 ± 27.2	99	71.0 ± 28.0
Parity	Nulliparous	181	74.5 ± 27.6	125	69.9 ± 28.8
	Multiparous	326	72.8 ± 28.9	57	67.7 ± 27.4
Length of gestation	<32 weeks	–	–	7	43.0 ± 33.9
	32–36 weeks	19	41.4 ± 20.5	38	55.4 ± 22.1*
	37–38 weeks	72	70.1 ± 25.7	42	65.4 ± 24.3
	39–40 weeks	273	76.4 ± 30.2	76	80.1 ± 29.0
	≥41 weeks	147	73.7 ± 24.0	19	71.0 ± 25.1
Weight for gestational age	SGA (≤–2 SD)	13	65.7 ± 20.1	15	47.1 ± 32.6
	Moderately small (–2 <SD <–1)	67	66.5 ± 22.8	38	71.9 ± 28.5
	Appropriate (–1 ≤SD <1)	359	74.3 ± 29.1	101	71.2 ± 26.3
	Moderately large (1 ≤SD <2)	56	79.5 ± 31.4	24	70.3 ± 30.9
	Large for gestational age (≥2 SD)	16	67.1 ± 20.5	4	68.4 ± 17.3
Type of delivery	No contractions	18	61.8 ± 24.7	30	50.2 ± 24.3
	Induced contractions	28	65.4 ± 20.2	111	68.4 ± 25.2
	Spontaneous contractions	457	74.4 ± 28.8	40	84.9 ± 30.5**
Maternal age at delivery	<25 years	111	73.0 ± 27.9	49	70.0 ± 29.6
	25–29 years	214	73.4 ± 26.8	85	70.8 ± 28.8
	30–34 years	126	75.2 ± 31.7	36	64.0 ± 27.2
	≥35 years	60	70.2 ± 27.4	12	70.0 ± 24.1

* $p = 0.02$; test for interaction, $p < 0.01$. ** $p = 0.04$; test for interaction, $p < 0.01$.

cumference, standardized birth weight and ponderal index were also lower than in offspring of pregnancies without preeclampsia. In the preeclampsia group, crude levels of cord blood adiponectin were slightly lower, but the difference was not statistically significant.

Table 2 displays adiponectin concentrations in cord blood between the groups, according to strata of various co-variates. In pregnancies with preterm delivery (during gestational weeks 32–36), cord blood adiponectin was higher in the preeclampsia group compared to pregnancies without preeclampsia (55.4 vs. 41.4 μg/ml, $p = 0.02$, test for interaction between preeclampsia status and length of gestation, $p < 0.01$). There was no difference in gestational age (in days) within the strata of gestational age between the preeclampsia group and normotensive group (data not shown). In pregnancies with delivery after spontaneous contractions, cord blood levels of adiponectin were also higher in the preeclampsia group (84.9 vs. 74.4 μg/ml, $p = 0.04$, test for interaction between preeclampsia status and type of delivery, $p < 0.01$). Gestational age was lower in pregnancies with delivery without contractions, but cord adiponectin was still significantly different after adjustment for gestational age (87.1 vs. 75.0 μg/ml, 95% CI for difference, 0.5–2.4 μg/ml). Within categories of the other co-variates, the differences in cord blood adiponectin between pregnancies with and without preeclampsia were not statistically significant.

In pregnancies with preeclampsia, 57 of the 182 women were treated with antihypertensive medication. We explored whether this treatment could have influenced the differences in adiponectin between the groups, but found no evidence for any such influence (data not shown). We also explored if maternal BMI could have modified the level of adiponectin in cord blood, but there was no evidence that maternal BMI influenced adiponectin concentrations (data not shown).

In relation to smoking, there was information available from the early stage of pregnancy, but there was no association of smoking with cord blood adiponectin in either pregnancy group (data not shown).

Discussion

In this population study of adiponectin levels in cord blood of pregnancies with preeclampsia and pregnancies without preeclampsia, we found that in preterm pregnancies, the preeclampsia group had higher levels of adiponectin, and in pregnancies with delivery after spontaneous contractions, adiponectin levels were also higher in the preeclampsia group.

Previously, one study has reported no association of adiponectin with preeclampsia after adjustment for birth weight, gestational age and gender of the offspring [13]. That study included only 22 pregnancies with preeclampsia, and differences in adiponectin levels could not be reliably studied. In another Norwegian study, there was no difference in cord blood levels of adiponectin in the offspring of preeclamptic pregnancies and pregnancies without preeclampsia, after adjustment for length of gestation [26]. That study was hospital-based, and the comparison groups were rather small (30 preeclampsia and 62 control pregnancies).

In our study, concentrations of adiponectin in cord blood were comparable to those of another study [27], but slightly higher than reported by others [13, 28]. At low temperatures (~ –80°C), adiponectin concentrations are believed to be stable (Linco Research, Inc.). The samples were stored for a few hours at 4°C before deep freezing. To explore the stability of adiponectin, we conducted a pilot study and applied the same method of measurement in 10 fresh cord blood samples. Concentrations of adiponectin in fresh cord blood were similar to those obtained using the stored blood of the study. There was no difference in the handling of samples between the groups.

In a previous study, cord blood adiponectin was lower in pregnancies of mothers who smoked compared to nonsmokers [29]. This observation could be of relevance for our findings, because maternal smoking is negatively associated with risk of preeclampsia [30]. We had information about smoking at the beginning of pregnancy, but there was no association of smoking with cord blood adiponectin in our data, in either normotensive or preeclamptic pregnancies.

Fetal adiponectin is believed to increase with increasing length of pregnancy [13], and our findings concur with this. Given the consistently shorter length of gestation of preeclamptic pregnancies, it was appropriate to adjust for gestational age in the initial analyses. However, adiponectin concentrations did not differ between the groups, also after adjustment, and differences were only observed in the subgroup analyses, with higher cord adiponectin in preterm preeclampsia, and in preeclampsia with delivery after spontaneous contractions. Therefore, the higher levels of adiponectin in cord blood that we report in preeclamptic pregnancies with spontaneous delivery, and in preterm preeclampsia, should be interpreted with caution.

The study was based on preeclampsia cases and selected controls that occurred within a cohort of nearly 13,000 pregnant women. Controls were selected to minimize bias both in selection and cord blood measurements, and cord blood adiponectin was measured with standardized methods, where the technicians were blinded to the preeclampsia status of the blood samples.

There was not sufficient cord blood to analyze adiponectin from all participants of the original study. Among controls, there were no differences in perinatal data between the group with missing blood and those with available cord blood. However, in the preeclampsia group, those with missing cord blood tended to have lower gestational age and lower birth size compared to pregnancies with available cord blood. Thus, more severe cases of preeclampsia appear to have missing blood. This suggests that the differences that we report in this paper may be underestimates of the true differences. Also, the number of samples was low from normotensive pregnancies with low gestational age and from preeclampsia pregnancies with high gestational age. Therefore, the study does not have statistical power to detect differences between offspring with high or low gestational age.

Adiponectin is widely expressed both in the fetus and placenta and in various isoforms that were not measured in this study. In a recent study the most biological active isoform of adiponectin was found to represent the greatest part of total adiponectin in cord blood [26]. However, we do not know if this is the case in offspring of mothers with preeclampsia or in prematurely born offspring, and it would be of interest to study different isoforms of adiponectin in cord blood. In general, adiponectin will promote energy expenditure, and in cases of placental dysfunction, such as in preeclampsia, nutritional supply to the fetus may be compromised. It has been suggested that high levels of cord blood adiponectin is associated with greater central adiposity in children, and therefore, adiponectin could play a role in optimizing energy supply to the fetus as well as energy expenditure in infancy [18–21]. The higher levels of cord adiponectin that we found in pregnancies with preterm preeclampsia could be consistent with the hypothesis that upregulation of adiponectin may represent an adaptive response to relative scarcity of nutritional and energy input, maybe caused by placental

dysfunction/placentation problems. Since we only have data on the result of such scarcity (preeclampsia in the mother, lower birth weight and gestational age in the offspring) we do not have data to show this directly and this suggestion is still speculative.

In adults, low adiponectin levels are associated with endothelial dysfunction related to atherosclerosis and angiogenesis, and low levels have been associated with increased risk of vascular disease, diabetes, prostate cancer and breast cancer [31–35]. Women who have experienced preeclampsia, either in one of their own pregnancies, or as offspring, appear to be at reduced risk of breast cancer later in life [34, 36] whereas men whose mothers had preeclampsia may be at reduced risk of prostate cancer [37]. It has also been shown that offspring of preeclamptic pregnancies may have higher blood pressure already in puberty compared to other children [38]. It has therefore been suggested that adiponectin and preeclampsia share associations with several diseases that may occur subsequent to pregnancy. By comparing adiponectin levels through the life course in offspring of preeclamptic and normotensive pregnancies, associations with adult diseases may be further elucidated.

In this study we found that in preterm pregnancies and in pregnancies with delivery after spontaneous contractions, cord blood levels of adiponectin were higher in pregnancies with preeclampsia than in pregnancies without preeclampsia.

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