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Is there a relationship between the umbilical cord coiling index and oxidative stress markers and SGA Fetuses?

Gul Nihal Buyuk[1]*, Zeynep Asli Oskovi Kaplan[1], Umit Yasemin Sert[1], Inci Halilzade[1], Salim Neselioglu[2], Ozcan Erel[2], Huseyin Levent Keskin[1]

1 Department of Obstetrics and Gynecology, Ankara City Hospital, Ankara, TR
2 Department of Clinical Biochemistry, Faculty of Medicine, Yildirim Beyazit, University, Ankara, TR

*** Corresponding Author:** Gul Nihal Buyuk **E-mail:** gnu@windowslive.com

ABSTRACT

Objective: We aimed to investigate the relationship between umblical coiling index and thiol/disulfide balance in SGA newborns to compare with AGA newborns.

Material and Methods: Fetal umbilical cord serum samples were collected during labour and the thiol/disulfide homeostasis was measured. After birth, umbilical cords were collected and cord parameters were examined including, length, number of coils, umbilical cord index.

Results: Significant decrease in native thiol, total thiol, and a significant increase in disulfide, disulfide/native thiol ratio and disulfide/total thiol ratios were observed in the study group while native thiol/total thiol ratio levels of the two groups did not reach to a statistical significance.

Conclusion: The results of this study showed that SGA babies had altered thiol homeostasis in favor of oxidative stress.

Keywords: Oxidative Stress, SGA, Thiol/disulfide, Coilling, Index

INTRODUCTION

A small for gestational age (SGA) fetus is defined when the fetal weight is <10th percentile (1). SGA fetuses carry higher risk for adverse outcomes, such as impaired performance of cognitive and sensorimotor functions (1). Although most SGA infants will catch up growth during the early childhood, in obstetric practice, the increased risk of perinatal morbidity and mortality is a matter of concern (2).

Umbilical cord is the bond of life between the fetus and the placenta, which is believed to be simple in both structure and function (3, 4). Umbilical coiling index (UCI) defines the umbilical coil structure, and it is calculated by dividing number of coils to the cord length. An increased fetal risk is present in cases of hypercoiling (UCI>0,3 spiral/cm) and hypocoiling (UCI<0,1 spiral/cm) (5, 6). A relationship has been reported between the fetal chromosomal anomalies, fetal growth restriction, fetal death, preterm labor, abnormal fetal heart trace, fetal distress and abnormal coiling index (7). A higher risk for intrauterine growth restriction was reported in cases with hypercoiling (8). Hypocoiling was reported to be associated with meconium stained amniotic fluid and higher rates of admission to the neonatal intensive care unit (9).

Oxygen is essential for life, however, the excessive amounts of oxygen causes production of free radicals which are toxic to the protein structures of cell membranes, enzymes and neurotransmitters (10, 11). Antioxidant defense systems prevent the formation of these oxidants and their harmful effects. When this redox homeostasis is tipped toward an overbalance of free radicals, then oxidative stress occurs. Thiols are compounds that contain sulfur and are the most important part of the antioxidant defense system (11). In 2014, Erel and Neselioglu developed a method for detecting total thiol/disulfide homeostasis (12).

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Thiol/disulfide homeostasis represents the oxidative stress and indirectly reflects the anti-oxidative defense, and is previously reported to have an association in the pathogenesis of various acute and chronic diseases (**11, 12**).

To the best of authors' knowledge, an analysis of oxidative stress markers and its relationship between the umbilical cord coiling and SGA fetuses have not been reported yet. This study was designed to investigate the relationship between umbilical coiling index and thiol/disulfide balance in full term SGA newborns to compare with appropriate for gestational age (AGA) newborns.

MATERIAL and METHODS

This prospective study was performed between May 2019 and August 2019 in a tertiary obstetric care center. Ethical approval was obtained from the Zekai Tahir Burak Educational and Research Hospital Ethics Committee with the number (No: 02-37/2019). A verbal and written informed consent was obtained from all participants. A total of 160 women with term (>37 weeks), singleton pregnancies and vertex presentation who delivered at term, either by an elective cesarean section or a spontaneous vaginal delivery were included.

High-risk pregnancies (gestational diabetes, hypertension, oligohydramnios, polyhydramnios, multiple pregnancies); fetuses with single umbilical artery, congenital anomalies, or fetal growth restriction and women with chronic systemic diseases were excluded. Pregnancies of assisted reproductive techniques were also excluded from the study. Gestational age was determined by the last menstrual period or by adjustment regarding the ultrasound measurements in the first trimester.

Maternal demographic characteristics, age, BMI, parity, gestational age, fetal gender, mode of delivery, admission to neonatal intensive care unit (NICU), Apgar scores and arterial blood pH were recorded. An Apgar score of <7 at the 5th min was considered low. Birth weights <10th percentile were accepted as small for gestational age and >90th percentiles were accepted as large for gestational age according to Ballard's chart (**1**).

The umbilical cord of patients were cut and collected after delivery. The following cord parameters were examined: the cord length and number of coils. Umbilical cord index (UCI) was also calculated as a demonstrator of the ratio of the number of coils and the cord length. Blood from umbilical artery was drawn after the fetal cord was clamped, centrifuged at 5000 r.p.m for ten minutes and stored at - 80 0C until the analysis.

The blood samples were analyzed in the biochemistry laboratory of the Yıldırım Beyazıt University Medical School. Thiol/disulfide homeostasis tests were measured by an automated spectrophotometric method described by Erel et al. (**12**). Native (NT) and total thiol levels (tNT), disulfide levels (D), disulfide/total thiol ratios (D/tNT), disulfide/native thiol ratios (D/NT) and native thiol/total thiol ratios (NT/tNT) were calculated (Cobas 501, Roche, Mannheim, Germany).

The patients were divided into two groups regarding the fetal growth, 41 women formed with a fetus <10th percentile formed the SGA group and 119 women with appropriate for gestational age fetuses formed the control group. The two groups were compared regarding the maternal characteristics, neonatal outcomes, oxidative stress markers and the coiling of the umbilical cord.

Statistical analysis: Statistical analysis was performed by SPSS (Statistical Package for the Social Sciences) 24 (SPSS Inc., Chicago, IL). The distribution of parameters was assessed by visual (histograms, probability plots) tests and Kolmogorov Smirnov normality test. Descriptive analyses were reported using medians and minimum-maximum levels for the non-normally distributed and categorical variables and mean and standard deviation for the normally distributed variables.

Independent samples t-test were used for the normally distributed data and Mann–Whitney U-test was used for non-normal distributed data in two independent groups. The comparison of categorical variables was performed by the chi-square test. P values <0.05 were considered statistically significant. P values <0.05 was considered statistically significant. Pearson correlation, coefficient was used to determine the correlation between presence of hypercoiled umblical cord index and fetal umbilical cord thiol/disulfide homeostasis values.

RESULTS

A total of 160 term, singleton pregnant women were enrolled in the study; 41 pregnancies with SGA newborns formed the study group and were compared with 119 AGA fetuses in the control group.

The two groups were similar in terms of maternal age, gestational week, parity, mode of delivery and the fetal gender. In Table 1 main characteristics of the two groups are compared. The mean 1st and 5th minute Apgar scores were significantly lower in SGA infants (p: 0.003 and p:<0.001, respectively). The need for neonatal intensive care unit was higher in SGA deliveries than AGA fetuses (33.3% vs. 7.1% respectively; p<0.001). The mean umbilical cord pH was also lower in the SGA group (p<0.001).

In Table 2 the umbilical cord coiling findings were compared between the two groups. The rate of normal UCI index was more common in neonates with appropriate gestational age than SGA group (85.5 vs 53.6% respectively; p=0.036). The rate of hypocoiling was similar between groups while hypercoiling was more common in SGA group than controls (41.6% vs. 10% respectively; p=0.021).

Oxidative stress measures are presented in Table 3. Significant decrease in native thiol (p:0.021), total thiol (p:0.041), and significant increase in disulfide (p:0.035), disulfide/native thiol ratio (p:<0.001), and disulfide/total thiol ratios (p:<0.001) were observed in the study group while native thiol/total thiol ratio levels of the two groups did not reach to a statistical significance. No significant correlation was observed between presence of hypercoiled umbilical cord and fetal umbilical cord thiol/disulfide homeostasis values (Table 4).

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Table 1: The participant characteristics and clinical outcomes for groups.

	SGA Group (n:41)	Control Group (n:119)	P values
Age (years)	28.2±2.3	27.8±2.6	0.560
Gestational week (weeks)	39.8±0.9	39.5±0.7	0.879
Parity	1.2±0.7	1.5±0.8	0.128
Birthweight (grams)	2893±783	3293±535	0.001*
Mode of delivery	6(14.6%)	17(14.2%)	0.536
1 minute Apgar	6.7±1.3	7.5±1.1	0.003*
5 minute Apgar	8.8±1.1	9.5±0.7	<0.001*
NICU	(33.3%)	(7.1%)	<0.001*
Umbilical cord Ph	7.26	7.38	<0.001

* P<0.05, significant. NICU: Requirement of neonatal intensive care unit. SGA: Small for gestational age

Table 2: The distribution of small and normal for gestational age neonates by antenatal umbilical cord coiling.

	SGA Group (n:41)	Control Group (n:119)	P values
hypocoil	2(4.8%)	5(4.2%)	0.648
normocoil	22(53.6%)	102(85%)	0.036*
hypercoil	17(41.6)	12(10%)	0.021*

* P <0.05, significant.

Table 3: The thiol/disulfide homeostasis parameters of the groups.

	SGA Group (n:41)	Control Group (n:119)	P values
Native thiol (lmol/l)	271.8±49.3	296±44.3	0.021*
Total thiol (lmol/l)	316±52.7	340.1±48.9	0.041*
Disulfide (lmol/l)	26.2±8.5	21.9±8.6	0.035*
Disulfide/native thiol (%)	10.3±5.5	7.5±3.1	<0.001*
Disulfide/total thiol (%)	8.5±3.4	6.4±2.3	<0.001*
Native thiol/total thiol (%)	86.7±16.9	87.2±4.6	0.789

*p<0.05, significant.

Table 4. Correlations of thiol-disulfide levels with coiling index

	Native thiol (lmol/l)	Total thiol (lmol/l)	Disulfide (lmol/l)	Disulfide/native thiol (%)	Disulfide/total thiol (%)	Native thiol/total thiol (%)
Coiling index	r:-0.49 p:0.320	r:-0.030 p:0.701	r:0.142 p:0.072	r:0.162 p:0.031	r:0.167 p:0.031	r:0.087 p:0.271

The correlation between the two variables was a weak correlation of -0.5 r< 0 <r <0.5

DISCUSSION

Hypercoiled umbilical cord has been reported to have an association with SGA fetuses, however a relationship with oxydative stress has not been analyzed yet. In current study, we have demonstrated that SGA newborns had altered thiol homeostasis in favor of oxidative stress. To the best of authors knowledge, this is the first report on the association between thiol/disulfide balance and hypercoiling of the umbilical cord. Higher levels of disulfide, disulfide/native thiol ratio and disulfide/total thiol ratio were found in the SGA group compared to the AGA group. Concurrent with previous studies in SGA group, an increase in the coiling index was observed. Ezimokhai et al. showed that hypercoiled cords were correlated with poor perinatal outcomes such as low birthweight and meconium stained amniotic fluid at birth, and fetal growth retardation (**13**).

Laat et al. reported an increased risk for the need of operative deliveries in patients with hypercoiled umbilical cord structure in SGA fetuses (**14**). Concurrent with their results; hypercoiled structure was higher in SGA group, however, no increased risk was observed for operative delivery in our study. This findings suggested that hypercoiling of the umbilical cord may result in compression of the umbilical vein and consequent compromise of the placento-fetal blood flow.

Abnormal umbilical cord coiling is associated with adverse perinatal outcomes; however, the etiology of the umbilical coiling pattern is poorly understood. Numerous studies have demonstrated relationships between aberrancies in coiling and adverse perinatal outcomes including abnormal fetal heart rate patterns in labor and an increased incidence of perinatal morbidity and mortality (**15, 16**).

In a study by Mittal et al, it was revealed that hypercoiling (UCI higher than 0.30) was associated with intrauterine death and an inverse correlation was found between the UCI and the gestational age of intrauterine death (17). In our study, Apgar scores and the cord blood pH were significantly different between the two groups. Similarly, the need for neonatal intensive care unit admission was higher than the control group.

Several oxidative stress markers were used to determine the oxidative stress in SGA fetuses (18). Gupta et al. showed that SGA newborns had double the concentration of malondialdehyde as compared to AGA controls indicating significant oxidative damage that there is evidence of oxidative stress in SGA births as evidenced by increased lipid peroxidation (19). Dede et al. showed oxidative stress markers were increased while levels of antioxidant were decreased in SGA neonates when compared with normal weight newborn infants (20). Similarly Lindeman et al. studied the total radical trapping capacity of the antioxidants in plasma (TRAP) and compared the TRAP level in the preterm and term baby (cord blood) with that in adults. The concentrations of various known antioxidants were measured and the theoretical contribution of these antioxidants to the TRAP was calculated. They showed that measured and calculated TRAP were higher in the newborn babies than the adults (21).

Thiol-disulfide homeostasis is an essential for the antioxidant system. Oxygen bound thiols with many disulfide bonds are accepted to be a sign of oxidative stress (22). Since thiol/disulfide homeostasis is a novel, available, easily calculated and relatively cheap marker for oxidative stress, it was used to evaluate fetal oxidation and obstetric outcomes in pregnancies complicated by SGA in present study. We observed significant differences in thiol/disulfide homeostasis markers when the SGA and AGA fetuses were compared. Thiol/disulfide homeostasis was found to shift towards disulfide formation in SGA group. Higher levels of disulfide in umbilical cord blood of SGA newborns show that these babies suffered from lipid peroxidation and more pronounced oxidative stress than the AGA newborns. Our study has shown onset of oxidative stress during birth in SGA infants, as was observed already by other researchers using different analytical methods.

The weakness of our study were that it had a moderate patient number and not determine the number of coils with antenatal ultrasound. The strength of our study is that it is a prospective study and a single observer was involved, thus eliminating the inter-observer bias.

CONCLUSION

This is the first study on the association between thiol/disulfide balance and hypercoiling of the umbilical cord. In light of our findings, SGA newborns had altered thiol homeostasis in favor of oxidative stress. SGA newborns had increased frequency of hypercoiled cords. According to our results that there was no significant correlations between the hypercoiled umbilical cord and thiol/disulfide balance.

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