European Review for Medical and Pharmacological Sciences 2024; 28: 1471-1479

Comparative analysis of thiol-disulfide homeostasis dynamics between elective cesarean section and uncomplicated vaginal delivery: insights into perinatal oxidative balance

B.D. CENDEK[1,2], B. BAYRAKTAR[3,4], N.V. TONYALI[3,4], B.T. CAKIR[3,4], M. ALISIK[5,6], S. KOC[1], O. EREL[6]

[1]Department of Obstetrics and Gynecology, Health Sciences University Etlik Zubeyde Hanim Maternity, Teaching and Research Hospital, Ankara, Turkey
[2]Department of Obstetrics and Gynecology, Health Sciences University Ankara Etlik City Hospital, Ankara, Turkey
[3]Department of Obstetrics and Gynecology, Division of Perinatology, Health Sciences University Etlik Zubeyde Hanim Maternity, Teaching and Research Hospital, Ankara, Turkey
[4]Department of Obstetrics and Gynecology, Division of Perinatology, Health Sciences University Ankara Etlik City Hospital, Ankara, Turkey
[5]Department of Biochemistry, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu, Turkey
[6]Department of Biochemistry, Ankara Yildirim Beyazit University, Ankara, Turkey

Abstract. – OBJECTIVE: Thiols are organic compounds containing sulfhydryl groups that exert antioxidant effects *via* dynamic thiol-disulfide homeostasis. The shift towards disulfide indicates the presence of an oxidative environment. Different modes of delivery can affect thiol-disulfide homeostasis. Accordingly, we planned this research to evaluate the effects of the mode of delivery on thiol-disulfide homeostasis in both maternal serum and fetal cord blood samples.

PATIENTS AND METHODS: We conducted a prospective case-control study involving two groups: vaginal delivery (n=50) and elective cesarean section (CS) (n=45). The vaginal delivery group exclusively comprised uncomplicated term deliveries, while the CS group included pregnant individuals with scheduled cesarean deliveries due to the absence of spontaneous labor onset. Maternal serum and fetal cord blood samples were collected, and thiol-disulfide exchanges were analyzed using an automated method capable of measuring both aspects of the thiol-disulfide balance.

RESULTS: The levels of native thiol (-SH) and total thiol in both maternal serum and fetal cord blood samples were significantly higher in the vaginal delivery group than those in the CS group. An important discovery of our study was that fetal cord disulfide (-SS) level, which may reflect oxidative stress, was higher in newborns born *via* vaginal delivery when examined alone. However, in both maternal and fetal cord blood, the combined ratios, SS/SH ratio (%), SS/Total thiol ratio (%), and SH/Total thiol ratio (%) were observed to be similar between the groups in both maternal and fetal cord blood. It was observed that as the mother's weight gained during pregnancy increased, SS/SH and SS/total thiol increased (positive correlation), while SH/total thiol decreased (negative correlation).

CONCLUSIONS: Our results showed that the dynamic thiol-disulfide homeostasis was greatly influenced by the way of delivery and supported the idea that vaginally-delivered infants may have more oxidative stress.

Key Words:
Mode of delivery, Cesarean section, Vaginal delivery, Thiols, Disulfides, Oxidative stress.

Introduction

Reactive oxygen species (ROS), also known as free radicals, are natural byproducts of cellular metabolism and play important roles in cellular responses, enzymatic reactions, and biological functions, albeit at low concentrations. However, an excessive accumulation of ROS can lead to harmful effects. To counterbalance this, both enzymatic and non-enzymatic antioxidant mechanisms work in the body, and protection is provided against the harmful effects of ROS[1]. As a result of the loss of bal-

Corresponding Author: Busra Demir Cendek, MD; e-mail: dr.busra_demir@hotmail.com; busra.demircendek1@saglik.gov.tr

ance between ROS production and the body's antioxidant system, molecular and cellular functions deteriorate, and this is defined as oxidative stress (OS)[2,3]. OS causes the accumulation of reactive oxygen and nitrogen species, attacks the sulfhydryl groups of many molecules, and forms disulfide bonds[4]. Thiol is an organic compound containing the sulfhydryl (-SH) group, which has a critical role in preventing the formation of any oxidative stress condition. During OS, sulfhydryl groups transform into disulfide (-SS) bridges, and when the oxidative stress conditions are eliminated, these disulfide bond structures can revert to thiol groups[5-7]. This dynamic cycle maintains a balanced state called dynamic thiol-disulfide homeostasis (TDH)[8].

During pregnancy, the balance between oxidant and antioxidant systems is vital to prevent adverse maternal-fetal outcomes[9]. Beyond its impact on maternal health, this balance significantly influences optimal fetal development and growth[10]. Throughout pregnancy, oxidative and antioxidative mechanisms adjust dynamically to adapt to changing metabolic needs. These mechanisms not only optimize energy utilization but also protect the developing fetus from potential oxidative stress, which can profoundly affect fetal well-being. Especially considering the increased oxygen consumption and ROS release specific to the birth process, the moment of birth significantly increases the load on antioxidant mechanisms.

Uterine contractions during vaginal delivery may cause intermittent hypoxia and reoxygenation, leading to uteroplacental hypoperfusion[11]. On the other hand, it is known[12,13] that oxidative stress that occurs during cesarean section (CS) and anesthesia triggers many events in the organism. Consequently, both vaginal birth and CS expose both mother and newborn to stressful situations. It is known[14] that newborns are very sensitive to the harmful effects of free radicals secondary to oxidative stress, so minimizing OS is important for the newborn. TDH, which can easily and inexpensively be evaluated by a spectrophotometric method described by Erel and Neselioglu[15] is a marker of OS. In this study, we aimed to investigate maternal and neonatal oxidative stress using TDH in cases of uncomplicated vaginal delivery and elective cesarean section.

Patients and Methods

Study Design

This prospective study was carried out at the Health Sciences University Etlik Zubeyde Hanim Maternity, Teaching and Research Hospital, Ankara, Turkey, during the period from August to December 2016. The research was executed in accordance with the principles outlined in the Declaration of Helsinki and obtained approval from the Ethics Committee of Ankara Yildirim Beyazit University (Date: 13/07/2016, Approval No.: 213). Written informed consent was obtained from all participating patients before their involvement in the study.

Participants

A total of 95 women aged over 18, who were admitted to the delivery room of Health Sciences University Etlik Zubeyde Hanim Maternity, Teaching and Research Hospital were included in the study. Healthy pregnant women in the gestational age range 37th-41st week, who did not use drugs except for iron and folic acid supplementation, whose newborns' birth weight ranged between 2,500 grams (g) and 4,500 g, and with Apgar scores ≥7 at 5th minutes, were included in the study. Mothers with chronic or gestational diseases such as polyhydramnios, oligohydramnios, intrauterine growth retardation, gestational diabetes mellitus (GDM), hypertensive diseases, preterm premature rupture of membranes more than 24 hours, endocrine diseases, and rheumatologic diseases were excluded. Additionally, mothers who underwent CS due to maternal/fetal emergency indications (preeclampsia, eclampsia, placentation anomalies, ablatio placenta, cord prolapse, fetal distress) and those who received labor induction medication, operative vaginal delivery (vacuum and forceps extraction), or mothers who received anesthesia during vaginal delivery were also excluded. Pregnant women with multiple pregnancies, labor-related complications such as fever, meconium-stained amniotic fluid, chorioamnionitis, and intrauterine fetal exitus were also not included. Neonates admitted to the neonatal intensive care unit (NICU) were not included.

Study Groups

Gestational age was calculated using the last menstrual date and ultrasonographic examination in the first trimester. Participants were categorized into either the vaginal delivery group (n=50) or the elective CS group (n=45) based on their mode of labor. This group consisted of pregnant women with head presentation, unassisted, and complication-free vaginal deliveries without the need for medication, oxygen, or intravenous fluid infusion throughout the labor process. In the CS group, pregnant women with scheduled cesarean deliv-

eries that did not initiate spontaneously were included. For standardization, pregnant women who underwent spinal anesthesia for cesarean section were included in this group.

Sample Collection and Analysis

In both groups, the umbilical cord was clamped immediately after birth, and 3 ml of blood serum samples were simultaneously collected from the mother's peripheral vein and the umbilical cord. These samples were centrifuged at 3,600 rpm for 10 minutes, and the resulting supernatants were stored at -80°C until analysis. TDH of maternal and cord blood samples, as well as the demographic characteristics and laboratory parameters of all participants, were evaluated. The measurement of serum native thiol (SH) (μmol/L), disulfide (SS) (μmol/L), and total thiol (SH+SS) was performed using the method described by Erel and Neseliogl[15]. Ratios of SS/SH (%), SS/total thiol (%), and SH/total thiol (%) were calculated.

Statistical Analysis

The data were analyzed using IBM SPSS® Statistics, version 26.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Before conducting the analysis, the normality of the distributions was assessed using the Shapiro-Wilk test. For normally distributed data, Student's *t*-test was employed, and the results were presented as mean±SD. In cases where the data were not normally distributed, the Mann-Whitney U test was used, and the data were reported as median (minimum, maximum). Categorical variables were compared using the Chi-square test. To evaluate the correlation between groups, Spearman's correlation test was utilized. A significance level of $p<0.05$ was considered statistically significant.

Results

During the study period, a total of 112 eligible mothers were identified. We excluded 7 mother-infant pairs due to meconium-stained amniotic fluid and 10 mother-infant pairs as their serum samples hemolyzed. A total of 95 healthy mothers (vaginal delivery group, n=50 and CS group, n=45) and their babies who met the study entry criteria were included. Maternal and newborn characteristics and perinatal outcomes of the study groups are shown in Table I. No statistically significant dif-

Table I. Maternal and newborn characteristics and perinatal outcomes of the participants.

	Vaginal delivery n=50	Caesarean section n=45	*p*
Maternal age (year) median (min-max)	27 (22-41)	29 (22-37)	0.131
BMI at during test (kg/m^2) (mean±SD)	29.1±4.1	29.5±3.9	0.341
Weight gained during pregnancy (kg) (mean±SD)	10.6±4.8	12.3±6.3	0.342
Newborn gender (n, %)			0.532
Female	31 (62%)	25 (55.6%)	
Male	19 (38%)	20 (44.4%)	
Gestational age at delivery (week) (mean±SD)	38.6±1.1	38.5±0.5	0.140
Birth weight (gram) (mean±SD)	3,283±375	3,437±446	0.170
Body length of newborns (centimeter) (mean±SD)	51±2	52±2	0.092
APGAR Score at 1st-minute median (min-max)	9 (8-9)	9 (9-9)	0.342
APGAR Score at 5th-minute median (min-max)	10 (10-10)	10 (10-10)	N/A
Albumin (g/dL) (mean±SD)	3.74±0.29	3.56±0.37	0.046
Total protein (g/dL) (mean±SD)	6.47±0.4	6.24±0.59	0.095
WBC (*10^3/mm^3) (mean±SD)	11.1±2.6	9.4±1.7	0.002
Hemoglobin (g/dL) (mean±SD)	11.7±1.3	11.3±1.1	0.058
Hematocrit (%) (mean±SD)	36.4±3.6	35±2.9	0.067
Neutrophil (*10^3/mm^3) (mean±SD)	8.7±2.7	6.8±1.7	0.001
Lymphocyte (*10^3/mm^3) (mean±SD)	1.8±0.6	1.8±0.5	0.599
Platelet (*10^3/mm^3) (mean±SD)	251.7±71.4	233.5±63.5	0.157
Neutrophil-to-lymphocyte ratio (mean±SD)	4.9±2.2	3.9±1.2	0.015
Platelet-to-lymphocyte ratio (mean±SD)	144.9±65.6	135.8±41.1	0.899
MCV (fL) (mean±SD)	83.2±7.2	85±5.5	0.234
RDW (%) (mean±SD)	15.7±1.5	15.8±1.9	0.843
MPV (fL) (mean±SD)	8.3±1.2	8.3±1.2	0.961

BMI: Body mass index, WBC: White blood cell, MCV: Mean corpuscular volume, RDW: Red cell distribution width, MPV: Mean platelet volume.

ferences were observed in terms of maternal age, body mass index (BMI) during test, weight gained during pregnancy, newborn gender, gestational age at delivery, birth weight, body length of newborns, 1st and 5th minute Apgar scores of the newborns, total protein, hemoglobin, hematocrit, lymphocyte, platelet, platelet-to-lymphocyte ratio (PLR), mean corpuscular volume (MCV), red cell distribution width (RDW), and mean platelet volume (MPV) (p>0.05 for all). Notably, albumin, white blood cell (WBC), neutrophil, and neutrophil-to-lymphocyte ratio (NLR) displayed significant differences between the two groups (p<0.05 for all).

A comparison of maternal thiol and disulfide levels between vaginal delivery and CS groups is presented in Table II. There were no significant differences observed for SS levels (16.38 ± 4.71 µmol/L *vs.* 15.21 ± 5.95 µmol/L, p=0.202), SS/SH ratio (%) (5.36 ± 1.80 *vs.* 5.58 ± 3.13, p=0.668), SS/Total thiol ratio (%) (4.79 ± 1.46 *vs.* 4.90 ± 2.28, p=0.663), and SH/Total thiol ratio (%) (90.42 ± 2.92 *vs.* 90.20 ± 4.56, p=0.676) between the vaginal delivery and CS groups. However, the maternal serum SH levels (312.95 ± 41.82 µmol/l *vs.* 288.63 ± 52.86 µmol/L, p=0.028) and total thiol levels (345.71 ± 41.85 µmol/L *vs.* 319.05 ± 51.54 µmol/L, p=0.017) in the vaginal delivery group were significantly higher compared to those in the CS group.

A comparison of fetal cord blood thiol and disulfide levels between vaginal delivery and CS groups is shown in Table III. No significant differences were observed for SS/SH ratio (%) (5 ± 2.99 *vs.* 4.23 ± 2.10, p=0.153), SS/Total thiol ratio (%) (4.43 ± 2.28 *vs.* 3.83 ± 1.73, p=0.153), and SH/Total thiol ratio (%) (91.15 ± 4.56 *vs.* 92.34 ± 3.46, p=0.150) between the vaginal delivery and CS groups. However, the cord blood serum SH levels (366.03 ± 66.68 µmol/l *vs.* 328.50 ± 48.49 µmol/L, p=0.003), SS levels (17.46 ± 8.80 µmol/l *vs.* 13.59 ± 6.37 µmol/L, p=0.010), and total thiol levels (400.95 ± 69.30 µmol/l *vs.* 355.68 ± 49.74 µmol/L, p=0.001) in the vaginal delivery group were significantly higher compared to those in the CS group.

The relationships between maternal thiol-disulfide profiles and maternal parameters were also investigated. As seen in Table IV, there were significant positive correlations between weight gained during pregnancy with SS/SH ratio (%) and SS/Total thiol ratio (%) (r=0.251, p=0.014; r=0.241, p=0.019, respectively). Furthermore, a noteworthy negative correlation was identified between the weight gained during pregnancy and the SH/Total thiol ratio (%) in all mothers participating in the study (r=-0.241, p=0.019). There were significant positive correlations between SH levels and albumin, total protein, WBC, hematocrit, neutrophil levels, and NLR (r=0.405, p<0.001; r=0.469, p<0.001; r=0.228, p=0.026; r=0.212, p=0.039; r=0.254, p=0.013; r=0.229, p=0.026, respectively). There were also significant positive correlations between total thiol levels and albumin, total protein, WBC, hematocrit, neutrophil levels, and NLR (r=0.443, p<0.001; r=0.515, p<0.001; r=0.242, p=0.018; r=0.206, p=0.045; r=0.274, p=0.007; r=0.226, p=0.027, respectively).

Discussion

The onset of vaginal delivery is associated with increased production of pro-inflammatory mediators, which may lead to increased production of free radicals[16,17]. Uterine contractions during vaginal labor cause intermittent uteroplacental hypoperfusion, leading to recurrent periods of hypoxia and re-oxygenation[18]. It has been reported in molecular studies in the literature that vaginal delivery is associated with significantly increased oxidative stress compared to elective cesarean section and emergency cesarean section. Various markers that can predict oxidative stress in maternal care have

Table II. Comparison of maternal thiol and disulfide levels between vaginal delivery and cesarean section groups.

	Vaginal delivery n=50	Caesarean section n=45	p
Native thiol (SH) (µmol/L) (mean±SD)	312.95±41.82	288.63±52.86	0.028
Disulphide (SS) (µmol/L) (mean±SD)	16.38±4.71	15.21±5.95	0.202
Total thiol (SH+SS) (µmol/L) (mean±SD)	345.71±41.85	319.05±51.54	0.017
SS/SH (%) (mean±SD)	5.36±1.80	5.58±3.13	0.668
SS/Total thiol (SH+SS) (%) (mean±SD)	4.79±1.46	4.90±2.28	0.663
SH/Total thiol (SH+SS) (%) (mean±SD)	90.42±2.92	90.20±4.56	0.676

SH: Native thiol, SS: Disulfide, SH+SS: Total thiol.

Table III. Comparison of fetal cord blood thiol and disulfide levels between vaginal delivery and cesarean section groups.

	Vaginal delivery n=50	Caesarean section n=45	p
Native thiol (SH) (µmol/Lt) (mean±SD)	366.03±66.68	328.50±48.49	0.003
Disulphide (SS) (µmol/Lt) (mean±SD)	17.46±8.80	13.59±6.37	0.010
Total thiol (SH+SS) (µmol/Lt) (mean±SD)	400.95±69.30	355.68±49.74	0.001
SS/SH (%) (mean±SD)	5±2.99	4.23±2.10	0.153
SS/Total thiol (SH+SS) (%) (mean±SD)	4.43±2.28	3.83±1.73	0.153
SH/Total thiol (SH+SS) (%) (mean±SD)	91.15±4.56	92.34±3.46	0.150

SH: Native thiol, SS: Disulfide, SH+SS: Total thiol.

been tried in various studies[19-23] for this situation, and results such as increased[19,20], decreased[21], and similar[22,23] in vaginal delivery compared to cesarean section have changed according to these markers. Therefore, there is a need for a reliable marker. Plasma thiols serve as potent antioxidants, actively scavenging free radicals in the body. The balance between thiols and disulfides plays a pivotal role in maintaining cellular redox homeostasis, known as TDH. OS occurs when thiols commonly shift toward the disulfide direction. TDH stands as an innovative marker of OS that holds critical importance within the antioxidant system[15,24].

In our study, we evaluated thiol balance concurrently in samples of maternal serum and cord blood. The utilization of simultaneous samples holds considerable value as it enables a robust validation of our findings. An important discovery of our study was that fetal cord SS level, which may reflect oxidative stress, was higher in newborns born *via* vaginal delivery when examined alone. Additionally, SH and total thiol levels were significantly lower in both maternal and fetal cord serum samples in the CS group. However, in both maternal and fetal cord blood, the combined ratios, SS/SH ratio (%), SS/Total thiol ratio (%), and SH/Total thiol ratio (%) were observed to be similar between the groups in both maternal and fetal cord blood.

In their study in 2018, Ulubas Isik et al[25] demonstrated that fetal cord blood levels of SH and total thiol were higher in the vaginal delivery group, consistent with our findings. However, while the fetal cord blood SS level, which reflects oxidative stress, was significantly higher in the vaginal birth group than in the cesarean birth group in our study, it did not show a significant difference between the groups in their study[25]. In addition, similarities were seen between the groups in both maternal and fetal cord blood in terms of SS/SH ratio (%), SS/Total thiol ratio (%), and SH/Total thiol ratio (%), consistent with the results of our study. Nevertheless, their studies did not provide information on the application of a standardized anesthesia protocol. Notably, the type of anesthesia administered, the specific drugs employed, and the oxygen levels administered have the potential to influence oxidative stress[26,27]. To reduce such factors affecting oxidative stress levels, we included only women who underwent standard spinal anesthesia during cesarean section.

In the study conducted by Dağli and Dağli[28] in 2020, similar to our research, fetal cord blood values of native thiol, total thiol, and disulfide in the CS group were significantly lower compared to those in the vaginal delivery group. No significant difference was observed between the groups concerning SS/SH and SH/total thiol ratios, reflecting our findings. Unlike our study, though, their research demonstrated significantly lower SS/total thiol ratios in the vaginal delivery group. No significant change in SS/total thiol ratios was detected in our study. The most important limitation of their study was that the 1st-minute and 5th-minute APGAR scores were higher in the cesarean section group, indicating that the groups were not equally distributed in terms of distress. It is worth noting that this study did not analyze maternal thiol levels.

In the study conducted by Ceran et al[29] in 2021, they observed higher levels of SH, SS, and total thiol in fetal cord blood within the vaginal delivery group compared to the cesarean section group. Fetal cord SS/SH, SS/total thiol ratios, and SH/total thiol ratios were similar between all groups. However, the inclusion of fetuses with high blood lactate levels in this study may have affected the results, because fetuses with high distress levels may indicate that the population is oxidatively affected. In this study, maternal thiol levels were not analyzed.

Examining oxidative stress markers during birth, Argüelles et al[30] discovered a direct link between elevated oxidative stress in mothers and even greater oxidative stress in the umbilical cord

Table IV. Relationship between maternal thiol-disulfide profiles and maternal parameters.

	Native thiol (SH) (µmol/Lt)		Disulfide (SS) (µmol/Lt)		Total thiol (SH+SS) (µmol/Lt)		SS/SH (%)		SS/Total thiol (%)		SH/Total thiol (%)	
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
Maternal age (year)	-0.184	0.073	0.116	0.264	-0.160	0.121	0.193	0.060	0.178	0.084	-0.178	0.084
BMI at during test (kg/m^2)	-0130	0.209	0.015	0.887	-0.128	0.218	0.086	0.408	0.078	0.452	-0.078	0.453
Weight gained during pregnancy (kg)	-0.151	0.145	0.201	0.051	-0.107	0.300	0.251	0.014	0.241	0.019	-0.241	0.019
Gestational age at delivery (week)	-0.050	0.630	0.072	0.488	-0.034	0.740	0.064	0.535	0.071	0.491	-0.071	0.492
Albumin (g/dL)	0.405	<0.001	0.193	0.061	0.443	<0.001	-0.002	0.985	-0.013	0.904	0.013	0.904
Total protein (g/dL)	0.469	<0.001	0.158	0.125	0.515	<0.001	-0.020	0.849	-0.021	0.842	0.021	0.842
WBC (*10^3/mm^3)	0.228	0.026	0.053	0.609	0.242	0.018	-0.059	0.569	-0.059	0.572	0.059	0.572
Hemoglobin (g/dL)	0.180	0.080	-0.058	0.574	0.169	0.102	-0.081	0.437	-0.094	0.363	0.094	0.363
Hematocrit (%)	0.212	0.039	-0.032	0.759	0.206	0.045	-0.080	0.443	-0.088	0.398	0.088	0.397
Neutrophil (*10^3/mm^3)	0.254	0.013	0.081	0.434	0.274	0.007	-0.054	0.600	-0.050	0.631	0.050	0.631
Lymphocyte (*10^3/mm^3)	-0.029	0.784	0.114	0.270	-0.003	0.973	0.102	0.324	0.100	0.335	-0.100	0.335
Platelet (*10^3/mm^3)	-0.005	0.959	0.062	0.552	0.008	0.937	0.032	0.759	0.040	0.698	-0.040	0.698
Neutrophil-to-lymphocyte ratio	0.229	0.026	-0.018	0.865	0.226	0.027	-0.118	0.253	-0.115	0.267	0.115	0.268
Platelet-to-lymphocyte ratio	0.038	0.718	-0.003	0.980	0.980	0.720	-0.033	0.752	-0.023	0.823	0.023	0.824
MCV (fL)	0.051	0.622	-0.084	0.421	0.033	0.750	-0.056	0.587	-0.074	0.476	0.074	0.478
RDW (%)	0.128	0.216	-0.020	0.847	0.125	0.229	-0.083	0.426	-0.077	0.461	0.077	0.460
MPV (fL)	-0.079	0.449	-0.095	0.358	-0.100	0.334	-0.028	0.790	-0.037	0.719	0.038	0.717

BMI: Body mass index, WBC: White blood cell, MCV: Mean corpuscular volume, RDW: Red cell distribution width, MPV: Mean platelet volume.

blood of newborns. Gitto et al[31] suggested that instances of hypoxia and oxidative stress may alternate throughout labor and delivery. They noted that fetal plasma contains a limited amount of antioxidants to combat such oxidative harm. This discrepancy in antioxidant levels could clarify the heightened oxidative stress observed in neonates compared to their mothers.

In our study, we took a distinctive approach by exploring the relationship between thiol levels and various blood parameters, making our research different from previous studies in the literature. Specifically, we investigated potential correlations between thiol levels and two important blood components: albumin and total protein. This different aspect of our investigation allowed us to uncover potential associations between thiol concentrations and the levels of these blood components. Accordingly, maternal total thiol levels were correlated with albumin (r=0.443, $p<0.001$) and total protein (r=0.515, $p<0.001$). It is possible for thiol molecules to play a role in the regulation of protein synthesis, oxidation-reduction reactions, or other biochemical processes that affect albumin and total protein concentrations; nevertheless, more detailed molecular studies are required.

Previously, a preliminary report by Erel and Neselioglu[15] showed that plasma disulfide levels were higher in patients with degenerative diseases such as diabetes, obesity, and smoking, while lower in patients with proliferative diseases such as multiple myeloma and cancer. When our results were examined without discrimination of the delivery types, it was observed that as the mother's weight gained during pregnancy increased, SS/SH and SS/total thiol increased (positive correlation), while SH/total thiol decreased (negative correlation). Our findings strongly suggest that excessive weight gain during pregnancy exerts an oxidative impact on thiol dynamics.

Numerous hematological changes occur throughout pregnancy and often serve as potential indicators for some pregnancy-related disorders and prognostic determinants. When we look at the literature, there are mostly studies aimed at predicting preeclampsia and its severity[32,33]. It has been reported[32-35] that first- and second-trimester

NLR elevation is a marker that can be used to predict preeclampsia[33,34], while NLR and PLR are high in pregnant women with preeclampsia[32,35]. Second-trimester NLR, PLR, and MPV are risk factors for GDM[36,37]. It has been reported[38,39] that the ratio of PLR and NLR increases in pregnant women with hyperemesis gravidarum, and this increase develops secondary to metabolic changes and inflammation. In our study, WBC, neutrophil, and NLR were found to be statistically significantly higher in the vaginal delivery group. This result supports increased physiological OS during vaginal delivery. In addition, when maternal thiol levels were compared with all maternal parameters, regardless of delivery type, it was observed that there was a significant positive correlation between SH and total thiol levels as WBC, neutrophil, and NLR increased ($p<0.05$ for all).

Limitations

A limitation of this study is the absence of assessment based on the duration of the operation. Fasting intervals and variations in anxiety levels can influence the metabolic rates of both the mother and the fetus[40]. Regrettably, we did not control for these variables in our study. However, a notable strength of our research lies in the mitigation of biases through the uniform application of the standard cesarean section surgery protocol across all participants. The balance between oxidant and antioxidant mechanisms undergoes dynamic shifts throughout pregnancy, influenced by changes in maternal hormonal equilibrium and adjustments in both fetal and maternal metabolic requirements. In particular, existing literature[41,42] indicates a fluctuating OS level across distinct trimesters of pregnancy. The OS level may be affected by changes in steroid hormone and melatonin levels during the day[40]. In our study, CSs and vaginal deliveries were performed during daytime. In other studies, time was not specified. Moreover, we expanded our research by delving into the complex relationships between thiol levels and various blood parameters.

Conclusions

Our findings underscore the influence of the delivery route on the TDH in both maternal and cord blood. The increase in cord plasma SS level of neonates indicates increased OS in the neonates born with vaginal delivery compared with CS without initiation of labor. Additionally, as maternal weight gain increases, oxidation increases. Future studies involving larger participant groups and using randomized methodologies are necessary to collect more comprehensive information on the role of delivery mode on TDH.

Conflict of Interest
The authors have no conflicts of interest to declare.

Funding
The authors received no funding for this work.

Ethics Approval
The research was executed in accordance with the principles outlined in the Declaration of Helsinki and obtained approval from the Ethics Committee of Ankara Yildirim Beyazit University (Date: 13/07/2016, Approval No.: 213).

Informed Consent
Written informed consent was obtained from all participating patients before their involvement in the study.

Availability of Data and Materials
The data supporting this study is available through the corresponding author upon reasonable request.

Authors' Contributions
BDC conducted the population study, analyzed and interpreted the data, and drafted the manuscript. BB analyzed and interpreted the data, and drafted the manuscript. NVT and BTC participated in the interpretation and draft revision. MA, SGK, and OE participated in data collection and result interpretation. All authors declare that they approve the final version of the article.

ORCID ID
Busra Demir Cendek: 0000-0002-6338-1408
Burak Bayraktar: 0000-0001-6233-4207
Nazan Vanli Tonyali: 0000-0002-7284-6887
Betul Tokgoz Cakir: 0000-0003-0202-4981
Murat Alisik: 0000-0003-0434-3206
Sevgi Koc: 0000-0002-1703-0690
Ozcan Erel: 0000-0002-2996-3236

References

1) Ulrich K, Jakob U. The role of thiols in antioxidant systems. Free Radic Biol Med 2019; 140: 14-27.
2) Murthy K, Grobman WA, Lee TA, Holl JL. Trends in induction of labor at early-term gestation. Am J Obstet Gynecol 2011; 204: 435.e1-6.
3) Alchalabi HA, Obeidat BR, Jallad MF, Khader YS. Induction of labor and perinatal outcome: the im-

pact of the amniotic fluid index. Eur J Obstet Gynecol Reprod Biol 2006; 129: 124-127.

4) Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organ J 2012; 5: 9-19.
5) Baba SP, Bhatnagar A. Role of thiols in oxidative stress. Curr Opin Toxicol 2018; 7: 133-139.
6) Cindoglu C, Uyanikoglu A, Sari S, Ozkutlu M, Erel O. Thiol-disulfide homeostasis in irritable bowel syndrome. Eur Rev Med Pharmacol Sci 2023; 27: 10569-10576.
7) Babaoglu E, Kilic H, Hezer H, Dag O, Parlak E, Senturk A, Karalezli A, Alisik M, Erel O, Hasanoglu HC. Comparison of thiol/disulfide homeostasis parameters in patients with COPD, asthma and ACOS. Eur Rev Med Pharmacol Sci 2016; 20: 1537-1543.
8) Sen CK, Packer L. Thiol homeostasis and supplements in physical exercise. Am J Clin Nutr 2000; 72: 653S-669S.
9) Karaçor T, Sak S, Başaranoğlu S, Peker N, Ağaçayak E, Sak ME, Turgut A, Evsen MS, Evliyaoğlu O, Gül T. Assessment of oxidative stress markers in cord blood of newborns to patients with oxytocin-induced labor. J Obstet Gynaecol Res 2017; 43: 860-865.
10) Hussain T, Murtaza G, Metwally E, Kalhoro DH, Kalhoro MS, Rahu BA, Sahito RGA, Yin Y, Yang H, Chughtai MI, Tan B. The Role of Oxidative Stress and Antioxidant Balance in Pregnancy. Mediators Inflamm 2021; 2021: 9962860.
11) Mota-Rojas D, Villanueva-García D, Solimano A, Muns R, Ibarra-Ríos D, Mota-Reyes A. Pathophysiology of Perinatal Asphyxia in Humans and Animal Models. Biomedicines 2022; 10: 347.
12) Kutlesic MS, Kocic G, Kutlesic RM. Os efeitos do remifentanil sobre os marcadores do estresse oxidativo durante a cesariana, em correlação com a hemodinâmica materna e o desfecho neonatal: um estudo randômico controlado. Rev Bras Anestesiol 2020; 69: 537-545.
13) Gascoigne DA, Minhaj MM, Aksenov DP. Neonatal Anesthesia and Oxidative Stress. Antioxidants (Basel) 2022; 11: 787.
14) Ozsurekci Y, Aykac K. Oxidative Stress Related Diseases in Newborns. Oxid Med Cell Longev 2016; 2016: 2768365.
15) Erel O, Neselioglu S. A novel and automated assay for thiol/disulfide homeostasis. Clin Biochem 2014; 47: 326-332.
16) Cindrova-Davies T, Yung HW, Johns J, Spasic-Boskovic O, Korolchuk S, Jauniaux E, Burton GJ, Charnock-Jones DS. Oxidative stress, gene expression, and protein changes induced in the human placenta during labor. Am J Pathol 2007; 171: 1168-1179.
17) Hung TH, Chen SF, Hsieh TT, Lo LM, Li MJ, Yeh YL. The associations between labor and delivery mode and maternal and placental oxidative stress. Reprod Toxicol 2011; 31: 144-150.
18) Fainaru O, Almog B, Pinchuk I, Kupferminc MJ, Lichtenberg D, Many A. Active labour is associated with increased oxidisibility of serum lipids ex vivo. BJOG 2002; 109: 938-941.
19) Vakilian K, Ranjbar A, Zarganjfard A, Mortazavi M, Vosough-Ghanbari S, Mashaiee S, Abdollahi M. On the relation of oxidative stress in delivery mode in pregnant women; a toxicological concern. Toxicol Mech Methods 2009; 19: 94-99.
20) Greco A, Minghetti L, Puopolo M, Pietrobon B, Franzoi M, Chiandetti L, Suppiej A. Plasma levels of 15-F(2t)-isoprostane in newborn infants are affected by mode of delivery. Clin Biochem 2007; 40: 1420-1422.
21) Paamoni-Keren O, Silberstein T, Burg A, Raz I, Mazor M, Saphier O, Weintraub AY. Oxidative stress as determined by glutathione (GSH) concentrations in venous cord blood in elective cesarean delivery versus uncomplicated vaginal delivery. Arch Gynecol Obstet 2007; 276: 43-46.
22) Fogel I, Pinchuk I, Kupferminc MJ, Lichtenberg D, Fainaru O. Oxidative stress in the fetal circulation does not depend on mode of delivery. Am J Obstet Gynecol 2005; 193: 241-246.
23) Hracsko Z, Safar Z, Orvos H, Novak Z, Pal A, Varga IS. Evaluation of oxidative stress markers after vaginal delivery or Caesarean section. In Vivo 2007; 21: 703-706.
24) Davies KJ. Oxidative stress, antioxidant defenses, and damage removal, repair, and replacement systems. IUBMB Life 2000; 50: 279-289.
25) Ulubas Isik D, Akdaş Reis Y, Bas AY, Unal S, Ozcan B, Mollamahmutoğlu L, Neselioglu S, Erel Ö, Demirel N. The effect of the modes of delivery on the maternal and neonatal dynamic thiol-disulfide homeostasis. J Matern Fetal Neonatal Med 2019; 32: 3993-3997.
26) Yalcin S, Aydoğan H, Kucuk A, Yuce HH, Altay N, Karahan MA, Buyukfirat E, Camuzcuoğlu A, Incebiyik A, Yalcin F, Aksoy N. Supplemental oxygen in elective cesarean section under spinal anesthesia: Handle the sword with care. Braz J Anesthesiol 2013; 63: 393-397.
27) Kulacoglu H, Ozdogan M, Gurer A, Ersoy EP, Onder Devay A, Duygulu Devay S, Gulbahar O, Gogkus S. Prospective comparison of local, spinal, and general types of anaesthesia regarding oxidative stress following Lichtenstein hernia repair. Bratisl Lek Listy 2007; 108: 335-339.
28) Dağli SS, Dağli R. The Effect of Delivery Mode on Thiol-Disulfide Balance in the Umbilical Cord Blood. Ahi Evran Med J 2021; 5: 22-27.
29) Ceran B, Sarı FN, Beşer E, Alyamaç Dizdar E, Neşelioğlu S, Tayman C, Erel Ö. The Association of Cord Blood Lactate and Thiol-disulfide Homeostasis in Vaginal or Cesarean Delivered Term Newborns (without Fetal Distress). Anatol J Med 2022; 32: 378-383.
30) Argüelles S, Machado MJ, Ayala A, Machado A, Hervías B. Correlation between circulating biomarkers of oxidative stress of maternal and umbilical cord blood at birth. Free Radic Res 2006; 40: 565-570.

31) Gitto E, Pellegrino S, D'Arrigo S, Barberi I, Reiter RJ. Oxidative stress in resuscitation and in ventilation of newborns. Eur Respir J 2009; 34: 1461-1469.

32) Kang Q, Li W, Yu N, Fan L, Zhang Y, Sha M, Xiao J, Wu J, Kang Q, Chen S. Predictive role of neutrophil-to-lymphocyte ratio in preeclampsia: A meta-analysis including 3982 patients. Pregnancy Hypertens 2020; 20: 111-118.

33) Yücel B, Ustun B. Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume, red cell distribution width and plateletcrit in preeclampsia. Pregnancy Hypertens 2017; 7: 29-32.

34) Yavuzcan A, Cağlar M, Ustün Y, Dilbaz S, Ozdemir I, Yildiz E, Ozbilgeç S, Kumru S. Mean platelet volume, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in severe preeclampsia. Ginekol Pol 2014; 85: 197-203.

35) Panwar M, Kumari A, Hp A, Arora R, Singh V, Bansiwal R. Raised neutrophil lymphocyte ratio and serum beta hCG level in early second trimester of pregnancy as predictors for development and severity of preeclampsia. Drug Discov Ther 2019; 13: 34-37.

36) Liu W, Lou X, Zhang Z, Chai Y, Yu Q. Association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume with the risk of gestational diabetes mellitus. Gynecol Endocrinol 2021; 37: 105-107.

37) Yilmaz H, Celik HT, Namuslu M, Inan O, Onaran Y, Karakurt F, Ayyildiz A, Bilgic MA, Bavbek N, Akcay A. Benefits of the neutrophil-to-lymphocyte ratio for the prediction of gestational diabetes mellitus in pregnant women. Exp Clin Endocrinol Diabetes 2014; 122: 39-43.

38) Caglayan EK, Engin-Ustun Y, Gocmen AY, Sarı N, Seckin L, Kara M, Polat MF. Is there any relationship between serum sirtuin-1 level and neutrophil-lymphocyte ratio in hyperemesis gravidarum? J Perinat Med 2016; 44: 315-320.

39) Çintesun E, Akar S, Gul A, Çintesun FNI, Sahin G, Ezveci H, Akyürek F, Çelik Ç. Subclinical inflammation markers in hyperemesis gravidarum and ketonuria: A case-control study. J Lab Physicians 2019; 11: 149-153.

40) Chiba T, Omori A, Takahashi K, Tanaka K, Kudo K, Manabe M, Mariya Y, Kashiwakura I. Correlations between the detection of stress-associated hormone/oxidative stress markers in umbilical cord blood and the physical condition of the mother and neonate. J Obstet Gynaecol Res 2010; 36: 958-964.

41) Yüksel S, Yiğit AA. Malondialdehyde and nitric oxide levels and catalase, superoxide dismutase, and glutathione peroxidase levels in maternal blood during different trimesters of pregnancy and in the cord blood of newborns. Turk J Med Sci 2015; 45: 454-459.

42) Oghagbon SE, Agu KC, Omorowa FE, Okolie NP, Okwumabua M, Omo-Erhabor JA. Oxidative stress parameters as markers of the different trimesters in normal pregnancy. J Appl Sci and Environ Manage 2016; 20: 567-571.