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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

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Background/aim: To determine whether levels of malondialdehyde (MDA), nitric oxide (NO), superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) change during the 3 trimesters of pregnancy, and to compare the third trimester of pregnancy with newborn cord blood in respect to the levels of MDA, NO, and antioxidant enzymes.

Materials and methods: Maternal blood samples were collected at 9–13, 22–26, and 36–40 weeks of gestation. Cord blood was collected at the time of delivery.

Results: NO levels and GPx activity were higher in the second and third trimesters than in the first trimester. MDA level was lower in the third trimester and SOD and CAT activities were lower in the second and third trimesters than the first trimester. In cord blood, MDA and NO levels were lower while CAT and GPx activities were higher than in the third trimester of pregnancy.

Conclusion: These results suggest that the balance of free radical and antioxidant production during pregnancy ensures healthy fetus growth and development.

Key words: Maternal blood, catalase, cord blood, glutathione peroxidase, malondialdehyde, nitric oxide, superoxide dismutase

1. Introduction

Reactive oxygen species (ROS) are generated during aerobic respiration and metabolism. In response, mammalian cells have developed antioxidant defense mechanisms that prevent ROS-induced damage of lipids, proteins, and DNA. If the balance between oxidative stress and antioxidant defense deteriorates, pathological processes develop (1).

The production of ROS and the activation of antioxidant defense mechanisms are important components of female reproductive physiology. During pregnancy, the placenta supplies a connection between the maternal and fetal blood streams in order to meet the respiration, alimentation, and excretion needs of the fetus. Uterine blood flow must increase to support placental and fetal growth throughout the gestational period (2). Oxidative stress increases during early pregnancy because the high metabolic rate of the placenta causes increased generation of ROS (3). Placental progesterone also induces the augmentation of blood lipids and malondialdehyde (MDA) (4). When ROS interact with polyunsaturated fatty acids in membranes or lipoproteins, the lipid peroxidation (LPO) process begins (5). ROS and LPO induce the oxidative disturbance that is implicated in the pathogenesis of some diseases, such as pregnancy-induced hypertension, preeclampsia, and eclampsia. Although some studies reported that plasma LPO levels decreased in the third trimester of pregnancy (5,6,7), others reported the opposite (8,9).

For the fetus, delivery is an important stress that involves passing from a hypoxic intrauterine environment to a normoxic extrauterine environment (10). LPO and antioxidant status change during delivery, and these changes affect the fetus (8). Maternal LPO levels increase before delivery and decrease 48 h postpartum (11). While newborn cord blood has higher levels of ascorbic acid than maternal blood, levels of other antioxidants, like α-tocopherol, retinol, and β-carotene, are lower in cord blood than in maternal blood (12).

Previous findings suggest that the method of delivery (13,14), the kind of anesthesia (15), and the time of delivery (16) affect oxidative stress in maternal and cord blood (17,18). However, oxidant and antioxidant status have not been studied over the course of normal pregnancy or compared between maternal blood from late in pregnancy

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and newborn cord blood. The first objective of this study was to determine whether levels of MDA, nitric oxide (NO), and endogenous antioxidant status markers superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) change during the 3 trimesters of pregnancy. The second objective was to compare maternal blood in the third trimester of pregnancy and newborn cord blood with respect to the levels of MDA, NO, and antioxidant enzymes.

2. Materials and methods

This study was conducted in the Department of Obstetrics and Gynecology at Fatih University Hospital. Participants were recruited randomly from among pregnant women admitted to the hospital. Written consent was obtained from all participants, and the study was approved by the local ethics committee (2009/13).

All participants were 20–30 years old, nulliparous, healthy, and nonsmoking. Participants also had similar weights. All participants had uncomplicated singleton pregnancies and delivered vaginally without anesthesia between 38 and 40 weeks of pregnancy. None of the participants had any complications during delivery.

Blood samples were collected from 30 healthy pregnant women and their umbilical cords. Maternal blood samples were obtained in the first trimester (9–13 weeks), second trimester (22–26 weeks), and third trimester (36–40 weeks) of gestation. Mixed venous and arterial cord blood was obtained at the time of delivery by double-clamping of the umbilical cord. Samples were centrifuged at 1000 × *g* for 10 min at 4 °C, and plasma was separated and stored at –80 °C for determination of MDA and NO levels. The buffy coat was removed and discarded. The remaining erythrocytes were lysed by the addition of cold distilled water and centrifuged at 10,000 × *g* for 15 min at 4 °C. Supernatant was collected and stored at –80 °C for determination of antioxidant enzyme activities.

Plasma MDA and NO levels were measured using colorimetric assay kits (Cat. No. 10009055 and 780001, respectively, Cayman Chemical Company, USA). CAT, SOD, and GPx activities in erythrocyte lysates were measured with commercial kits from the same company (Catalog No. 707002, 706002, and 703102, respectively, Cayman Chemical Company). The hemoglobin (Hb) contents of erythrocyte lysates were measured using a Cromatest kit (Catalog No. 1134010, Linear Chemicals, Spain). Antioxidant enzyme activities are expressed as U/g Hb concentration.

Data were expressed as the mean and standard error (X ± SEM). Statistical analysis was performed using SAS version 8.02 (SAS Institute, USA). Data from the 3 trimesters of pregnancy were analyzed using the general linear model. Duncan's multiple range test was used to identify differences between groups. The significance of differences between maternal blood from the third trimester of pregnancy and cord blood was assessed using Student's t-test. Differences were considered significant when the P-value was less than 0.05. Figures were drawn with Origin 6.0.

3. Results

As shown in Figure 1, MDA levels were lower in the third trimester than they were in the first and second trimesters ($P < 0.001$). The NO level was higher in the third trimester than in the first and second trimesters ($P < 0.001$) (Figure 2). In the second and third trimesters, CAT activity was lower than in the first trimester ($P < 0.05$) (Figure 3). GPx activity was significantly higher ($P < 0.05$) in the second and third trimesters than in the first trimester (Figure 4). SOD activity decreased over the course of pregnancy as shown in Figure 5 ($P < 0.05$).

As shown in Figure 6, plasma MDA and NO levels were lower ($P < 0.001$ and $P < 0.05$, respectively) and

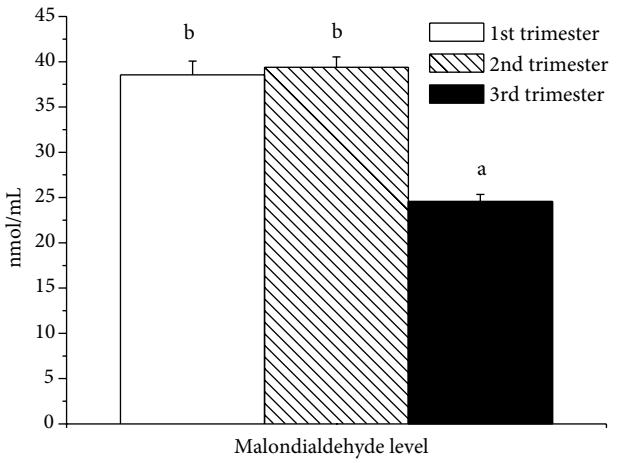

Figure 1. Plasma MDA levels in different trimesters of pregnancy (n = 30). a, b: $P < 0.001$.

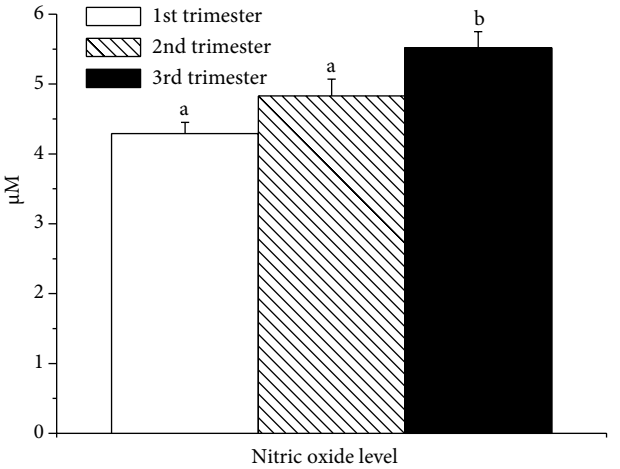

Figure 2. Plasma NO levels in different trimesters of pregnancy (n = 30). a, b: $P < 0.001$.

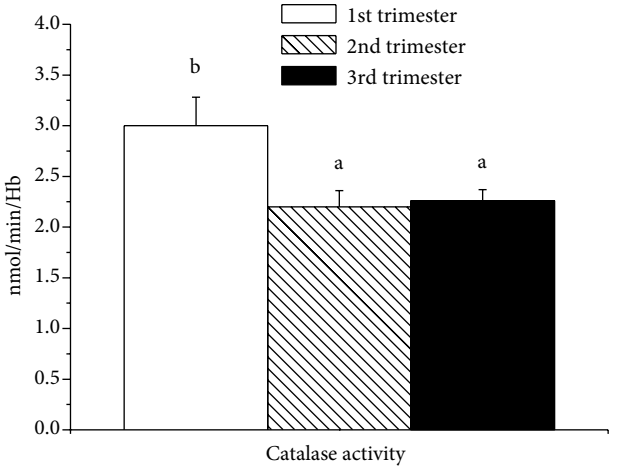

Figure 3. Erythrocyte CAT activity in different trimesters of pregnancy (n = 30). a, b: $P < 0.05$.

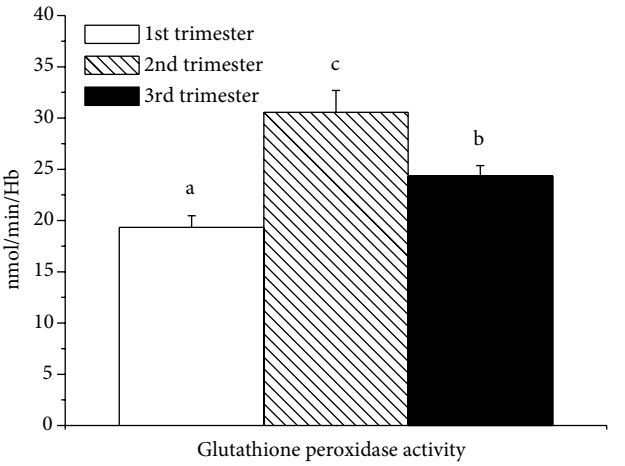

Figure 4. Erythrocyte GPx activity in different trimesters of pregnancy (n = 30). a, b, c: $P < 0.05$.

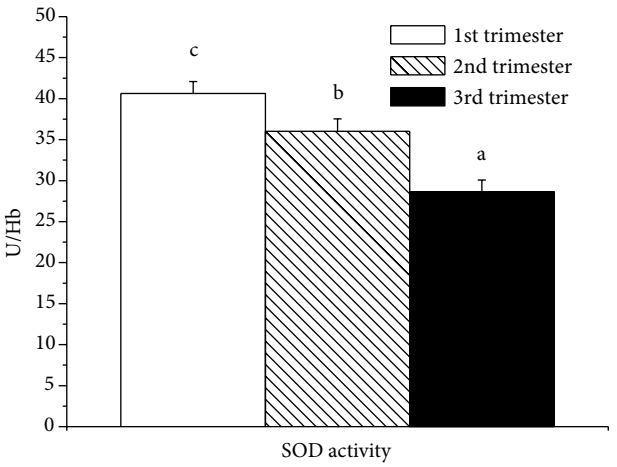

Figure 5. Erythrocyte SOD activity in different trimesters of pregnancy (n = 30). a, b, c: $P < 0.05$.

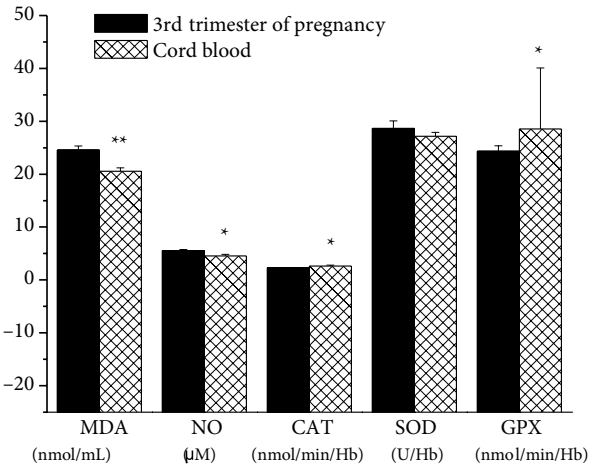

Figure 6. Comparison of MDA and NO levels and CAT, SOD, and GPx activities in maternal blood from the third trimester of pregnancy and newborn cord blood (n = 30). * $P < 0.05$, ** $P < 0.001$.

CAT and GPx activities were higher ($P < 0.05$) in the cord blood than in the maternal blood. There was no significant difference in SOD activity between maternal blood in the third trimester and cord blood ($P > 0.05$).

4. Discussion

There are many anatomical, physiological, biochemical, and psychological changes that occur during pregnancy to protect the mother from the risks of gestation and delivery and to ensure the healthy growth and development of the fetus. These changes are reversed during the 6–8 weeks following delivery (19).

There is a balance between the production of ROS and antioxidant status in the predelivery period (20). Oxidative stress increases during pregnancy because of the increased oxygen requirements of the placenta, which contains a large number of mitochondria (21). ROS are produced as a consequence of tissue reoxygenation, and increased LPO causes maternal oxidative stress (22). However, increased antioxidant enzyme activity inactivates ROS and decreases LPO. This balance between the production of ROS and activation of antioxidant mechanisms protects the tissues from damage and prevents disorders. Stipek et al. (22) and Uotila et al. (23) reported that the antioxidant system was stronger than peroxidation during pregnancy. Although some reports (9,24,25) showed that LPO increased during the course of pregnancy, other reports (6,23) observed that LPO decreased as pregnancy progressed. In normal pregnancy, placental lipid production is controlled by placental antioxidant systems (26). MDA, a metabolite of lipid peroxides, is detectable in plasma and is used as an indicator of LPO. Mihailovic et al. (27) reported an

inverse correlation between GPx activity and MDA levels during pregnancy. In the current study, decreased MDA concentrations in the third trimester of pregnancy could be due to increased GPx activity. These findings (Figure 1) are in agreement with previous reports (6,7,23).

In the present study, cord blood had lower MDA levels than maternal blood from the third trimester of pregnancy. This result is consistent with the findings reported by Upadhyaya et al. (12) and Saker et al. (20). Increased CAT and GPx activities might lead to reduced MDA levels in cord blood.

NO is a biological vasodilator, synthesized from L-arginine by endothelial nitric oxide synthase (28). Previous studies have reported conflicting results pertaining to NO levels in pregnancy. Hata et al. (29) reported that NO levels decreased during pregnancy, and Brown et al. (30) and Smarason et al. (31) reported that there were no changes in NO levels over the course of pregnancy. In the present study, NO levels in maternal blood significantly increased during pregnancy, and maternal blood in the third trimester of pregnancy had higher NO levels than cord blood. These findings are consistent with the results of some previous studies (14,32,33,34). There is an increased need for NO during pregnancy to support the arrangement of vascular functions in both the developing placental tissue and the developing fetus (35). Previous studies (32,33) also suggested that NO controls the contractility of the uterus. When delivery begins and uterine contractility increases, the NO requirement diminishes (36). Karabulut et al. (28) and Choi et al. (31) reported that NO levels in maternal blood decreased after delivery and returned to prepregnancy levels in 9–12 weeks. Consistent with these reports, the increased third trimester NO levels observed in this study could support the increased NO requirements of the placental and fetal tissues and the myometrial relaxation that is necessary for continuing pregnancy.

CAT, SOD, and GPx are important components of the antioxidant defense system. They control the level of free radicals in cells. Although Ademuyiwa et al. (37) reported that CAT activity did not change, Djordjevic et al. (38) showed increased CAT activity during the course of pregnancy. Our finding that CAT activity in maternal blood decreases during pregnancy is consistent with studies carried out in pregnant ewes (39,40). The decreased activity of CAT could be due to decreases in LPO in the third trimester of pregnancy.

In the present study, GPX activity was higher in the second and third trimesters than in the first trimester. This result is consistent with the findings of Mihailovic et al. (26) and Cochrane (41), who reported that GPx activity increased during pregnancy. Gutman et al. (42) reported that increased GPx activity in pregnancy is a defense mechanism to protect the fetus against the harmful effects of hydrogen peroxide. The results of the current study suggest that increased GPx activity suppresses the MDA level in the third trimester of pregnancy in order to protect the fetus.

Novak et al. (43) reported that CAT activity in cord blood was significantly lower than in maternal blood before delivery. In contrast, our findings are consistent with other studies (6,44,45,46), which reported that CAT and GPx activities were higher in cord blood than in maternal blood during the third trimester. The significant elevation in cord blood CAT and GPx activities observed in this study suggests that these enzymes prevent the accumulation of toxic molecules, protecting the fetus from the effects of ROS and promoting normal fetal development.

SOD activity decreased during the course of pregnancy in the present study. Similar findings were reported by Wisdom et al. (47). The observed decrease in SOD activity over the course of pregnancy may be due to the corresponding decrease in MDA levels.

Some previous studies reported no significant differences in SOD activity between maternal blood and cord blood (48,49,50). In the present study, we confirmed those findings. In contrast, several researchers reported decreased SOD activity in cord blood (51) and newborn blood (20), and other studies (11,43,44,45,52) reported increased SOD activity in cord blood. These differences may arise from the balance of oxidant and antioxidant systems (53,54,55).

In this study, we found that while maternal MDA levels and CAT and SOD activities decreased during pregnancy, NO levels and GPx activity increased. These results indicate that both peroxidation and antioxidant protection, with the exception of GPx activity, decreased during pregnancy. Increased GPx activity in late pregnancy suggests that GPx plays an important role in reducing MDA levels in the third trimester of pregnancy and it provides the balance of oxidant and antioxidant systems. We posit that NO levels increase during pregnancy to support necessary vascular functions in placental and fetal tissues. When comparing the maternal blood in late pregnancy to newborn cord blood, a negative correlation is found between oxidative stress and CAT and GPx that also supports the existence of an oxidant/antioxidant balance. As a result of this study, we infer that the antioxidant system provides the maintaining of pregnancy and the antioxidant capacity of the cord blood is sufficient to protect the baby from the oxidative stress of delivery.

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