―**Original**―

Effect of Regular Maternal Exercise on Lipid Peroxidation Levels and Antioxidant Enzymatic Activities Before and After Delivery

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Abstract

This study was designed to investigate the influence of maternal aerobic exercise on lipid peroxidation levels and antioxidant enzymatic activities before and after delivery.

Predelivery and 1- and 24-hour post partum blood samples were collected from 18 nulliparous healthy pregnant women who exercised regularly throughout the whole period of pregnancy and from 22 matched controls. The plasma concentration of malondialdehyde (MDA) was measured as an indicator of lipid peroxidation. Erythrocyte enzymes, superoxide dismutase (SOD), glutathione peroxidase (GSHPx) and catalase (CAT), were measured as intracellular antioxidant markers.

In the control group, MDA increased slightly from predelivery to 1 hour post partum and then increased significantly at 24 hours post partum, with significant increase in SOD and CAT activities. On the other hand, MDA of the exercise group remained unaltered at 1 and 24 hours after delivery. At 1 hour post partum, the SOD and CAT levels of the exercise group increased markedly and then decreased to predelivery levels.

The present results indicate that uncontrolled lipid peroxidation occurs during labor and suggest that continuing regular maternal exercise may reduce labor-induced lipid peroxidation by improving the defense capabilities against free radical generation.
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Key words: lipid peroxidation, antioxidant activity, delivery, pregnancy

Introduction

During normal respiration, the human body produces oxygen free radicals[1]. When reactive oxygen free radicals interact with the polyunsaturated fatty acids in membranes or lipoproteins, the process of lipid peroxidation begins. Although these peroxidation reactions are normally controlled by countervailing biologic mechanisms[2], severe oxidative stress produces reactive oxygen free radicals and induces uncontrolled lipid peroxidation[3]. Because the cell membranes consist primarily of lipids, the uncontrolled lipid peroxidation can cause cell injury and death via DNA strand breakage and membrane damage[4].

It is known that during labor oxygenation of both maternal and fetal tissue oscillate frequently[5]. Maternal oxygen consumption increases significantly in normal labor[6,7]. It has also been reported that there are unstable respiratory conditions including periods of apnea and/or shallow respirations during

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uterine contractions[8]. These findings lead us to postulate that tissue reoxygenation may occur during labor. In consequence, reactive oxygen species may cause uncontrolled lipid peroxidation. In fact, our preliminary study[9], which examined the time course of changes in maternal lipid peroxidation levels and in antioxidant enzymatic activities before and after delivery, demonstrated that uncontrolled lipid peroxidation occurred during labor.

In recent years there has been a dramatic increase in the number of pregnant women engaging in physical activity. Although previous studies on sports medicine demonstrated that physical training improves erythrocyte antioxidant enzymatic activity at rest and during postexercise recovery[10-12], relatively little is known about the antioxidant defenses in pregnant women who exercise vigorously during pregnancy. Therefore, the current study was designed to explore the effect of maternal exercise on lipid peroxidation levels and antioxidant enzymatic activities before and after delivery.

Subjects and Methods

Measurements of the plasma index of lipid peroxidation and erythrocyte antioxidant enzymatic activities were performed on 18 nulliparous healthy pregnant women who exercised regularly throughout the whole period of pregnancy and on 22 matched controls at Tama Nagayama Hospital of Nippon Medical School. All of these subjects provided written informed consent for participation in this study, which was approved by the institutional review board. Although overall exercise performance varied widely between subjects, the women recruited as the exercise group continued to perform aerobic exercise vigorously three or more times each week for at least 20 minutes per session at an intensity in excess of 50% of maximal capacity throughout the whole period of pregnancy. A similar number of nulliparous healthy pregnant women who discontinued regular sustained exercise during pregnancy were recruited to serve as the control group.

Demographic and clinical data were collected at routine obstetric visits. All of these subjects had uncomplicated singleton pregnancies. Liver, kidney, and thyroid functions were normal both before and during pregnancy. These women also denied having a history of chronic disease and cigarette or illicit drug use. A first-trimester or early second-trimester ultrasonographic study confirmed the gestational age.

Progress of labor was determined by vaginal examinations every one to two hours and as indicated by clinical conditions. Uterine contractions and fetal heart rate were monitored continuously with a cardiotocograph. None of these subjects had any abnormalities during labor and delivered spontaneously.

Blood samples were obtained by venous puncture from the antecubital vein of each woman before delivery and 1, and 24 hours post partum and immediately transferred to chilled heparinized glass tubes. Predelivery samples were collected at 36 weeks of gestation. Samples were centrifuged at 1,000 g for 10 minutes, and the plasma was divided into aliquots and frozen in dry ice prior to being stored at $-80℃$. Erythrocyte fractions were resuspended to the original blood volume and washed with cold isotonic saline solution. The erythrocytes were hemolyzed in distilled water and stored at $-80℃$ until analysis.

Malondialdehyde (MDA), a metabolite of lipid peroxides detectable in plasma, was used as an indicator of lipid peroxidation. Plasma MDA concentrations were estimated as reactive substances by a thiobarbituric acid adduction (TBARS) method described by Yagi[13] and Wang et al.[14]: the assay indirectly quantifies lipid hydroperoxides by measuring aldehyde breakdown products of lipid peroxidation. In summary, four milliliters of 1/12 sulfuric acid and 0.5 ml of 10% phosphotungstic acid were added to 20 μl sample and mixed thoroughly. After centrifugation at 3,000 g for 10 minutes, the liquid phase was decanted. Four milliliters of double-distilled water and 1.0 ml TBA reagent (0.67% 2-thiobarbituric acid/acetic acid, 1: 1) were then added to each sample, mixed, and heated at 95℃ for 1 hour. Samples were cooled with tap

water. Five milliliters of *n*-butyl-alcohol were added, and the samples were vigorously shaken for 1 minute and centrifuged. The *n*-butyl-alcohol phase, which contained the lipid peroxides, was used for MDA analysis with a fluorospectrophotometer (Shimadzu RF-5000, Tokyo, Japan) with excitation at 515 nm and emission at 553 nm. The individual performing the assay was blinded to the identity of the samples.

Erythrocyte enzymes superoxide dismutase(SOD), glutathione peroxidase (GSHPx) and catalase (CAT) were used as intracellular antioxidant markers. SOD and GSHPx activities were determined with a spectrophotometric assay described respectively by Flohe and Otting (1984)[15] and Flohe and Gunzler (1984)[16], while CAT activity was measured using the first order rate constant (K) of decomposition of hydrogen peroxide[17]. All of these antioxidant enzymatic activities were expressed relative to the hemoglobin concentration[11].

All data were expressed as mean ± standard deviation (SD). One-way analysis of variance followed by Scheffé's *F* test were used to compare the values within each experimental group. Mann-Whitney *U*-test was used to compare the values between the exercise and the control groups. Differences with a *P* value of less than 0.05 were considered to be statistically significant.

Results

The characteristics of the subjects are shown in **Table 1**. There were no significant differences in

gestational age, duration of labor and blood loss between the study groups. None of the subjects showed secondary arrest of labor, which requires stimulation of uterine activity and active management of labor(e.g. forceps delivery and vacuum extraction), and abnormal hemorrhage, which requires blood transfusion. There were no subjects requiring oxygenation due to abnormal fetal heart rate monitoring. All of the newborn weights were appropriate for gestational age, and there were no significant differences between the study groups. Their Apgar scores at 1 and 5 minutes were within the normal range.

The plasma index of lipid peroxidation and the erythrocyte antioxidant enzymatic activities before and after delivery are shown in **Table 2**. Before delivery there were no significant differences in the plasma concentration of MDA and the erythrocyte antioxidant enzymatic activities between the study groups. In the control group, the plasma concentration of MDA increased slightly from predelivery to 1 hour post partum (not significant) and then increased significantly at 24 hours post partum. In contrast to the results obtained from the control group, the plasma concentration of MDA of the exercise group remained unaltered at 1 and 24 hours after delivery.

In the control group, at 1 and 24 hours after delivery, SOD activities in erythrocytes increased significantly to 115% and 113% of the predelivery levels, respectively. CAT activities increased slightly at 1 hour after delivery (not significant) and then increased significantly to 147% of the predelivery

Table 1 Characteristics of subjects

	Control (n=22)		Exercise (n=18)	
	Mean ± SD	*Range*	*Mean ± SD*	*Range*
Mother				
Age (yr)	27.4 ± 3.9	23 to 34	28.1 ± 4.0	23 to 38
Gestational age at delivery (wks)	38.8 ± 1.2	37 to 40	38.7 ± 1.1	37 to 40
Duration of labor (hr)	9.5 ± 6	1 to 30	7.0 ± 4.9	2 to 18
Blood loss during delivery (gm)	338 ± 199	60 to 630	346 ± 192	90 to 800
Neonate				
Weight (gm)	3,081 ± 382	2,510 to 3,618	2,973 ± 374	2,500 to 3,480
1-minute Apgar score*	9	7 to 10	9	7 to 10
5-minute Apgar score*	9	7 to 10	9	7 to 10

Note. * Median value

Values are not statistically significant

Table 2 Changes in plasmatic lipoperoxidative index: malondialdehyde (MDA) and erythrocytic antioxidant enzymatic superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSHPx) activities before and after delivery

	MDA nmol/ml	SOD μ g/gHb	CAT K/gHb	GSHPx IU/gHb
Control				
predelivery	2.2 ± 0.2	171.5 ± 20.1	77.6 ± 29.1	26.2 ± 4.2
1h post partum	2.4 ± 0.2	196.8 ± 17.9*	83.5 ± 48.2	28.8 ± 4.3
24h post partum	2.8 ± 0.3*	193.8 ± 17.2*	114.4 ± 13.2*	29.8 ± 4.1
Exercise				
predelivery	2.4 ± 0.3	180.6 ± 18.9	72.4 ± 40.4	25.2 ± 5.5
1h post partum	2.2 ± 0.2[†]	220.8 ± 27.9*[†]	157.8 ± 52.3*[†]	26.8 ± 5.9
24h post partum	2.4 ± 0.4[†]	172.9 ± 26.2[†]	93.3 ± 37.7[†]	27.5 ± 4.2

Note. Values are mean ± SD

*p < 0.05 for the difference against predelivery in each study group (one factor ANOVA followed by Scheffe's post hoc test)

[†]p < 0.05 for the difference against control group (Mann-Whitney U-test)

level at 24 hours after delivery. Changes in GSHPx activity were qualitatively similar to those in SOD and CAT, but these changes did not reach significance.

Contrarity, at 1 hour after delivery, levels of the erythrocyte enzymes, SOD and CAT, in the exercise group increased significantly to about 122% and 218% of the predelivery levels, respectively. These values were significantly higher than those of the control group. Thereafter, these values decreased significantly to the predelivery levels at 24 hours post partum. The SOD and CAT activities at 24 hours post partum were significantly lower than those of the control group. GSHPx activity remained unchanged at 1 and 24 hours after delivery.

Discussion

The present results, as well as those presented in a preliminary publication[9], provide novel information on the effect of maternal exercise on lipid peroxidation levels and antioxidant enzymatic activities before and after delivery. The results obtained with the healthy pregnant women who discontinued regular exercise during pregnancy showed that the plasma index of lipid peroxidation increased slightly immediately after delivery and then increased significantly at 24 hours post partum with significant increase in antioxidant levels. In contrast, continuation of regular aerobic exercise

during pregnancy was not associated with an increase in maternal lipid peroxide levels in the blood after delivery. Because the levels of antioxidant enzymatic activities of the exercise group are higher than those of the control group immediately after delivery, maternal exercise may reduce labor-induced lipid peroxidation by improving the defense capabilities against free radical generation.

Previous studies, which examined maternal lipid peroxidation in healthy pregnant and non-pregnant women[14,18-23], demonstrated that lipid peroxide levels in the first trimester of pregnancy were sometimes higher and sometimes lower than the level of the non-pregnant control group. By the second trimester, increases of 10 to 50% over the first trimester values were usually seen. Third trimester levels were inconsistent and sometimes declined. The present results in both the control and the exercise groups, similar to our preliminary results[9] and those reported by Wang et al.[14], showed a moderate increase in maternal lipid peroxide levels before delivery compared with those in the non-pregnant controls[2,11,14]. These increased levels of lipid peroxide may be related to the increase in serum lipids, because serum lipids spontaneously autooxidize to form lipid peroxides. Maseki et al.[19] demonstrated that as the serum concentrations of total lipids increased during pregnancy, so also did the concentrations of lipid peroxides; hence the ratio

of lipid peroxides to total lipids did not change. Lipid peroxidation is also induced in the placenta during pregnancy[24,25]. Lipid peroxides originating from both the trophoblast and the villous core compartments[26] are secreted into the maternal effluent, possibly adding to levels in the maternal blood as additional peroxidation cascades are initiated.

There are conflicting reports on antioxidant activities throughout gestation. Selenium and GSHPx, both components of the antioxidant system, are decreased during pregnancy[27]. However, similar to our study, the antioxidant enzyme, SOD, increases in activity throughout normal pregnancy[28]. The protective antioxidant mechanisms are complex and multifactorial. The susceptibility of cells to oxidative stress is a function of the overall balance between the degree of oxidative stress and the antioxidant defense capability. It is possible that during gestation, the increase in antioxidant activity occurs in response to normal oxidative stress arising from pregnancy. At present, the nature of such a mechanism is not known.

In the present study, maternal lipid peroxide levels in the control group increased slightly from predelivery to 1 hour post partum and then increased significantly at 24 hours post partum with a significant increase in antioxidant levels. The results are in agreement with those presented in our preliminary publication[9] and suggest that uncontrolled lipid peroxidation caused by reactive oxygen species, which are produced in consequence of tissue reoxygenation, may occur during labor. In contrast to this, Davidge et al.[29] and Hubel et al.[30] demonstrated a decrease in antioxidant activities after delivery compared with those in the third trimester. These results suggest that the placenta may be a source of maternal lipid peroxides. However, because all of these measurements were performed from one to three days after delivery, there were no data obtained immediately after delivery.

During labor, oxygenation of both maternal and fetal tissue oscillates frequently[5]. There are unstable maternal respiratory conditions including periods of apnea and/or shallow respirations during labor[8]. In addition to this, during uterine contractions,

the relationship between pressures in the uterine artery and vein and blood flow no longer holds, which results in a proportional fall in blood flow[31-33]. Furthermore, previous investigators examined the maternal response to the pain and the stress of labor in terms of the release of certain hormones and reported increases in epinephrine and norepinephrine throughout labor[34,35]. Both epinephrine[36] and norepinephrine[37] cause a reduction in uterine blood flow. These findings support our results, because ischemia-reperfusion and/or hypoxia-reoxygenation in human and other species lead to free radicals that induce lipid peroxidation[38-41].

In contrast to this, our results obtained from the exercise group showed that continuing regular aerobic exercise during pregnancy was not associated with an increase in maternal lipid peroxide levels in the blood after delivery. During strenuous exercise, the aerobic metabolic rate in the skeletal muscle is raised up to 10 times the resting levels, enhancing leakage of superoxide anion from the mitochondria to the cytosol[42,43]. The subsequent reactions give rise to other reactive oxygen species such as reactive hydroxyl radicals[4]. These reactive oxygen species have been shown to induce damage in all cellular macromolecules, such as lipid, protein, and DNA[44]. Therefore, an increase in the generation of reactive oxygen species during exercise has been considered to be an oxidative stress[42]. Recently, several studies in humans[10-12] and animals[45-48] have shown that chronic aerobic training reduces exercise-increased lipid peroxidation, likely as a result of an adaptative increase in the activities of the scavenger enzyme system. In agreement with those reports, regular maternal exercise improved the level of antioxidant enzymatic activities immediately after delivery in this study. There is a large difference in the intensity of the training between our subjects and others, because the subjects recruited in the other studies performed aerobic endurance training at professional level. However, the women recruited as the exercise group of this study continued aerobic exercise vigorously throughout the whole period of pregnancy, at least for 30 weeks, while the other training programme was for 12 weeks[12]. Thus, our

results suggest that even moderate exercise may improve the antioxidant activities when it continues for a long period.

In conclusion, the present study showed that the uncontrolled lipid peroxidation occur during labor and suggested that continuing regular maternal exercise may reduce labor-induced lipid peroxidation by improving the defense capabilities against free radical generation.

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