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The Effect of Aerobic and Resistance Exercise on Oxidative Stress during Pregnancy: A Non-randomized Controlled Trial

Mochizuki C[1*] and Adachi K[2]
[1]*Graduate Midwifery Course, Teikyo University, Japan*
[2]*Department of Nursing Science, Graduate School of Human Health Sciences, Tokyo Metropolitan University, Japan*

Abstract

Aim: The effects of combined moderate-intensity aerobic and resistance exercise on physiological indicators of oxidative stress in pregnant women have not been investigated. We aimed to determine whether aerobic and resistance exercise during the second trimester reduces oxidative stress in pregnant women. **Methods:** Women with low-risk singleton pregnancies at 20–27 gestational weeks were recruited at two antenatal clinics in Tokyo, Japan. The intervention (*n* = 43) and control (*n* = 45) groups included pregnant women who planned and did not plan to attend maternity aerobics classes three times weekly for 10 weeks. Participants' data were collected at baseline and after the program completion. Heart Rate (HR), maximum HR, and VO_{2max} uptake were monitored. The General Health Questionnaire and International Physical Activity Questionnaire were administered at baseline. Oxidative stress was measured at baseline and 10 weeks later using urinary DNA-derived 8-hydroxy-2-deoxyguanosine levels (8-OHdG) and urinary lipid-derived 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) levels. **Results:** The exercise program reduced urinary 8-OHdG levels and prevented urinary 8-iso-$PGF_{2\alpha}$ level increase. The between-group differences in urinary 8-OHdG and urinary 8-iso-$PGF_{2\alpha}$ levels were not affected by being overweight, mental health status, iodine supplement uptake, and previous exercise habits. However, passive smoking was associated with elevated urinary 8-OHdG. **Conclusion:** Our study indicates that 30 combined moderate-intensity aerobic and resistance exercise sessions at 40%–60% VO_{2max}, starting from the second pregnancy trimester, can reduce oxidative stress in the third trimester.

Keywords: Exercise; Oxidative stress; Pregnancy; Non-randomized controlled trial

Introduction

During pregnancy, oxidative stress is enhanced by increased mitochondrial activity due to active energy metabolism in the placenta as well as increased active oxygen species production [1]. Oxidative stress is implicated in multiple pathological processes associated with human disorders, including those occurring during pregnancy [2]. Currently, the best method to measure oxidative stress in vivo is to detect changes in the levels of oxidation products of endogenous molecules such as DNA, proteins, or lipids [3]. The marker which is used to measure oxidative stress in vivo most commonly is an arachidonic acid oxidation product (F_2isoprostanes) [4,5]. There is a variety of F_2-isoprostanes, but the chemical species often used is 8-iso- prostaglandin $F_{2\alpha}$ (8-iso-PGF2α). The excessive generation of 8-iso-$PGF_{2\alpha}$ is merely nonenzymatic, and in particular reflect the increase of the chemical lipid peroxidation [6]. Because of various oxidation materials and an antioxidant material present in blood, 8-iso-$PGF_{2\alpha}$ exhibits unsteadiness [7]. However, urinary sample is used as, in urine, it is relatively stable [8]. Hypertensive disorders of pregnancy (HDP) and depression are associated with elevated urinary lipid-derived 8-iso-$PGF_{2\alpha}$ levels [9,10], 8-hydroxy-2′-deoxyguanosine (8-OHdG), a damage of DNA oxidation, has been used for this purpose in many epidemiological studies [11-16], because its chemical stability and urinary excretion make it easy to collect and manipulate specimens [17,18]. Whereas gestational diabetes mellitus (GDM) and depression are associated with elevated urinary DNA-derived 8-OHdG [19,20].

Acute aerobic exercise leads to oxidative stress, which can damage enzymes, protein receptors, lipid membranes, and DNA [21]. Regular moderate strength aerobic exercise enhances antioxidant levels and suppresses oxidative stress induced by a single bout of aerobic and resistance exercise [22-24].

Exercise during pregnancy reduces the risks of pregnancy-induced hypertensive disorders [25], gestational diabetes [26] and depression [27]. Previous studies have shown its benefits in pregnant women, including controlling weight [28], preventing lower extremity edema [29], decreasing blood pressure (BP) [30], reducing back pain [31], lowering blood loss during delivery [32], boosting self-efficacy [33], alleviating postpartum fatigue and stress, and improving sleep quality [34]. The American College of Sports Medicine (ACSM) recommends aerobic exercise during pregnancy at a 3–4 days per week frequency, as exercise frequency is reportedly a birth weight determinant [35]. Further, aerobic exercise should last ≥ 15 min per day, with a gradual increase to a maximum of 30 min per day and a total duration of moderate-intensity exercise of 120 min/week during pregnancy [35]. ACSM recommends exercise intensity of 40–60% VO_{2max} to improve the health and physical strength of pregnant women and emphasizes the importance of combining aerobic and resistance exercises [36,37]. There have been few reports on pregnant women following a program combining moderate-intensity aerobic and resistance exercises, and no investigation has assessed oxidative stress. This study aimed to determine whether an exercise program for women in the second trimester may alleviate oxidative stress markers elevation.

Material and Method

Design and Setting

We conducted a non-randomized controlled trial based on an exercise program with a trainer for 10 weeks beginning from the second trimester of pregnancy. This investigation was performed in an urban setting in Japan. This study was approved by the Institutional Review Board of Tokyo Metropolitan University, Arakawa campus (reference number: 15066, 08 December 2015) and Teikyo University Ethics Committee (reference number: TUIC-COI16-0476, 17 August 2016). Written informed consent was obtained from all participants. Data were collected between September 2017 and September 2018.

Participants and Sample Size

Participants were recruited from two antenatal clinics with posters displayed at the hospital reception. The inclusion criteria were: (a) a low-risk singleton pregnancy (without a mental and physical health pregnancy complication) at (b) 20–27 gestational weeks (GW) and (c) either having the intention to participate in maternity aerobics three times a week or no intention to attend maternity aerobics at all. The study purpose was explained to the potential participants by a study representative. After recruitment, participants willing to attend aerobics were assigned to the intervention group, and the non-willing were assigned to the control group.

The data were collected at the baseline appointment at 20–27 GW and at a follow-up assessment after the 10 weeks intervention completion of (≥ 30 GW). We coded participants' details to anonymous IDs linked to full names and addresses.

Based on a previous study [38], the required sample size was calculated [39], and the required participant number in each group was estimated to be 90 (statistical power: 0.80, significance: 0.05, effect size: 0.6). Assuming a 15% withdrawal rate of participants, 110 participants were necessary for this study. The data collection flow chart is shown in Figure 1.

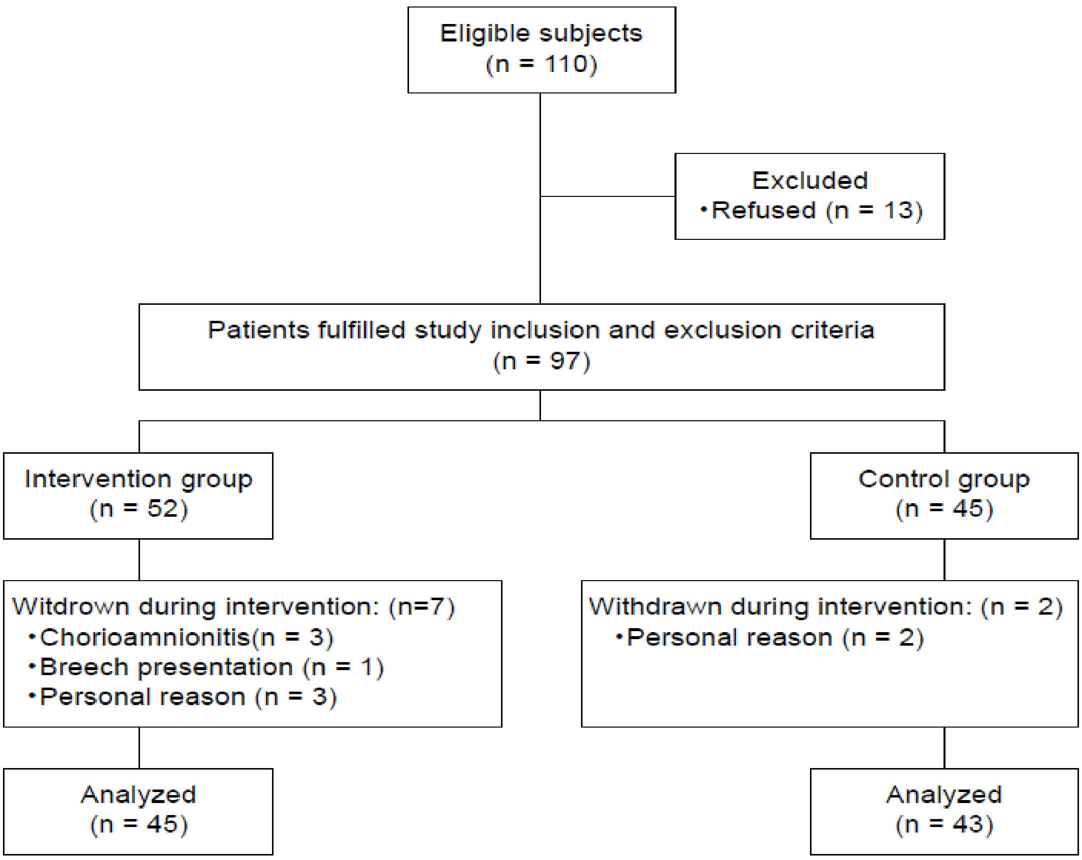

Figure 1: Schematic representation of the recruitment procedure.

We obtained consent from 97 subjects. Thirteen subjects in the intervention group refused to participate because of relocation plans and were excluded from the study. Among the remaining 97 subjects, 52 and 45 individuals consented to participate in the intervention and control groups, respectively. By 10 weeks after the intervention commencement, seven intervention group subjects withdrew due to chorioamnionitis (*n*=3), urgent cesarean section due to breech presentation with unsuccessful abdominal version (*n*=1), and personal reasons (*n*=3), whereas two control group subjects withdrew from the study due to personal reasons.

Exercise Program

The exercise program, developed by the Japan Maternitybics Association (presently known as the Japan Maternity Fitness Association), consisted of 15 min warm-up, 5 min slow training, 25 min moderate-intensity aerobic exercise at 40–60% VO_{2max}, 10 min resistance exercise, and 5 min cool-down [40]. The intervention group performed aerobic exercise thrice a week. A maternal aerobic exercise certified instructor demonstrated and supervised the entire aerobic exercise program choreographed to music.

Before the beginning of the program, all patients underwent a midwife-led clinical review of BP, pulse, respiration rate, weight, and fetal heart sounds, an interview about their physical condition, and a review of the maternal and child health notebook. We consulted the nurse-midwife before each aerobic exercise session to confirm that abdominal measurements and fetal cardiac rates are within normal ranges. We measured BP at rest to confirm that the values were within an acceptable range (systolic BP<140 mmHg and diastolic BP <90 mmHg). The target heart rate (HR) calculation was performed using the Karvonen method as follows: 220 - age = maximal HR (maximal HR - resting HR) × exercise intensity 40%–60% + resting HR. If necessary, the midwife performed a similar check-up after the exercise program.

Participants were asked to rate the Maternitybics Association perceived exertion using a scale of 7–19 [40]. For the determination of VO_{2max}, participants were required to maintain an HR of 130–150 bpm while performing aerobic exercise at moderate intensity (perceived exertion score: 13–15). During the exercise, HR was measured using a Polar FT1 monitor (Polar Electro, Kempele, Finland). If a participant felt tired, she was instructed to stop exercising immediately. Control group participants received only standard pregnancy health assessments without exercise.

Demographic and Clinical Characteristics

Initial measurements were obtained for all participants at 20–27 GW. We obtained the following baseline information: age, height, body weight, BP, GW, iodine supplement intake, smoking before and during pregnancy, passive smoking, and exercise habits before pregnancy. We classified the body mass index (BMI) as BMI <25 or 25 ≥ BMI < 30 according to the definition of the World Health Organization (WHO). Patients' physical activity and psychological state at inclusion were also assessed. At the basement assessment, physical activity and the psychological state were assessed using the long Japanese version of the International Physical Activity Questionnaire (IPAQ) and the Japanese version of the General Health Questionnaire-28, respectively (GHQ-28) [41,42]. The WHO developed the IPAQ to compare physical activity levels internationally. The reliability and validity of the Japanese version of the IPAQ have been evaluated previously [41]. The GHQ-28 is a self-rated questionnaire to detect psychological well-being, and its use has been validated in women during pregnancy and the postpartum period [43].

Urinary 8-OHdG and Urinary 8-iso-$PGF_{2\alpha}$ Analysis

Total volume urine samples were collected from pregnant women at the baseline examination during the second trimester or after completion of a 10-week maternity aerobics program (2 h after the last session). Ten ml of urine samples were moved to an exclusive spitz, immediately stored at -100 °C, and analyzed for up to 3 months. Urinary 8-OHdG and urinary 8-iso-$PGF_{2\alpha}$ analysis was performed using enzyme-linked immunosorbent assay (ELISA) kits from Nikken Zail (Shizuoka, Japan). The analytical detection limits for urinary 8-OHdG and urinary 8-iso-$PGF_{2\alpha}$ were 0.125 ng/ml and 0.05 ng/ml, respectively. Creatinine (Cr) concentrations were determined in spot urine with a creatinine colorimetric assay kit, and urine samples were corrected for Cr levels.

Maximum Oxygen Uptake

Maximum oxygen uptake was measured using the maternal HR at the completion of slow training until prior to the resistance exercise. It correlated with the maximum HR and oxygen uptake (VO_{2max}); therefore, the target HR was determined using the Karvonen formula (target HR = {(220 - age) - HR at rest} × exercise intensity + HR at rest) [44]. The maximum HR was estimated by subtracting the participant's age from 220. Resting maternal HR before the start of the aerobic exercise program was used as resting HR. For exercise intensity, 60%, 50%, and 40% of VO_{2max} were entered to calculate the respective target HR. VO_{2max} was estimated by comparing the target HR and the maternal HR during moderate-intensity aerobic exercise.

Data Analysis

Continuous variables are presented as mean ± standard deviation (*SD*). Fisher's exact test and Mann-Whitney U test were used for discrete and continuous variables, respectively. We performed goodness of fit test (W test of Shapiro-Wilk) for the normality of urinary 8-OHdG and urinary 8-iso-$PGF_{2\alpha}$ distribution and found that both values were normally distributed. To compare differences in urinary 8-iso-$PGF_{2\alpha}$ and urinary 8-OHdG in the second and third trimester, we used paired *t*-test. Comparisons between the study and control groups in the second trimester and late pregnancy were performed using unpaired *t*-tests. We conducted a multivariable regression analysis with the urinary 8-OHdG or urinary 8-iso-$PGF_{2\alpha}$ as the dependent variables, belonging to the intervention or control group as the independent variable, and overweight, mental health status, passive smoking, iodine supplement intake, high-intensity physical activity, and previous exercise habits as covariates. Overweight, mental health status, passive smoking, iodine supplement intake, and previous exercise habits were selected since they had demonstrated an effect on oxidative stress in previous studies. High-intensity physical activity was selected because its levels differed between the groups ($p<0.01$). All results with $p<0.05$ were considered statistically significant. We performed data analyses using JMP for Windows version 13.0.

Results

Baseline Characteristics

Baseline characteristics are shown in Table 1. The intervention (n=45) and control (n=43) groups did not differ with respect to age, GW, BP, BMI, sleep, iodine intake, vitamin use, folic acid supplementation, exercise in the expectant mother, moderate-intensity physical activity or walking during work, moderate-level physical activity during domestic work, moderate-intensity physical activity or walking during recreation, exercise or outdoor activities, and means of transportation use, bicycles or walking for transportation. There was a significant difference between the intervention and control groups with regards to passive smoking (p=0.012), mental health status, exercise habits before pregnancy, and high-intensity physical activity (equivalent to carrying heavy baggage with disturbed breathing), during exercise and outdoor activities ($p<0.01$).

Variable		Intervention group (n=45)	Control group (n = 43)	p
Age, (years, mean ± SD)		(33.5 ± 3.8)	(32.4 ± 3.9)	0.227
Gestational weeks, (mean ± SD)		(23.3 ± 2.6)	(22.7 ± 2.3)	0.302
Blood pressure				
Systolic, (mmHg, mean ± SD)		(104.7 ± 25.3)	(101.9 ± 19.2)	0.203
Diastolic, (mmHg, mean ± SD)		(57.2 ± 15.7)	(53.6 ± 23.2)	0.429
Weight				
BMI before pregnancy ≥25<30, n (%)		0 (0%)	3 (7.0%)	0.112
BMI before pregnancy <25, n (%)		45 (100%)	40 (93.0%)	
Pregnancy weight gain (mean ± SD)		(4.8 ± 2.1)	(4.4 ± 2.2)	0.491
Sleep duration (h, mean ± SD)		(7.6 ± 1.1)	(7.6 ± 1.2)	0.940
Subjective insomnia				0.093
Blank response, n (%)		5 (11.1%)	0 (0.0%)	
No, n (%)		30 (66.7%)	30 (69.7%)	
Yes, n (%)		10 (22.2%)	13 (30.3%)	
Current smoking status				
First-hand smoker	No, n (%)	45 (100%)	43 (100%)	
	Yes, n (%)	0 (0%)	0 (0%)	
Passive smoker[b]	No, n (%)	41 (91.2%)	29 (67.4%)	0.012
	Yes, n (%)	4 (8.8%)	14 (32.4%)	
Supplements				
Iodine	No, n (%)	42 (93.4%)	43 (100.0%)	0.241
	Yes, n (%)	3 (6.6%)	0 (0.0%)	
Vitamin	Yes, n (%)	5 (11.1%)	4 (9.7%)	1.000
Folic acid	Yes, n (%)	22 (66.7%)	22 (51.2%)	1.000
Exercise				
Exercise habits before pregnancy[c]	No, n (%)	21 (46.7%)	36 (83.7%)	<0.01
	Yes, n (%)	24 (53.3%)	7 (6.3%)	
Exercise during pregnancy[a]	No, n (%)	38 (84.5%)	39 (90.8%)	0.058
	Yes, n (%)	7 (15.5%)	4 (9.2%)	

Note: [a]Exercise during pregnancy: [b]Exercise during pregnancy of outside the exercise class

Table 1: Demographic and clinical characteristics of the control and intervention groups.

Changes in Urinary 8-OHdG Levels with Exercise

There was no significant difference in the baseline urinary 8-OHdG levels between the groups (p=0.674) (Table 3). The mean value of urinary 8-OHdG ± SD in the intervention group at baseline and after 10 weeks was 8.3 ± 2.5 and 6.7 ± 2.2, respectively. The mean value of the urinary 8-OHdG level change from baseline to after 10 weeks ± SD was -1.5 ± 2.3, and the value was significantly lower at 10 weeks after the start than at baseline ($p<0.01$). The mean value ± *SD* of urinary 8-OHdG of the control group at baseline and after 10 weeks was 7.8 ± 2.6 and 8.0 ± 2.7, respectively. The mean value ± *SD* of the urinary 8-OHdG level change from baseline to after 10 weeks was 0.1 ± 3.5, and there was no significant difference between the baseline value and that of after 10 weeks (p=0.791) (Table 3).

The intervention and control groups had significant differences in urinary 8-OHdG level change (p<0.01), as determined by the Student's t-test. A multivariable regression analysis confirmed that the exercise program decreased urinary 8-OHdG levels (p<0.05); however, passive smoking increased urinary 8-OHdG levels (Table 2).

	8-OHdG (ng/mgCr)		8-iso-PGF2α (ng/mgCr)	
	t	*p*	*t*	*p*
Intervention or control group	-2.18	**0.032**	-2.71	**0.008**
Being overweight[1)]	-0.52	0.604	-1.26	0.211
Mental health status[2)]	-0.69	0.492	0.96	0.338
Passive smoker[3)]	2.06	**0.043**	0.28	0.781
Iodine supplements[4)]	1.02	0.310	1.18	0.243
Exercise habits before the pregnancy[5)]	-0.50	0.621	0.69	0.493
High-intensity physical activity[6)]	-1.23	0.223	-0.13	0.896

[1)]BMI before pregnancy: greater than 25 = 0, smaller than 25 = 1.
[2)]Without diagnosis = 0, with diagnosis of a psychological disorder = 1.
[3)]Passive smoker: no = 0, yes=1.
[4)]Iodine supplements: no = 0, yes=1.
[5)]Exercise habits before the pregnancy: no = 0, yes = 1.
[6)]Feel to have a custom to conduct high-intensity of physical activity: no = 0, yes = 1.

Table 2: Multivariable analysis for the changes of 8-OHdG and 8-iso-$PGF_{2α}$ levels between the groups.

Changes in Urinary 8-Iso-$PGF_{2α}$ Levels with Exercise

The baseline urinary 8-iso-$PGF_{2α}$ levels did not differ between the intervention and control groups (p=0.696) (Table 3). The mean ± *SD* value of the urinary 8-iso-$PGF_{2α}$ level at baseline and after 10 weeks was 3.7 ± 1.7 and 3.8 ± 1.8, respectively. The mean ± *SD* of the changes in urinary 8-iso-$PGF_{2α}$ between baseline and after 10 weeks was 0.2 ± 2.1, showing no significant difference between baseline and after 10 weeks (p=0.763). Meanwhile, in the control group, the mean ± *SD* value at baseline and after 10 weeks was 3.7 ± 1.4 and 5.3 ± 1.5, respectively. The mean change in the value of urinary 8-iso-$PGF_{2α}$ after 10 weeks from baseline ± SD was 1.5 ± 1.8, while the value was significantly higher after 10 weeks compared to the baseline levels (p<0.01) (Table 3).

8-OHdG (ng/mgCr)	***Intervention group***	***p***	***Control group***	***p***
Baseline	8.3 ± 2.5		7.8 ± 2.6	0.674
After 10 weeks	6.7 ± 2.2		8.0 ± 2.7	
Change from baseline to after 10 weeks	−1.5 ± 2.3	<0.01	0.1 ± 3.5	0.791
8-iso-$PGF_{2α}$ (ng/mgCr)	***Intervention group***	***p***	***Control group***	***p***
Baseline	3.7 ± 1.7		3.7 ± 1.4	0.696
After 10 weeks	3.8 ± 1.8		5.3 ± 1.5	
Change from baseline to after 10 weeks	0.2 ± 2.1	0.763	1.5 ± 1.8	<0.01

Table 3: Urine 8-OHdG and 8-iso-PGF2α level changes in the intervention and control groups.

The intervention and control groups differed significantly in the changes regarding urinary 8-iso-$PGF_{2α}$ levels (p<0.01) from baseline to after 10 weeks of aerobic exercise, as determined by the Student's t-test. We performed a multivariable regression analysis to account for the effect of any potential confounding factors. A multivariable regression analysis confirmed that the changes in urinary 8-iso-$PGF_{2\alpha}$ levels significantly differed between the groups ($p<0.01$), indicating that a moderate-intensity exercise program may alleviate oxidative stress markers (Table 2).

Maximum Oxygen Uptake of The Intervention Group

The mean target HR (± *SD*) required to attain 60%, 50%, and 40% VO_{2max} was 150.6 (± 6.1) beats per minute (bpm), 138.8 (± 5.7) bpm, and 132.7 (± 7.6) bpm, respectively. The mean HR of the test group (± *SD*) was 137.7 (± 9.8) bpm. Here, the intensity of the aerobic exercise performed corresponded to 40%–60% VO_{2max}.

Discussion

Increased oxidative stress has been associated with physical and psychiatric disorders during pregnancy. We implemented a three-times-weekly fitness program combining a moderate-intensity aerobic and resistance exercise regime starting in the second trimester and running continuously for 10 weeks to reduce oxidative stress in pregnant women. We measured the intervention effect by testing urinary 8-OHdG and urinary 8-iso-$PGF_{2\alpha}$ levels. 8-OHdG level comes from the nucleic acid oxidation. It is related with the increased risk with of some retrograde and cancer diseases [45]. Urinary 8-OHdG level is known to increase due to smoking, aging, or physical, chemical, or biological substances [46,47]. It is specific metabolites of a free radical and the cell membrane arachidonic acid by lipid peroxidation effects, and 8-iso-$PGF_{2\alpha}$ does not depend on the enzyme catalyst process [48]. As for the multiple investigations, the smokers are shown to have increased 8-iso-$PGF_{2\alpha}$ with urine as compared with nonsmokers [49,50]. The subjects employed in this study have no smokers, so we conducted statistical analysis for BMI, passive smoking, BP, sleep, and exercise habit.

A moderate-intensity aerobic program performed continuously for 10 weeks starting in the second trimester decreased urinary 8-OHdG levels and prevented urinary 8-iso-$PGF_{2\alpha}$ level increase at the end of the program compared to baseline.

Minimum exercise intensity of 40% VO_{2max} is necessary to improve physical function [51]. Less than 40% VO_{2max} cannot expect the effect for the making of health [52]. Reactive oxygen species do not increase with exercise intensities of less than 70% VO_{2max} [53]. According to ACSM, the smallest exercise intensity necessary for improvement of health, the physical strength is done more than 40 with a range less than 70% VO_{2max} [54]. Performing a moderate-intensity exercise program including 30 sessions improves maximum oxygen uptake, thereby improving aerobic fitness [55]. Therefore, we attribute the oxidative stress decrease, measured by changes in urinary 8-OHdG and urinary 8-iso-$PGF_{2\alpha}$, to the 30-session moderate-intensity aerobic exercise program at 40%–60% VO_{2max}. Here, the exercise program consisted of moderate-intensity aerobic exercise combined with resistance exercise. Resistance exercise promotes muscle protein anabolism regardless of age [56]. The significant muscle protein synthesis increase by acute resistance exercise is maintained for at least 48 h [57]. Resistance exercises prevent muscle weakness, and programs that combine resistance exercise with moderate-intensity aerobic exercise three times a week can be safely continued throughout pregnancy. Many pregnant women tend to decrease the exercise time and intensity before pregnancy [58,59]. The results were not affected by being overweight, mental health status, iodine supplement intake, and high-intensity physical activity. However, 8-OHdG levels were increased by passive smoking, which is consistent with previous findings [60]. It is noted that after 10 weeks, 8-OHdG decreased in the intervention group whereas it unchanged in the control group. This trend was not seen for 8-iso-$PGF_{2\alpha}$ which unchanged in the intervention group whereas increasing in the control group. This difference may have been associated with the difference of these markers in biological implications; 8-OHdG is a marker for DNA oxidation, 8-iso-$PGF_{2\alpha}$ is a marker for lipid oxidation. For the late pregnancy, a maternal energy source varies from glucose to lipids. As a result, free fatty acids in blood and phosphorus lipid concentrations increase [61]. We surmise that the observed feature of 8-iso-$PGF_{2\alpha}$ may suggest the possibility that, for the third trimester, an oxidation power derived from lipids is enhanced.

The optimal type and intensity of exercise during the second and third trimesters of pregnancy are still being investigated [62]. As for our study, 30 moderate aerobic and resistance exercise sessions with an intensity of 40–60% VO_{2max} alleviated the increase of 8-OHdG and 8-iso-$PGF_{2\alpha}$ associated with GDM, HDP, and depression.

There are several limitations to this study. First, even though we controlled for several factors, including obesity [63], mental health [64], passive smoking [65], iodine deficiency [66], and exercise habits [67], other factors may also affect oxidative stress and should be investigated. Second, even though we measured stress markers at two points, we did not assess long-term outcomes. Third, at the end of the program in the test group, oxidative stress was measured only 2 h after exercise. Future studies should measure the markers at multiple time points after the last exercise session. Fourth, the potential physiological significance of the findings on oxidative stress should be investigated, and the involved molecular pathways should be elucidated. Finally, participants were recruited from two medical centers in one city in Japan, and all were primiparous with singleton pregnancies. Future studies should incorporate multigravida to further our understanding of the effects of exercise on different pregnancy types.

The combined aerobic and resistance exercise program of this study was comprised of: warming-up of 15 minutes, slow training of 5 minutes, resistance exercise of 10 minutes, aerobic exercise of 25 minutes, cooling down of 5 minutes. The warm-up was intended to raise the temperature of the muscle and articular flexibility, enlarging the movable range. The slow training was a resistance exercise to increase the muscular strength. Cooling down was an exercise intended to normalize maternal heart rate. The following five elements are considered necessary for health: cardiorespiratory function, body system, flexibility, muscular strength, muscular endurance [68]. This combined aerobic and resistance exercise program is considered to enhance these five elements.

In summary, combined aerobic and resistance exercise, reaching 40–60% VO_{2max}, three times a week for 10 weeks starting from the second trimester of pregnancy decreases DNA-derived urinary 8-OHdG and suppresses the lipid-derived urinary 8-iso-$PGF_{2\alpha}$ level increase in the third trimester, raising the possibility that it may reduce oxidative stress. Our findings may be useful for nurses and midwives who work with pregnant women and counsel them on lifestyle modifications. However, the results should be confirmed in further investigations.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' contributions

CM and KA designed the study. CM and KA collected the data. CM and KA analyzed the data. CM and KA prepared the manuscript. All authors approved the final version for submission. All authors meet the authorship criteria and are in agreement with the content of the manuscript.

Ethics and consent

This study was approved by the Institutional Review Board of Tokyo Metropolitan University, Arakawa campus (reference number: 15066, 08 December 2015) and Teikyo University Ethics Committee (reference number: TUIC-COI16-0476, 17 August 2016). Written informed consent was obtained from all participants.

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***Corresponding author:** Chikako Mochizuki, MD, Graduate Midwifery Course, Teikyo University, 2-11-1 Kaga, Itabashi, Tokyo 173-8605, Japan, Tel: +81-3-3964-1211(41611); Email: mchikako@med.teikyo-u.ac.jp

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