The Effects of Exercise and Race on Placental C-Reactive Protein and Maternal Metabolism

by

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**Abstract**

**Background-** Cardiovascular disease (CVD) is the leading cause of death in women. C-reactive protein (CRP) is an inflammatory metabolite that is indicative of CVD. Pregnant women tend to have higher levels of CRP. Additionally, levels of CRP are reported to be higher in BIPOC (Black, Indigenous, and People of Color) individuals; however, this has not been assessed during pregnancy. Although inflammation is associated with high lipids, glucose, lactate, and excess body fat, little research has investigated the interaction between CRP and lipids, glucose, lactate, and body composition during pregnancy. Conversely, exercise has been shown to lower CRP, lipids, glucose, and body composition in nongravid individuals. To date, the effects of exercise on CRP levels in placental tissue has not been investigated. However, the influence of exercise during pregnancy on CRP, lipids, glucose, lactate, and maternal body composition is unknown.

**Purpose-** The purpose of this study is to explore the effects of exercise on placental CRP, blood lipids, glucose, lactate, and body composition with the intent to answer the question whether exercise lowers placental CRP and other maternal metabolic measures. Additionally, this study will determine the difference of placental CRP and other maternal metabolic measures between Caucasian women as well as women who identify as BIPOC (Black, Indigenous, and People of Color) community.

**Methods-** Pregnant women were enrolled between 13-16 weeks' gestation. Subjects (n=19) completed body composition measurements and venipuncture at enrollment and 36 weeks' gestation. Participants were randomized to one of four groups: Aerobic, Resistance, Combination (aerobic + resistance), Stretching. After randomization, women were exercised three times a week from enrollment to delivery. Once participants delivered, placental samples were collected and stored in -80° C. Samples were then homogenized, and analysis was completed via the Millipore tissue sample protocol. ANOVA was completed for assessments between exercise groups and t-tests for assessments between BIPOC and Caucasian women.

**Results-** There are no differences between exercise and placental CRP between exercise groups. However, when comparing the difference between racial groups, CRP levels trended towards significance (p=0.14).

**Conclusion-** These data suggest that exercise does not increase placental inflammatory or maternal metabolic markers, regardless of race. Further investigation with larger sample sizes is required.

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AND MATERNAL METABOLISM

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# Chapter 1: Introduction

The leading cause of death in women is cardiovascular disease (CVD) (35). Pregnancy is considered a physiological stressor that provides a window of assessment into a woman's potential future cardiovascular health (35). Many inflammatory markers indicative of CVD, such as C-Reactive Protein (CRP), are measurable during pregnancy, and in the placenta. High levels of inflammatory markers could be associated with adverse pregnancy outcomes (i.e.: diabetes, preterm birth, low birth weight). CRP predicts offspring adiposity and head circumference along with birth weight and birth length (30). As a transient cardiovascular and endocrine organ, the placenta also makes CRP during pregnancy in response to an adverse maternal environment (i.e., obesity, diabetes, overnutrition, etc.). Maternal lipid metabolism can be linked to systemic inflammation (34).

Although a combination (aerobic with resistance) exercise regimen is associated with decreased inflammatory markers, such as CRP, in non-gravid adults, there have been inconsistent findings on the effects of exercise on CRP in gravid and non-gravid adults in terms of resistance only and aerobic only exercise regimens (24). In non-gravid adults, significant improvements in CRP were observed in the exercise group compared to non-exercisers when completing a personalized 3-month exercise program that included aerobic exercise such as walking, cycling, or swimming, depending on the preference of the subject as well as a strength training portion that included exercise for large muscles groups, time for individual exercises was not included (2). In a review completed by Michigan et al, literature showed significant findings with aerobic exercise. Studies showed CRP reduction with a regimen on kickboxing and dance sessions three times a week in children (24). Another study found saw a 30% reduction in CRP in children who complete mainly brisk walking with total body movement, the first week physical activity was limited to 20 minute and progressively increased, by the third week participants were completing 45 minutes of exercise with a 5-minute warm and cool down (4). A study with participants who were non-gravid obese women, there was a reduction in CRP levels, women were encouraged to walk, swim, or play aerobic ball games, though time was not mentioned (11). In 60 overweight non-gravid adults, a 6-month aerobic exercise program, completing workouts four times a week for 45-60 minutes a session yielded improved glucose control, lipid profile, exercise capacity as well as a reduction in high sensitivity CRP (21). In one study, completed by Hinman et al. found that an exercise regimen including aerobic, muscle strengthening, and endurance exercise appeared to have beneficial effects on reducing glucose level in the gravid population (20). During pregnancy, placental function is critical for successful fetal development (14). Gestational age has been known to effect placental function. In a study completed by Bowe et al. post-date placental growth factor was lower in the group of women labeled complicated pregnancy (7). In relation to physical activity, beginning exercise during the first trimester could increase placental function significantly (22). The effect of different types of exercise on maternal metabolic markers is unknown. Further, there has been no research assessing the effects of exercise on placental CRP levels.

African Americans have higher levels of inflammation and less engagement in physical activity when compared to European Americans (1). A study completed by Kretzschmar et al. found that aerobic exercise alone may not be enough to decrease CVD risk of non-gravid African Americans with high inflammation (23). In nongravid African American women, obesity was a key factor contributing to the association between race and elevated CRP (13). To date, the influence of race on maternal metabolic markers is unknown. Further, there has been no research assessing the effects of race on placental CRP levels.

Therefore, the purpose of this study is to determine the effects of exercise types during pregnancy on placental CRP and maternal metabolism. Based on current research, I hypothesize that any type of exercise will decrease placenta CRP and maternal metabolic measures (i.e., lipids, body composition, glucose, lactate) relative to non-exercise controls. A secondary purpose of this study is to determine the effects of race on placental CRP and maternal metabolism. Based on current research, I hypothesize that BIPOC women will have increased placenta CRP and maternal metabolic measures (i.e., lipids, body composition, glucose, lactate) relative to Caucasian women. The women in the study are restricted to healthy pregnant women who meet inclusion criteria. One major limitation to this study is the requirement of placenta collection after delivery, the time frame of placental retrieval from the hospital and processing of the sample, which could lead to intrasample variation. Attempts were made to minimize these limitations in methods. The outcomes of this study could help to determine which type of exercise is most beneficial for decreasing inflammatory markers that influence current and future maternal heart health outcomes.

# Chapter 2: Literature Review

## Introduction

### Description of the Placenta

*What is it and what does it do?*

The placenta is a specialized organ that aides in the development and growth of the fetus during pregnancy. The placenta provides oxygen, water, vitamins, minerals, and other nutrients to the fetus during growth and development (17). The placenta serves as a selective tissue barrier between mother and child. The placenta also provides protection for the fetus from the maternal immune system, infections, and maternal diseases. It also releases hormones into both maternal and fetal circulation (17). The placenta takes nutrients and oxygen from the maternal circulation and optimizes them to provide for appropriate fetal growth and development (14). Placental function is critical for successful fetal growth and development (14); however, there are factors that can help or hinder the proper functioning of the placenta. For example, a long gestation, beyond the estimated due date of 40 weeks, is known to adversely affect placental function. In a study completed by Bowe et al. post-date placental growth factor was lower in the group of women labeled complicated pregnancy (7). In relation to physical activity, beginning exercise during the first trimester is associated with placental function significantly (22). Furthermore, Clapp et al. found increased placental weight associated with aerobic exercise (9). Adherence to physical activity and gestational weight gain recommendations during pregnancy has been shown to improve maternal and fetal health outcomes. Prenatal physical activity does not compromise placental efficiency, though further research is required to investigate the benefits of meeting physical activity and gestational weight guidelines on the placenta (12).

*Why should we study it?*

As a transient cardiovascular and endocrine organ of pregnancy, the placenta mediates changes from the maternal environment to the fetus as it attempts to optimize fetal growth and development (8). Furthermore, current research demonstrates the placenta as an extension of the maternal cardiovascular system can act as a “window” into future maternal risk of cardiovascular disease. Thus, the placenta is a mediator of fetal health outcomes and a window of future maternal health; yet this organ is typically incinerated shortly after delivery. The placenta holds many answers as to adaptations for the fetus and maternal health; therefore, studying the placenta will enable researchers to understand adaptations to different maternal environments (i.e., race, exercise) as well as maternal cardiovascular health. Many of the diseases that arise during pregnancy are caused by, can be seen in, or impact the placenta (16).

Therefore, by investigating how the pathways, such as the inflammatory biomarkers, within the placenta are perturbed can provide answers to how the placental responds to different maternal environments; this ultimately can be applied to pregnancy conditions. The changes related to the development of the placenta during that stress of pregnancy is unknown.

<u>Inflammation and Exercise</u>

*What happens to CRP during exercise?*

CRP is one of the many inflammation markers in the body (19). Exercise lowers C-Reactive Protein (CRP) in general populations. In the general population, individuals who exercise have lower CRP compared to inactive individuals (19). Aerobic, Resistance, Combination (aerobic + resistance) have been research in gravid and non-gravid populations. Moderate intensity as well as vigorous intensity exercise prior to becoming pregnant reduces maternal CRP levels (34). In the study completed by Wang et al., 14 recreational activities were assigned a MET score to determine intensity, low intensity included activities such as walking, while moderate activities included a brisk walk, bicycling, fitness training, gymnastics, dance, and swimming, vigorous activities included skiing, running, aerobics with running (34). In a study completed by Borders et al. reported non-Hispanic black pregnant women had significantly higher CRP levels in the second and third trimesters relative to Caucasian women (6). In non-gravid obese women, there was a reduction in CRP levels, women were encouraged to walk, swim, or play aerobic ball games, though time was not mentioned (11). CRP decreased in pregnancy women who completed an individually tailored exercise program from pre- to post- intervention. Women completed a 12-week individually tailored exercise intervention or a comparison health and wellness intervention. In the exercise group, women were asked to complete at least 30 minutes of moderate intensity exercise most days of the week and the women picked activities such as dancing, walking, and yard work. (18). In non-gravid populations, leisure-time physical activity has been linked with lower levels of CRP, while sedentary behavior is associated with elevated CRP (19). In a study comparing inactive obese pregnant women with physically active obese pregnant women, CRP was lower in those women that participated in light and lifestyle to moderate. Women were asked to complete two visits, after the first visit, participants were given a nonremovable accelerometer that they wore the week after (33). In 60 overweight non-gravid adults, a 6-month aerobic exercise program, completing workouts four times a week for 45-60 minutes a session yielded improved glucose control, lipid profile, exercise capacity as well as a reduction in high sensitivity CRP (21).

*Inflammation and pregnancy*

Chronic inflammation, as seen in obesity, is physiologically stressful on organs and cells; chronic inflammation can lead to cardiovascular diseases, some cancers, and adverse pregnancy outcomes (i.e., low birth weight, pre-term birth, etc.). When disease is present on the maternal side of the placenta, such as diabetes, obesity, or hypertension, this alteration in maternal environment can affect fetal development. Typically, CRP is higher in pregnant women compared to the non-gravid population (19). CRP during pregnancy is linked with low grade systemic inflammation

(15). However, high levels of CRP can cause lasting effects for offspring, even after birth. For example, when levels of CRP are high during pregnancy, there is an increased chance offspring will have higher adiposity later in life (15). As maternal obesity is more common and associated with high levels of inflammation, which then lead to adverse pregnancy outcomes, it is imperative to understand the inflammatory process during pregnancy. Having a higher level of CRP and inflammation can lead to higher metabolic levels, such as lipids, like LDL, Ridker states "at all levels of metabolic syndrome, CRP provides additive information on vascular risk" (31). Maternal physical activity may reduce inflammation during pregnancy (33). Although exercise during pregnancy has been shown to decrease offspring adiposity after birth (34), the influence of prenatal exercise in inflammatory markers is still unknown.

Exercise During Pregnancy

*Why should this be done?*

Exercise is known to improve the quality of life in all stages of life, including pregnancy; exercise also has positive effects on both maternal and fetal health (3). Exercise during pregnancy is associated with fewer cesarean births decreased excessive gestational weight gain, as well as improved gestational diabetes management (20). Barakat et al. demonstrated that exercise through pregnancy can reduce the risk of excessive weight gain and lower the likelihood of developing gestational diabetes. Women in the exercise intervention group completed moderate exercise three days per week, 55-60 minutes per session. Sessions included a warmup, aerobic exercise, light muscle strengthening, coordination, stretching, pelvic floor strengthening, and relaxation (5). Kretzschmar et al. found lowered body mass index in the low inflammation group, plasma triglycerides, and lower glucose in the high inflammation group in African American women. These results come after completing an aerobic exercise at 50-65% of their $VO_2$max for 20-40 minutes (23). Thus, pregnant women should be encouraged to exercise throughout pregnancy (20).

There have been many studies that demonstrate that exercise has a positive impact on pregnancy and placental components, such as placenta size and weight. In a systematic review, four articles were included, demonstrating that exercise affects placental weight with a 95% confidence interval (4.66g-74.80g), as well as placental volume with a 95% confidence interval (37.99-56.23) (22).

It is important for pregnant women with any health concerns to be evaluated by a healthcare provider before beginning of continuing physical activity; the healthcare provider should assess whether there are any contraindications to exercising while pregnant.

### Multiplex Kits

Molas et al. utilized the multiplex software to identify the involvement of annexin A1 in human placental response to maternal Zika virus. This study utilized a lysis buffer and a cocktail of protease inhibitors before homogenizing. Protein concertation was then measured using a BCA protein assay (25). Sureshchandra et al. used the human cytokine/chemokine/growth factor pre-mixed kit as well as the human adipokine kit to measure immune mediators in plasma and supernatants. They used the high sensitivity ELISA to measure CRP and IL-6 (32).

## Conclusion

The placenta plays a vital role in pregnancy and is the mediator between mother and fetus. Not only is exercise safe for mother and fetus, but it is also encouraged to decrease the risk of gestational diabetes, and other adverse pregnancy outcomes. CRP as a marker of systemic inflammation is higher in pregnancy, however, other factors that influence this marker have not been evaluated. For example, this literature review includes articles that discussed exercise and pregnancy. There have been many studies that demonstrate that exercise has a positive impact on pregnancy and placental components, such as placenta size and weight (22).

# Chapter 3: Methods

## Participants

This study recruited healthy pregnant women ages 18-40 years of age between 13-16 weeks' gestation. Women were included in the study if they had a BMI of 18.5-39.99, singleton pregnancy, received clearance by their obstetric provider, had no contradictions to exercise, and were free from chronic illness. All protocols were approved by the East Carolina University Institutional Review Board. All participants signed an informed consent. Once the informed consent was signed, participants were scheduled for baseline measures: treadmill test, 1-repitition max strength test. Participants heart rate was measured before the submaximal test as resting to obtain a baseline.

## Design

At study consent, participants were given questionnaires to obtain information regarding maternal age, height, gravida, parity, and race/ethnicity. After study consent, participants completed a submaximal treadmill test to determine aerobic capacity and calculate specific target heart rate (THR) ranges for moderate-intensity exercise training. Peak oxygen consumption ($VO_2$ peak), also referred to as fitness level, was estimated via the modified Balke protocol previously validated by Mottola et al (27). Participants then completed a one-repetition maximum strength test for major muscle groups. Pre-pregnancy body mass index (BMI) was calculated by taking the weight of the participant in kg and dividing by the height in meters squares. After completing these tests, participants were randomized via computerized sequencing (GraphPad software) to aerobic, resistance, combination (aerobic and resistance), or a non-exercising, stretching/breathing comparison group.

## Exercise Intervention during Pregnancy

All participants were supervised by trained exercise instructors in two university facilities following a standard protocol. All sessions started around 13 to 16 weeks' gestation and were performed three times weekly until delivery (~40 weeks). All participants' sessions began with a 5-minute warm-up, 50 minutes of their randomized group activity, and ended with a 5-minute cool-down. The aerobic training group completed moderate intensity (40–59% $VO_2$peak) training on treadmills, ellipticals, recumbent bicycles, rowing and/or stair-stepping equipment. To maintain the appropriate HR zone, speed and grade were adjusted on the treadmill, and resistance and speed levels were adjusted on the elliptical and recumbent bike. The resistance training group completed sessions consisting of two to three sets of 12 to 15 repetitions of each exercise at a moderate intensity. Seated machines (Cybex) (leg extension, leg curl, shoulder press, chest press, triceps extension, latissimus dorsi pull down), dumbbells (biceps curls, lateral shoulder raises, front shoulder raises), resistance bands/dumbbells, exercise balls, benches, and/or mats were used. The combination training group performed half of the aerobic protocol and half of the resistance protocol exercises for 25 minutes each. For the combination group, resistance exercises were performed at 12 to 15 repetitions (same exercises and equipment as resistance training group). For the combination group, the aerobic exercises were performed on the same equipment as the aerobic group. Moderate intensity was monitored the same way as the aerobic group. The control group performed stretching, breathing, and flexibility exercises for the duration of the 50-minute session. Stretches targeted major muscle groups, breathing exercises combined stretching and breathing, and the flexibility exercises consisted of stretches with controlled breathing. Low intensity was confirmed during sessions using HR monitoring (<40% $VO_2$peak). To ensure that the proper intensity was achieved during sessions, the Borg scale rating of perceived exertion (RPE), and the "talk test" were used. HR monitoring (Polar FS2C) ensured appropriate target HR ranges were maintained; target HR zones validated for pregnant women were utilized.

## Maternal Measures

At enrollment and 36 weeks' gestation, the women completed body composition measurements to measure waist circumference and body fat percent, and a lipid panel was also completed to obtain HDL, LDL, triglycerides, total cholesterol, glucose, and lactate.

Body composition was measured using skinfolds to determine maternal percent body fat. Body fat percentage was determined using skin at three sites. Skin folds record skin thickness and was then entered into a standardized equation that accounts for age. Waist circumference was measured using a measuring tape.

Blood draws were collected in the morning, so participants were fasted. Study staff obtained a venipuncture as well as a finger stick. The venipuncture was separated red blood cells and plasma and stored in a -20° C freezer. The finger stick provided lactate and was run through a clostech machine to provide triglycerides, total cholesterol, glucose, HDL, and LDL.

Change scores will be calculated for all maternal data. These will be calculated by subtracting 16 wk values from the 36 week values. These will be represented as the value name and the term "change," such as Triglyceride Change.

## Sample collection

Placental samples were collected less than 24 hours after delivery. The placenta was processed by removing the chorionic, villous, and basal layer of the placenta at the central location and peripheral location in relation to the cord, yielding a total of six samples. Placental samples were then placed in a microcentrifuge tube. The samples were flash frozen in liquid nitrogen and stored in a -80° C freezer until the next step.

## Sample preparation

Placental samples were stored in -80° C freezer until needed, then thawed on ice prior to preparation. After thawing, a 200 mg sample constructed equally of 33-34 mg samples from the six locations was homogenized mechanically using ultrasonication in a buffer solution, the extraction medium did not contain any organic solvents. The tissue was centrifuged; the tissue pellet was then frozen below –20° C. The placental sample was tested against the standard curve and the quality controls.

**Multiplex Kits**

Placental tissue was then placed in a tube containing lysis buffer and a protease inhibitor cocktail. The sample was homogenized on ice using an electric homogenizer. After homogenization, samples were placed using the CVD kit and the map provided. Samples were prepared following the manufacturer's instructions and added to the well plate with the magnetic beads. Analysis was completed by Luminex software according to the protocol set forth by Millipore.

**Statistical analysis**

An Analysis of Variance (ANOVA) will be used to detect differences in descriptors among the four groups at baseline; variables that will be evaluated are age of participants at enrollment, gestation in weeks at time of delivery, pre-pregnancy body mass index (BMI), resting heart rate at time enrollment, $VO_2$ peak. Other measurements included those which were obtained during body composition at enrollment and 36 weeks, 16-week body fat, 36-week body fat, body fat change, 16-week circumference, 36-week circumference, 16-week HDL, 16-week LDL, 16-week triglycerides, 36-week triglycerides, triglyceride change, 36-week lactate, 16-week total cholesterol, 36-week cholesterol, cholesterol change, 16-week glucose, 36-week glucose, glucose change. ANOVA analysis was completed comparing CRP levels between the four groups.

Nonparametric analysis was conducted on variables that lacked normal distribution, such as gravida, parity, waist circumference change, 36-week HDL, HDL change, 36-week LDL, LDL change, 16-week lactate, and lactate change. An independent t-test was completed to compare the difference in maternal descriptors and measures, as well as placental measures between Caucasian and BIPOC women. Independent t-test was completed to identify difference in CRP between Caucasian and BIPOC women. Lastly, regression analysis was performed to determine if there were predictors of placental CRP levels.

## CHAPTER 4: RESULTS

### Descriptive Statistics

Our final analysis included 19 participants who were enrolled and then randomized into one of the four groups (control=5, combination=5, aerobic=5, or resistance=4). On average, pregnant women in the current study were 25.20 (SD=2.59) years old, overweight (BMI 25.36 ± 3.61;) with one prior pregnancy. Participants were similar in age, gestational week, gravida, parity, pre-pregnancy BMI, resting HR, and fitness level between groups (Table 1).

**Table 1: Maternal Descriptors by Exercise Group**

| | Control | Aerobic | Combo | Resistance | p-value |
|---|---|---|---|---|---|
| Maternal Age (yrs) | 25.20 ± 2.59 | 28.80 ± 5.22 | 29.20 ± 3.35 | 31.00 ± 3.27 | 0.17 |
| Gestation (weeks) | 39.66 ± 0.61 | 39.54 ± 0.99 | 39.74 ± 0.65 | 40.13 ± 1.06 | 0.76 |
| PrePregnancy BMI (kg/m$^2$) | 25.36 ± 3.61 | 25.93 ± 9.28 | 25.70 ± 2.05 | 24.08 ± 1.71 | 0.96 |
| Gravida * | 1 (1, 2) | 1 (1, 2) | 2 (1, 3) | 1 (1, 3) | 0.60 |
| Parity * | 1 (1, 2) | 1 (1, 2) | 1 (1, 2) | 1 (1, 3) | 0.89 |
| Resting HR (bpm) | 86.00 ± 11.55 | 82.00 ± 6.78 | 80.50 ± 2.89 | 80.67 ± 16.92 | 0.78 |
| $VO_2$ peak (mL/kg/min) | 22.84 ± 2.33 | 25.78 ± 2.84 | 23.85 ± 9.85 | 25.33 ± 5.16 | 0.89 |

*Due to no normal distribution values were run with Kruskal-Wallis.
BMI: body mass index, HR: Heart Rate, $VO_2$ peak: fitness level.

### Maternal Measures between Exercise groups

Results from ANOVA for maternal body composition, lipid levels, glucose, and lactate between exercise groups (Table 2). There are significant differences demonstrated in maternal body fat change between groups (Table 2).

**Table 2: Maternal Measures by Exercise Group**

| | Control | Aerobic | Combo | Resistance | p-value |
|---|---|---|---|---|---|
| 16 wk BF% | 35.47 ± 5.02 | 32.43 ± 5.32 | 33.50 ± 3.39 | 32.39 ± 0.98 | 0.73 |
| 36 wk BF% | 32.92 ± 1.48 | 33.23 ± 4.42 | 36.90 ± 2.00 | 33.81 ± 0.63 | 0.19 |
| BF% Change | -2.55 ± 3.54 | 0.80 ± 1.66 | 3.40 ± 2.36 | 1.85 ± 0.69 | 0.02 |
| 16 wk WC (cm) | 32.33 ± 3.21 | 32.61 ± 7.32 | 33.50 ± 2.72 | 32.00 ± 2.65 | 0.97 |

| | | | | | |
|---|---|---|---|---|---|
| 36 wk WC (cm) | 40.58 ± 4.22 | 33.25 ± 2.82 | 36.038 ± 3.01 | 35.64 ± 4.62 | 0.10 |
| WC Change * (cm) | 6 (3.5, 15.23) | 2.15 (-7.4, 4) | 2.95 (-0.08, 4.31) | 3.12 (0.69, 4) | 0.19 |
| 16 wk HDL (mg/dL) | 73.33 ± 10.21 | 48.00 ± 26.11 | 66.80 ± 7.76 | 65.25 ± 15.76 | 0.22 |
| 36 wk HDL* (mg/dL) | 64 (60, 70) | 55 (33, 87) | 76 (50, 226) | 57 (55, 72) | 0.68 |
| HDL Change * (mg/dL) | -9 (-15, -2) | 10 (-7, 52) | 19 (-19, 148) | -7 (-11, 14) | 0.28 |
| 16 wk LDL (mg/dL) | 122.33 ± 7.37 | 102.40 ± 33.62 | 83.00 ± 45.79 | 97.50 ± 28.21 | 0.50 |
| 36 wk LDL *(mg/dL) | 124 (103, 183) | 115 (72, 191) | 111 (108, 177) | 92 (46, 300) | 0.89 |
| LDL Change *(mg/dL) | 10 (-25, 58) | 21 (-26, 49) | 36.5 (16, 57) | 10 (-20, 184) | 0.76 |
| 16 wk TG (mg/dL) | 113.75 ± 15.95 | 80.00 ± 20.43 | 154.20 ± 103.85 | 111.00 ± 29.94 | 0.30 |
| 36 wk TG (mg/dL) | 209.33 ± 22.12 | 143.60 ± 41.76 | 276.40 ± 134.21 | 204.67 ± 65.58 | 0.17 |
| TG Change (mg/dL) | 100.67 ± 12.34 | 63.60 ± 30.32 | 122.20 ± 42.03 | 90.67 ± 42.19 | 0.12 |
| 16 wk Lactate * (mmol/L) | 1.2 (0.9, 5.6) | 0.8 (0.7, 1.8) | 1 (0.5, 2.6) | 1.15 (0.9, 3) | 0.57 |
| 36 wk Lactate (mmol/L) | 1.63 ± 0.70 | 1.08 ± 0.42 | 1.34 ± 0.25 | 1.00 ± 0.30 | 0.26 |
| Lactate Change * (mmol/L) | 1.7 (0.9, 2.3) | 0.9 (0.8, 1.8) | 1.2 (1.1, 1.7) | 1 (0.7, 1.3) | 0.44 |
| 16 wk TC (mg/dL) | 216.25 ± 11.33 | 166.60 ± 30.83 | 181.00 ± 44.03 | 184.75 ± 41.06 | 0.24 |
| 36 wk TC (mg/dL) | 243.00 ± 38.30 | 211.40 ± 43.02 | 233.40 ± 42.48 | 248.33 ± 146.12 | 0.88 |
| TC Change (mg/dL) | 26.00 ± 46.57 | 44.80 ± 29.03 | 52.40 ± 48.15 | 75.00 ± 108.76 | 0.78 |
| 16 wk Glucose (mg/dL) | 79.25 ± 2.63 | 74.60 ± 6.62 | 81.20 ± 4.32 | 74.00 ± 3.56 | 0.09 |
| 36 wk Glucose (mg/dL) | 84.33 ± 20.50 | 76.80 ± 4.32 | 81.20 ± 8.23 | 78.67 ± 2.52 | 0.76 |
| Glucose Change (mg/dL) | 4.33 ± 19.86 | 2.20 ± 9.18 | 0.00 ± 6.48 | 4.67 ± 6.43 | 0.92 |

*Due to no normal distribution values were run with Kruskal-Wallis.
BF%: body fat percent, WC: waist circumference, HDL: high density lipoprotein, LDL: low density lipoprotein, TG: triglyceride, TC: total cholesterol.

To answer the question of inflammatory marker placenta CRP levels between exercise groups, we completed ANOVA analyses of absolute CRP and relative to placental tissue level. Thus, Absolute, and relative levels of CRP in placental tissue were similar between groups (Table 3).

**Table 3: Placental Measures by Exercise Group**

| | Control | Aerobic | Combo | Resistance | p-value |
|---|---|---|---|---|---|
| Absolute CRP (ng/mL) | 105.40 ± 6.54 | 106.79 ± 18.34 | 96.75 ± 24.88 | 110.9900 ± 10.35 | 0.64 |

| | | | | | |
|---|---|---|---|---|---|
| Relative CRP (pg/mg) | 61193.13 ± 5794.22 | 89992.34 ± 29556.93 | 6633.75 ± 41256.03 | 92724.79 ± 20580.38 | 0.34 |

**Maternal Measures between Racial/Ethnic groups**

From our final analysis, we also evaluated the potential influence of race/ethnicity on outcomes. We included 19 participants who were either classified as Caucasian (n=14) or a BIPOC (n=5). Participants were similar in age, gestational week, gravida, parity, pre-pregnancy BMI, resting HR, and fitness level between groups (Table 4).

**Table 4: Maternal Descriptors between racial/ethnic groups**

| | Caucasian | BIPOC | p-value |
|---|---|---|---|
| Maternal Age (yrs) | 29.07 ± 4.14 | 26.60 ± 3.51 | 0.57 |
| Gestation (weeks) | 39.79 ± 0.88 | 39.64 ± 0.51 | 0.12 |
| Pre-Pregnancy BMI ($kg/m^2$) | 25.30 ± 5.41 | 25.41 ± 3.56 | 0.68 |
| Gravida * | 1 (1,3) | 1 (1, 2) | 0.53 |
| Parity * | 1 (1,3) | 1 (1, 2) | 0.33 |
| Resting HR (bpm) | 83.82 ± 9.80 | 85.50 ± 9.68 | 0.98 |
| $VO_2$ peak (mL/kg/min) | 26.03 ± 5.14 | 19.88 ± 3.21 | 0.48 |

*Due to no normal distribution values were run with Kruskal-Wallis.
BMI: body mass index, HR: Heart Rate, $VO_2$ peak: fitness level.

When comparing maternal body composition, lipid levels, glucose, and lactate between racial-ethnics group, we find similar values for most measures (Table 5). However, BIPOC pregnant women have greater increases in glucose across pregnancy (Table 5)

**Table 5: Maternal Measures between racial groups**

| | Caucasian | BIPOC | p-value |
|---|---|---|---|
| 16 wk BF% | 32.89 ± 4.09 | 35.05 ± 1.58 | 0.20 |
| 36 wk BF% | 34.14 ± 3.02 | 36.42 ± 4.21 | 0.61 |
| BF% Change | 1.25 ± 2.71 | 0.67 ± 5.64 | 0.15 |
| 16 wk WC (mg/dL) | 32.07 ± 4.44 | 35.50 ± 1.81 | 0.46 |
| 36 wk WC (mg/dL) | 35.30 ± 4.12 | 38.85 ± 2.85 | 0.54 |
| WC Change * (mg/dL) | 2.28 (-7.4, 15.23) | 3.5 (2.23, 4.31) | 0.73 |
| 16 wk HDL (mg/dL) | 60.64 ± 20.11 | 68.67 ± 3.79 | 0.06 |
| 36 wk HDL * (mg/dL) | 59 (33, 226) | 77 (64, 90) | 0.36 |
| HDL Change * (mg/dL) | -2.5 (19,148) | 10.5 (-2, 23) | 0.49 |
| 16 wk LDL (mg/dL) | 99.43 ± 34.21 | 97.33 ± 39.72 | 0.88 |
| 36 wk LDL * (mg/dL) | 113 (46, 300) | 116.5 (109, 124) | 0.88 |
| LDL Change *(mg/dL) | 21 (-26, 184) | 33.5 (10, 57) | 0.45 |
| 16 wk TG (mg/dL) | 108.71 ± 65.23 | 137.00 ± 37.97 | 0.67 |

| | | | |
|---|---|---|---|
| 36 wk TG (mg/dL) | 198.86 ± 94.75 | 279.00 ± 69.30 | 0.86 |
| TG Change (mg/dL) | 90.14 ± 40.40 | 120.50 ± 23.33 | 0.29 |
| 16 wk Lactate * (mmol/L) | 0.95 (0.7, 3) | 1.3 (1, 5.6) | 0.31 |
| 36 wk Lactate (mmol/L) | 1.20 ± 0.45 | 1.60 ± 0.14 | 0.31 |
| Lactate Change * (mmol/L) | 0.05 (-1.7, 1.4) | -1.8 (-3.9, 0.3) | 0.22 |
| 16 wk TC (mg/dL) | 181.86 ± 38.64 | 199.00 ± 27.94 | 0.52 |
| 36 wk TC (mg/dL) | 228.50 ± 69.21 | 249.50 ± 21.92 | 0.38 |
| TC Change (mg/dL) | 46.64 ± 55.86 | 68.00 ± 55.15 | 0.99 |
| 16 wk Glucose (mg/dL) | 76.79 ± 5.49 | 79.25 ± 4.79 | 0.87 |
| 36 wk Glucose (mg/dL) | 77.57 ± 5.73 | 96.50 ± 16.26 | 0.02 |
| Glucose Change (mg/dL) | 0.79 ± 7.77 | 13.50 ± 19.09 | 0.04 |

*Due to no normal distribution values were run with Kruskal-Wallis.
BF%: body fat percent, WC: waist circumference, HDL: high density lipoprotein, LDL: low density lipoprotein, TG: triglyceride, TC: total cholesterol.

To answer the question of inflammatory marker placenta CRP levels between racial/ethnic groups, we completed t-test analyses of absolute CRP and relative to placental tissue level. Thus, we observed absolute and relative levels of CRP in placental tissue were similar between groups (Table 3); though, we note BIPOC groups have trends of lower CRP placental levels.

**Table 6: Placental Measures by Racial/Ethnic Groups**

| | Caucasian | BIPOC | p-value |
|---|---|---|---|
| Absolute CRP (ng/mL) | 104.70 ± 18.86 | 104.57 ± 6.83 | 0.23 |
| Relative CRP (pg/mg) | 81325.61 ± 31194.83 | 72554.01 ± 20807.12 | 0.14 |

**Predictors of Placental CRP levels**

To determine the effects of prenatal exercise on placental CRP levels, ANCOVA regression models were performed while controlling for maternal measures. First, we assessed models including exercise group to predict placental CRP levels. After controlling for exercise group, pre-pregnancy BMI, 36 wk waist circumference, and 36 wk LDL, we found 36 wk HDL (p=0.007) and 36 wk lactate (p=0.02) predict placental CRP levels (Adjusted $R^2$= 0.581, p =

0.046). Next, we assessed models including racial/ethnic group to predict placental CRP levels. Controlling for pre-pregnancy BMI, 36 wk waist circumference, race/ethnicity, and fitness level, we found 36 wk HDL (p=0.045), 36 wk lactate (p=0.03) as well as gestational week (p=0.03) predict placental CRP levels (Adjusted $R^2$= 0.804, p = 0.036).

## CHAPTER 5: DISCUSSION

The purpose of this study is to determine the effects of exercise types during pregnancy on placental CRP and maternal metabolism. I hypothesize that any type of exercise will decrease placenta CRP and maternal metabolic measures (i.e., lipids, body composition, glucose, lactate) relative to non-exercise controls. I found that CRP values in placental tissue are similar regardless of exercise type or no exercise. A secondary purpose of this study is to determine the effects of race on placental CRP and maternal metabolism. Based on current research, I hypothesize that BIPOC women will have increased placenta CRP and maternal metabolic measures (i.e., lipids, body composition, glucose, lactate) relative to Caucasian women. We also found that in BIPOC women it seems that BIPOC women in general have lower placental CRP values. Lastly, the main predictors of placental CRP values are gestation length, as well as 36-week HDL and lactate. To my knowledge, this is the first study to investigate the effects of an exercise intervention on CRP in placental tissue.

CRP values in placental tissue are similar regardless of exercise intervention. Previous studies measured serum or plasma CRP levels during pregnancy. One randomized control trial found CRP decreased from pre- to post-intervention in the exercise intervention group with information provided via self-reported physical activity. Participants in this study were pregnant women with the mean weeks gestation at recruitment being 11 weeks gestion. The participants completed a 12-week individually tailored self-reporting aerobic exercise program and were encouraged to engage in activities they enjoyed such as walking, dancing, and yard work. The overall goal was for women to meet the American College of Obstetricians and Gynecologists' guidelines and accumulate at least 30 minutes of exercise most days of the week (18). Wang et al.

noted decreased CRP levels in maternal blood related to level of prenatal exercise, though we did not. However, Wang et al. utilized questionnaires that inquired about frequencies of recreational exercises 3 months before participant became pregnant as well as another questionnaire was sent during their pregnancy; thus, women may have over-reported exercise activity (33). Similar to our findings, one study found that self-reported physical activity was not associated with CRP levels in the third trimester (19).

In our study it appears that CRP levels are lower in BIPOC pregnant women compared to Caucasian pregnant women. According to a report written by Paul et al. the strongest proximal predictor of CRP levels was the number of stressful life events experienced with African American women reporting a higher number of stressful life events (29). A study including nongravid participants found that those who participated had lowers levels of CRP compared to those who were sedentary. Potentially this finding is related to the fact that the BIPOC women were exercising, and they are more sensitive to the exercise response to lower inflammation. The more vigorous the exercise the lower the CRP seemed (1). A study completed by Kretzschmar et al. 23 African Americans with low inflammation CRP (<3 mg/L) and 14 with high inflammation CRP (≥3 mg/L) participated in six months of aerobic exercise training. The high inflammation group had significantly higher levels of CRP which were then lowered by 31% after the aerobic intervention. The low inflammation group improved aerobic fitness, body mass index and plasma triglycerides by 10%, 3%, and 30% respectively. Researchers concluded that aerobic fitness alone may not be enough to reap the same benefits between low and high inflammation groups (23).

Predictors of CRP levels in placenta are gestational length, HDL, and lactate. Corsetti et al. identified HDL as an important factor that contributes to CVD in non-gravid women. One of the findings from Corsetti's study was that high levels of HDL particles in apolipoprotein A-II and apolipoprotein A-II is associated with incident of CVD risk in the high-risk group which contained women with high HDL-C and CRP (10). One study used spearman correlation that found age, anthropometric markers, such as BMI, waist circumference, hip circumference, waist-to-hip ration and upper-arm circumference, lipid profile variables, HbA1c and physical activity correlated significantly with CRP. Information was obtained via questionnaires sent out to participant including demographics, lifestyle factors, such as tobacco use, as well as physical activity. Researchers used the physical activity index that was developed and tested in the transition in health during urbanization in South Africa along with a step counter to determine physical activity. (28).

To my knowledge, this study is the first to investigate the effects of exercise on CRP in placental tissue. One of the strengths to this study is the randomized control trial, which is the highest level of evidence for a study. Further, the processing of the placental samples was done in blinded fashion. Some limitations to this study include sample size, which decreased power to detect differences. Future studies should consider using a larger and more diverse sample population of pregnant women to allow for a more generalized conclusion. Another consideration for future studies is the role diet has on CRP and other inflammatory pathways.

It is important to understand the role of exercise in the reduction of inflammation during pregnancy. This study yielded data that suggests exercise is safe during pregnancy. Additionally, the data suggests that exercise does not increase placental inflammatory or maternal metabolic markers, regardless of race. Further investigation with larger more diverse sample sizes is required.

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# Notification of Amendment Approval

From: Biomedical IRB
To: Linda May
CC:

Lindsey Rossa
Date: 2/6/2023
Re: Ame12_UMCIRB 19-001863
UMCIRB 19-001863
Exercise Modality on Childhood Obesity Risk

Your Amendment has been reviewed and approved using expedited review for the period of 2/3/2023 to 8/9/2023. It was the determination of the UMCIRB Chairperson (or designee) that this revision does not impact the overall risk/benefit ratio of the study and is appropriate for the population and procedures proposed.

Please note that any further changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. A continuing or final review must be submitted to the UMCIRB prior to the date of study expiration.The investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).

The approval includes the following items:

| Description |
|---|
| Need to add Demya Pratt, Casey Sutherland, Ayanna Miller, Ashley Arenella and Nini Vargas Suarez to the study team. |

For research studies where a waiver or alteration of HIPAA Authorization has been approved, the IRB states that each of the waiver criteria in 45 CFR 164.512(i)(1)(i)(A) and (2)(i) through (v) have been met. Additionally, the elements of PHI to be collected as described in items 1 and 2 of the Application for Waiver of Authorization have been determined to be the minimal necessary for the specified research.

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

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