

# Beginning regular exercise in early pregnancy: Effect on fetoplacental growth

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**OBJECTIVE:** Our purpose was to test the null hypothesis that beginning regular, moderate-intensity exercise in early pregnancy has no effect on fetoplacental growth.

**STUDY DESIGN:** Forty-six women who did not exercise regularly were randomly assigned at 8 weeks either to no exercise ( $n = 24$ ) or to weight-bearing exercise ( $n = 22$ ) 3 to 5 times a week for the remainder of pregnancy. Outcome variables included antenatal placental growth rate and neonatal and placental morphometric measurements.

**RESULTS:** The offspring of the exercising women were significantly heavier (corrected birth weight:  $3.75 \pm 0.08$  kg vs  $3.49 \pm 0.07$  kg) and longer ( $51.8 \pm 0.3$  cm vs  $50.6 \pm 0.3$  cm) than those born to control women. The difference in birth weight was the result of an increase in both lean body mass and fat mass. In addition, midtrimester placental growth rate was faster ( $26 \pm 2$  cm<sup>3</sup>/wk vs  $21 \pm 1$  cm<sup>3</sup>/wk) and morphometric indexes of placental function were greater in the exercise group. There were no significant differences in neonatal percentage body fat, head circumference, ponderal index, or maternal weight gain.

**CONCLUSIONS:** These data indicate that beginning a moderate regimen of weight-bearing exercise in early pregnancy enhances fetoplacental growth. (Am J Obstet Gynecol 2000;183:1484-8.)

**Key words:** Pregnancy, exercise, growth, fetus, placenta

Our laboratory has shown that fit women who continue their regular regimen of weight-bearing exercise throughout pregnancy grow larger placentas and deliver infants who are lighter and leaner than those born to physically active control women.<sup>1, 2</sup> However, others have been unable to demonstrate a similar effect on birth weight either in women who continue to exercise but at reduced levels<sup>3-5</sup> or in those who begin a relatively rigorous program of non-weight-bearing exercise in the mid trimester.<sup>6, 7</sup> This suggested that the observed differences in fetal morphometric outcome were probably the result of differences in the type, timing, duration, and intensity of the various maternal exercise regimens, which raised the possibility that one or more of these exercise variables modulate the impact of exercise on fetoplacental growth.

Therefore several years ago we began to explore the possibility that differences in one or more of these exer-

cise parameters explained the differences in morphometric outcome; we used prospective randomized protocols. This report details our findings in the initial experimental series, which was designed to examine the effect of beginning a program of moderate-intensity, weight-bearing exercise in early pregnancy on fetoplacental growth to test the null hypothesis that beginning regular, moderate-intensity, weight-bearing exercise in early pregnancy has no effect on fetoplacental growth.

## Material and methods

**General procedures.** The experimental protocol was approved by the hospital's internal review board for human experimentation and used a prospective randomized design in which healthy, non-substance-abusing women were enrolled before pregnancy. At that time they completed a demographic questionnaire and underwent a physical fitness assessment including a fixed-rate, progressive-incline treadmill evaluation of maximum aerobic capacity.<sup>8</sup> Then, after conception and ultrasonographic documentation of a viable singleton pregnancy, they were randomly assigned by envelope draw to a no-exercise control group or an exercise group. The women in the control group did not perform any recreational weight-bearing exercise for the remainder of pregnancy, whereas those in the exercise group performed 1 of 3 forms of weight-bearing exercise (treadmill, step aerobics, or stair stepper) for 20 minutes 3 to 5 times each week for the remainder of pregnancy at an intensity between 55% and 60% of the preconception maximum aerobic capacity.

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No attempt was made to assess the physical activity associated with everyday life or to challenge the veracity of the women about additional unmonitored recreational physical activity. Women in both groups had similar lifestyles, and most worked outside the home. All were seen regularly throughout the remainder of pregnancy for assessment of weight gain, fat deposition, diet, and placental growth. Exercise sessions were monitored and exercise intensity was checked every 2 weeks by means of respiratory calorimetry. A member of the study team was present during labor and delivery and performed morphometric assessment of the placenta and infant at the time of birth. The placentas were fixed in formalin for later histomorphometric analysis. Neonatal morphometrics were repeated at 5 days of age.

By design, women who did not maintain the specified exercise regimen throughout pregnancy or whose antenatal course was abnormal (premature labor, pregnancy-induced hypertension, gestational diabetes mellitus, intrauterine growth restriction) were excluded from the data analysis.

**Measurement techniques.** Oxygen consumption was measured with the use of a mouthpiece, nose clips, and an accurately calibrated indirect calorimetry system.<sup>8</sup> Pregnancy viability was determined with real-time ultrasonography at 8 weeks' gestation.<sup>1, 9</sup> Body weight was determined with an electronic balance beam scale, and fat retention was estimated from the sum of 5-site skinfold thicknesses.<sup>10</sup> Dietary intake was assessed by means of a weekly, random 24-hour dietary recall and analysis with Nutritionist 4 (First Data Bank, San Bruno, Calif) software.<sup>11</sup> Morphometric measurements of the newborn infants were obtained in a standardized fashion with a calibrated scale, tape measure, measurement box, and skinfold calipers.<sup>1, 9</sup> Total body electrical conductivity was measured at age 5 days and used to calculate lean body mass.<sup>12</sup> Antenatal estimates of placental volumes and growth rates were obtained at 16, 20, and 24 weeks' gestation by means of B-mode ultrasonography and a fixed-arm transducer that allowed us to obtain parallel images of the placenta at every centimeter.<sup>2</sup> Gross measurements of the placenta included trimmed, blotted weight, volume, and surface area.<sup>1, 2, 9</sup> After fixation, the volume of the various placental tissues was determined by systematic random sampling and point counting techniques.<sup>13</sup> To ensure representative values, we cut a minimum of 14 blocks per subject, and all sections were read blindly by 2 observers. The mean values obtained were used in data analysis.

**Data management.** The sample size calculation for this protocol used the variances encountered in our earlier studies.<sup>2, 9, 12-14</sup> It indicated that a minimum sample size of 15 women per group would be adequate to detect a 10% difference in each of our 3 primary outcome parameters at the .05 level with a power of .80. The 3 primary outcome parameters and analyses included birth weight,

midtrimester placental growth rate, and placental volume at term. Secondary analyses were then used to identify the specific morphometric components that explained the differences observed in the primary outcome parameters. These analyses included the corrected birth weight (gestational age, sex, and race); the lengths, circumferences, and estimates of fat mass of the offspring; the antenatal placental volumes; and the volumes of the component placental tissues. Other between-groups comparisons were simply carried out to ensure that the 2 groups were comparable in terms of maternal characteristics. Statistix (Analytical Software, Tallahassee, Fla) software was used for data analysis. Between-groups comparisons were made with the unpaired *t* test. Because measurements of the primary outcome parameters were independent of one another, significance was set at the .05 level. Group data are reported as mean  $\pm$  SEM.

To assess the interaction between placental and fetal growth, we sought correlations between placental parameters and birth weight; we used least-squares regression and the best subset regression technique. Finally, to determine whether the frequency of exercise made a difference in morphometric outcome, we also compared the same outcomes in 19 of the women within the exercise group whose exercise patterns were very consistent (9 women who consistently exercised 12-14 times a month vs 10 women who exercised 16-20 times a month throughout).

## Results

**General findings.** Of the 50 women enrolled, 46 had an uncomplicated pregnancy and completed the protocol. Two women randomly assigned to the exercise group were noncompliant, and 1 randomly assigned woman in each group had preterm labor. There were no other pregnancy complications. Twentyfour of the women who completed the protocol had been randomly assigned to the control group and 22 to the exercise group. All except 3 of these women (2 exercisers and 1 control woman) worked outside the home.

Compliance with the exercise regimen was excellent, with all subjects in the exercise group exercising between 12 and 20 sessions each lunar month and individual performances throughout the pregnancy being consistent in most women. Nine women exercised between 12 and 14 times each lunar month, and 10 women exercised between 16 and 20 times each lunar month. The remaining 3 individuals decreased their exercise from 15 to 20 sessions in early pregnancy to 12 to 14 sessions in the last 2 months.

Mean maternal age ( $31 \pm 1$  years), education ( $16 \pm 1$  years), and parity ( $0.42 \pm 0.13$ ) were identical in the 2 groups, and prepregnancy weight (control,  $61.7 \pm 1.3$  kg; exercise,  $62.1 \pm 1.1$  kg), prepregnancy percent body fat (control,  $21.3 \pm 2.1$ ; exercise,  $21.9 \pm 2.4$ ), pregnancy weight gain (control,  $16.3 \pm 0.7$  kg; exercise,  $15.7 \pm 1.0$  kg), and average daily caloric intake during pregnancy

**Table I.** Neonatal morphometrics

Characteristic	Control group	Exercise group	Statistical significance
Uncorrected birth weight (kg)	3.43 ± 0.9	3.66 ± 0.9	<i>P</i> = .05
Corrected birth weight (kg)*	3.49 ± 0.7	3.75 ± 0.8	<i>P</i> = .05
Crown-heel length (cm)	50.6 ± 0.3	51.8 ± 0.3	<i>P</i> = .05
Ponderal index	2.61 ± 0.05	2.65 ± 0.03	NS
Head circumference (cm)	35.0 ± 0.3	35.4 ± 0.3	NS
Head/abdomen ratio	1.09 ± 0.01	1.08 ± 0.01	NS
Percentage body fat	11.2 ± 0.7	11.5 ± 0.8	NS
Fat mass (kg)	0.40 ± 0.04	0.43 ± 0.04	NS
Lean body mass (kg)	3.04 ± 0.06	3.23 ± 0.07	<i>P</i> = .05

Data (except for statistical significance) are expressed as mean ± SEM. NS, Not significant.

\*Adjustment for race, sex, and gestational age.

(control, 43 ± 3 kcal/kg lean body mass; exercise, 45 ± 3 kcal/kg lean body mass) were similar. Gestational age at delivery was also similar, averaging 278 ± 2 days in the control women and 277 ± 2 days in the exercisers. No significant differences in any of these parameters were present between the 2 exercise subgroups.

**Offspring characteristics.** There were 11 male and 13 female infants born to women in the control group, and 10 male and 12 female infants were born to the women in the exercise group. All offspring were in good condition at birth (Apgar score ≥8 at 1 and 5 minutes).

The morphometric characteristics of the offspring are detailed in Table I. Note that the offspring of the exercising women were significantly heavier and longer and that the weight difference persisted when corrected for the potential confounders of gestational age, sex, and race with the use of institution-specific standards.<sup>15</sup> Also note that the mean head circumference, the head/abdominal circumference ratio, the ponderal index, and the percentage body fat were similar, indicating that the overgrowth was symmetric and accompanied by a significant increase in lean body mass.

The same analysis was carried out within the exercise group. The offspring of women who exercised 16 to 20 times each month had birth weights, corrected birth weights, lengths, ponderal indexes, head circumferences, and head/abdominal circumference ratios that were similar to those of the offspring of women who exercised 12 to 14 times each month. However, the percentage body fat was significantly (*P* < .01) less (9.5% ± 0.9% vs 13.9% ± 1.1%) in the offspring of women who exercised 16 to 20 times each month.

**Placental growth and morphometrics.** Midtrimester placental location was similar in the 2 groups (>75% were primarily anterior, posterior, or fundal). The midtrimester placental growth rate, gross placental volumes, and volumes of the placental component tissues are detailed in Tables II and III. Again it should be noted that calculated midtrimester placental growth rate and gross volumes at 20 and 24 weeks' gestation and at term were significantly greater in the exercise group. Likewise, his-

tologic estimates of the volumes of various component tissues indicate that the placentas of women who exercised contained less nonfunctional tissue and a significantly greater volume of villous tissue. The latter was primarily the result of an increase in volume at the level of the terminal villi, which are active in exchange rather than in the stem, and at the level of the intermediate villi, which are essentially conduits for the larger fetal umbilical vessels.

The same analysis was carried out within the exercise group. Over the range studied, monthly exercise frequency had no detectable effect on placental growth rates, crude volumes, or volumes of component tissues at term.

**Correlations between corrected birth weight and placental volumes.** As anticipated, placental volume, villous volume, and intermediate and terminal villous volumes had strong individual correlations (*r*<sup>2</sup> values between 0.5256 and 0.5358) with birth weight corrected for gestational age, sex, and race of the offspring.<sup>13, 16</sup> Weaker correlations were present between midtrimester placental growth and volumes (*r*<sup>2</sup> values between 0.2900 and 0.3109). They improved when analyzed by group (*r*<sup>2</sup> values between 0.3458 and 0.5679). However, they were much weaker than those reported in an earlier study, which examined similar relationships in the offspring of a more uniform group of trained women who continued to exercise throughout pregnancy.<sup>16</sup>

For further exploration we reexamined the data, using best subset regression controlled for parity. The inclusion of placental volumes at 24 weeks and at term,<sup>2</sup> maternal weight gain,<sup>9, 10</sup> and dietary carbohydrate intake<sup>12</sup> raised the correlation with birth weight further, indicating that other factors influencing fetoplacental substrate availability also play a role. This approach yielded a combined *r*<sup>2</sup> value of 0.7242 for the entire study group, 0.7409 for the control group alone, and 0.8612 for the exercise group alone, the latter being similar to the correlations reported earlier.<sup>16</sup>

### Comment

These data warrant several conclusions. First, beginning a program of regular, moderate-intensity, weight-

**Table II.** Placental growth rate and gross volumes

<i>Characteristic</i>	<i>Control group</i>	<i>Exercise group</i>	<i>Statistical significance</i>
Midtrimester placental growth rate (cm <sup>3</sup> /wk)	21 ± 1	26 ± 2	<i>P</i> = .04
Placental volume (cm <sup>3</sup> )			
At 20 wk	181 ± 9	225 ± 15	<i>P</i> = .02
At 24 wk	264 ± 13	327 ± 16	<i>P</i> = .004
After delivery	414 ± 14	462 ± 18	<i>P</i> = .05

Data (except for statistical significance) are expressed as mean ± SEM.

**Table III.** Histomorphometric volumes of placental tissue components

<i>Characteristic</i>	<i>Control group</i>	<i>Exercise group</i>	<i>Statistical significance</i>
Functional volume (cm <sup>3</sup> )	367 ± 14	434 ± 19	<i>P</i> = .006
Nonfunctional volume (cm <sup>3</sup> )*	45 ± 6	28 ± 4	<i>P</i> = .04
Intervillous space (cm <sup>3</sup> )	149 ± 6	166 ± 8	NS
Villous volume (cm <sup>3</sup> )	222 ± 9	268 ± 11	<i>P</i> = .009
Stem villi (cm <sup>3</sup> )	23 ± 2	29 ± 4	NS
Intermediate villi (cm <sup>3</sup> )	59 ± 3	62 ± 5	NS
Terminal villi (cm <sup>3</sup> )	141 ± 7	177 ± 8	<i>P</i> = .001

Data (except statistical significance) are expressed as mean ± SEM. NS, Not significant.

\*The sum of damaged tissue, membranes, and decidua.

bearing exercise at 8 or 9 weeks' gestation has a positive effect on fetoplacental growth rate and ultimately size at birth. This is not an entirely new finding; epidemiologic studies have suggested that birth weights may be heavier when any one of several weight-bearing regimens are either begun or continued during pregnancy.<sup>5, 17-19</sup> The fact that similar findings are not present when non-weight-bearing exercise is begun after week 16 suggests that the time in pregnancy when the exercise is begun and the type of exercise probably are important determinants of this effect.<sup>6, 7</sup>

Second, this exercise regimen was associated with a balanced increase in the growth of the placenta and fetus. The increased placental growth was documented as early as 20 weeks' gestation, persisted until term, and was associated with a normal fetoplacental weight ratio at that time. This also suggests that beginning a moderate-intensity exercise regimen early in the course of pregnancy, during the hyperplastic phase of placental growth, may be an important mechanism for improving placental functional capacity, which in turn increases nutrient delivery to and overall growth rate of the fetus later in gestation. The physiologic mechanism by which regular exercise improves placental growth is unknown, but it is probable that it is linked to the intermittent reductions in uterine blood flow that occur during sustained weight-bearing exercise, as well as to the markedly expanded blood volume found in regularly exercising pregnant women.<sup>1, 2, 20</sup>

Third, this exercise regimen was associated with a symmetric increase in fetal growth as assessed by morphometric measures at the time of birth. In the exercise group as a whole, the increase in weight was matched by a similar

increase in length, lean body mass, and fat mass. This was not the case in an earlier observational study that examined the offspring of fit women who voluntarily continued a higher-intensity weight-bearing exercise regimen of greater duration throughout early, mid, and late pregnancy.<sup>1, 9, 20</sup> Those women's infants were lighter and leaner relative to those of the control women. However, when the exercise group was subdivided to determine whether exercise frequency had an effect, the offspring of the women who exercised more frequently (16-20 times each month) were significantly leaner, suggesting that a gradient effect may exist even at these low exercise volumes.

Fourth, in both the overall exercise group and its subgroups, the increase in placental volume was in large part the result of an increase in the volume and presumably the number of terminal villi, which indicates that the exercise stimulus continued to act through mid and late gestation, when proliferation of the terminal villi occurs.<sup>21</sup> This finding is different from that seen in the placentas of fit women who continued their preconception weight-bearing exercise regimen throughout pregnancy.<sup>13</sup> In those women the placental effects were confined to the stem and intermediate villi. Again, most of these women exercised throughout early, mid, and late pregnancy at higher intensities and for longer periods. Thus the different neonatal and placental morphometric effects in the 2 studies probably reflect differences in the timing and overall volume of exercise during the various trimesters of pregnancy. Additional prospective randomized studies are currently underway to determine whether this is indeed the case.

Fifth, the amount of regular weight-bearing exercise needed to increase fetoplacental growth in normal pregnancy can be easily performed by any healthy, low-risk pregnant woman. The intensity of the exercise required can be easily achieved in most aerobics regimens or by walking briskly on the flat or up a gradual incline. If the pace is right, the woman should start to sweat after 5 to 10 minutes, but she should not feel that she is working hard and should be able to carry on a conversation without feeling out of breath.

Sixth, the fact that a moderate amount of weight-bearing exercise during pregnancy improved placental growth in this low-risk populace does not mean that it would have the same effect in other women, such as those who are at sociodemographic risk of having low-birth-weight outcomes. Nonetheless, we speculate that early introduction of a moderate-intensity regimen of weight-bearing exercise during pregnancy may have preventive value in individuals or populations at risk of having low-birth-weight outcomes. We also speculate that a similar exercise program in individuals with a risk of an overgrown fetus (such as women with a history of glucose intolerance) could compound the problem. However, a more arduous program involving daily, more prolonged, or twice-daily exercise may have a different effect.<sup>9, 14</sup> Clearly, additional prospective randomized trials in these populations will be necessary to address this issue definitively.

It is important to point out that several potential minor confounders were not examined in detail. For example, no attempt was made to control or correct for any between-subjects differences in the amount of physical activity required for various aspects of everyday life. Although it is possible that small between-groups differences may have had an effect, it is unlikely because of the randomized design, the similarities in overall lifestyle, and the fact that the physical activities associated with everyday life are usually of low intensity and intermittent. Likewise, small differences in dietary intake could possibly have influenced the result. However, this would be unlikely because both groups of women were well nourished, ate to appetite, and had similar weight gains during pregnancy. The same might well be true for the individual differences in exercise frequency within the exercise group. However, it is unlikely because all except one of the outcome parameters were similar whether the woman exercised 12 to 14 days or 16 to 20 days a month. Finally, it is theoretically possible that the identified significant between-groups differences occurred by chance alone as a result of the multiple between-groups comparisons that were made. That is statistically unlikely because unrelated methods were used to assess each of the 3 primary outcome measures, and the remaining comparisons simply examined their component parts.

In summary, beginning a moderate-intensity, weight-bearing exercise regimen in early pregnancy is associ-

ated with a significant, balanced increase in fetoplacental growth in normal pregnancy. We speculate that this information may be useful in establishing a care plan for women at risk of having low-birth-weight outcomes.

## REFERENCES

1. Clapp JF. Exercise during pregnancy. In: Bar-Or O, Lamb DR, Clarkson PM, editors. Volume 9: perspectives in exercise science and sports medicine: exercise and the female—a life span approach. Carmel (CA): Cooper Publishing Group; 1996. p. 413-51.
2. Clapp JF, Rizk KH. Effect of recreational exercise on mid-trimester placental growth. *Am J Obstet Gynecol* 1992;167:1518-21.
3. Bell RJ, Palma SM, Lumley JM. The effect of vigorous exercise during pregnancy on birth-weight. *Aust N Z J Obstet Gynaecol* 1995;35:46-51.
4. Kardel KR, Kase T. Training during pregnancy: effects on fetal development and birth. *Am J Obstet Gynecol* 1998;178:280-6.
5. Sternfeld B, Quesenberry CP, Eskenazi B, Newman LA. Exercise during pregnancy and pregnancy outcome. *Med Sci Sports Exerc* 1995;27:634-40.
6. Collings CA, Curet LB, Mullen JP. Maternal and fetal responses to a maternal aerobic exercise program. *Am J Obstet Gynecol* 1983;146:702-7.
7. Wolfe LA, Mottola MF, Bonen A, MacPhail A, Sloboda D, Hains SMJ, et al. Controlled randomized study of aerobic conditioning: effects on neonatal morphometrics [abstract]. *Med Sci Sports Exerc* 1999;31:S138.
8. Clapp JF, Capeless EL. The VO<sub>2</sub> max of recreational athletes before and after pregnancy. *Med Sci Sports Exerc* 1991;23:1128-91.
9. Clapp JF, Capeless EL. Neonatal morphometrics after endurance exercise during pregnancy. *Am J Obstet Gynecol* 1990;163:1805-11.
10. Clapp JF, Little KD. Effect of recreational exercise on pregnancy weight gain and subcutaneous fat deposition. *Med Sci Sports Exerc* 1995;27:170-7.
11. Clapp JF. The morphometric and neurodevelopmental outcome at five years of the offspring of women who continued to exercise throughout pregnancy. *J Pediatr* 1996;129:856-63.
12. Clapp JF. Diet, exercise, and fetoplacental growth. *Arch Gynecol Obstet* 1997;261:101-7.
13. Jackson MR, Gott P, Lye SJ, Ritchie JWK, Clapp JF. The effects of maternal exercise on human placental development: placental volumetric composition and surface areas. *Placenta* 1995;16:179-91.
14. Clapp JF 3d, Kiess W. Effects of pregnancy and exercise on concentrations of the metabolic markers tumor necrosis factor  $\alpha$  and leptin. *Am J Obstet Gynecol* 2000;182:300-6.
15. Amini SB, Catalano PM, Hirsch V, Mann LI. An analysis of birth weight by gestational age using a computerized perinatal data base, 1975-1992. *Obstet Gynecol* 1994;83:342-52.
16. Clapp JF, Rizk KH, Appleby-Wineberg SK, Crass JR. Mid-trimester placental volumes predict birth weight at term. *J Soc Gynecol Investig* 1995;2:19-22.
17. Berkowitz GS, Kelsey JL, Holford TR, Berkowitz RL. Physical activity and the risk of spontaneous premature delivery. *J Reprod Med* 1983;28:581-8.
18. Hatch CM, Shu XO, McLean DE, Levin B, Begg M, Reuss L, et al. Maternal exercise during pregnancy, physical fitness and fetal growth. *Am J Epidemiol* 1993;137:1105-14.
19. Rabkin CS, Anderson HR, Bland JM, Brooke OG, Chamberlain G, Peacock JL. Maternal activity and birth weight: a prospective population-based study. *Am J Epidemiol* 1990;131:522-31.
20. Clapp JF 3d, Stephanchak W, Tomaselli J, Kortan M, Faneslow S. Portal vein blood flow—effects of pregnancy, gravity, and exercise. *Am J Obstet Gynecol* 2000;183:167-72.
21. Jackson MR, Mayhew TM, Boyd PA. Quantitative description of the elaboration and maturation of villi from 10 weeks' gestation to term. *Placenta* 1992;13:357-70.