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Effects of exercise during pregnancy in women with short cervix: Secondary analysis from the Italian Pessary Trial in singletons

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ABSTRACT

Objective: To evaluate effects of exercise during pregnancy in asymptomatic singleton pregnancies without prior spontaneous preterm birth (SPTB) but with short transvaginal ultrasound cervical length (TVU CL).

Study design: This is a secondary analysis of the Italian Pessary Trial for the *Italian Preterm Birth Prevention (IPP) Working Group*. In the original prospective randomized controlled trial asymptomatic singleton pregnancies without prior SPTB but with TVU CL ≤ 25 mm at 18 0/6–23 6/7 weeks were randomized into 1:1 ratio to either cervical pessary or no pessary. During their follow-up visits, women were asked about their activity. For the purpose of this secondary analysis, women were classified in the following groups, using the information obtained in the follow-up visit one month after randomization: 1) Exercise group, defined as women performing exercise ≥2 days a week for ≥20 min each day. 2) No exercise group, defined as women performing exercise <2 days a week for ≥20 min each day. The primary outcome of this secondary analysis was PTB < 37 weeks.

Results: 300 women were included in this analysis. 99 (33.0%) were included in the exercise group. 201 (67.0%) were included in the no exercise group. Of the 201 women in the no exercise group, 90 (44.8%) affirmed that they had reduced their activity after the diagnosis of short cervix despite the research staff recommendations, while the other 111 (55.2%) women performed a sedentary life style even before the diagnosis of short cervix. PTB < 37 weeks occurred in 22 women (22.2%) in the exercise group, and 66 women (32.8%) in the no exercise group (aOR 0.65, 95% CI 0.33–1.03).

Conclusion: In asymptomatic singleton pregnancies with short cervix, performing exercise ≥2 days a week for ≥20 min each day does not increase the risk of PTB but is indeed associated with a non-significant reduction in PTB < 37 weeks by 32%.

Introduction

Preterm birth (PTB) is a leading cause of perinatal morbidity and mortality [1]. Over the last few years, cervical assessment has moved from digital examination to ultrasound evaluation, and ultrasound of the cervix has been the focus of much research [2–10].

Women found to have a short transvaginal ultrasound cervical length (TVU CL) are at increased risk of spontaneous PTB (SPTB) [2,3]. Different strategies have been studies for prevention of SPTB in singleton gestations with short TVU CL [11–17]. The evidence supports the daily use of vaginal progesterone [11,14], while cervical cerclage seems to be beneficial only in the subgroup of singleton gestations with both prior SPTB and TVU CL ≤ 25 mm [12], and not in singletons without prior SPTB [16], nor in multiple gestations [15]. Cervical pessary has also been studied in singleton pregnancies with short cervix with conflicting results.17]

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In the past, some pregnant women have been advised against exercise because of presumed increased risk of PTB [18–20]. However, some studies showed that exercise may reduce the risk of PTB by decreasing oxidative stress as well as increasing blood volume [20–23]. Recent evidence from randomized trials showed that exercise for about 30–60 minutes three to seven times per week during pregnancy is associated with a reduction in the incidence of PTB, [24,25] as well as with a reduction in the risk of gestational hypertensive disorders and cesarean delivery. [26,27].

Evidence of the effects of exercise in women at risk of SPTB, such as women with short TVU CL, is however limited. In a secondary analysis of a randomized trial on progesterone for prevention of PTB among nulliparous women with singleton gestations and TVU CL <30 mm, activity restriction did not reduce the rate of PTB, while the effect of exercise was not evaluated [28]. According to the American College of Obstetricians and Gynecologists (ACOG) [29], cervical insufficiency is an absolute contraindication to exercise, while no recommendations were made for asymptomatic women with short midtrimester TVU CL.

Objective

The aim of this study was to evaluate harms and benefits of exercise during pregnancy in asymptomatic singleton pregnancies without prior SPTB but short TVU CL.

Methods

Study design and participants

This is a secondary analysis of the Italian Pessary Trial for the *Italian Preterm Birth Prevention (IPP) Working Group*, a prospective randomized controlled trial of cervical pessary in asymptomatic singleton pregnancies without prior SPTB but with TVU CL ≤ 25 mm.[30]

The Italian Pessary Trial was a single center trial of asymptomatic singleton pregnancies without prior SPTB and with TVU CL ≤ 25 mm at 18 0/6–23 6/7 weeks who were randomized into 1:1 ratio to either cervical pessary or no pessary, at the University of Naples Federico II (Naples, Italy) from March 1, 2016 to May 25, 2017. Inclusion criteria for the original trial were: 18–50 years of age, singleton pregnancy, TVU CL ≤ 25 mm, gestational age at randomization between 18 0/6 and 23 6/7 weeks, no prior SPTB, defined as spontaneous preterm delivery at 16 0/7–36 6/7 weeks in a prior pregnancy. Full details of the study protocol have been previously reported [30].

In this trial, no bed rest or activity restriction was recommended. The research staffs recommended to all enrolled women to continue their routine activity as before the TVU CL screening.

For the purpose of this planned secondary analysis, at the time of randomization and during the follow-up visit one month after randomization, women were asked about their activity using the following questions:

Question A: Since the beginning of pregnancy (or since the diagnosis of the TVU CL at the follow-up visit) have you exercised in your leisure time, in a supervised program, or on your own? Yes or No. If yes, go to Question B

Question B: How many days per week did you exercise? ≥2 or <2 days a week. If ≥2 days a week, go to Question C

Question C: Taking into account the total duration of physical exercise continuously, how long did you exercise every day? ≥20 or <20 min per day

Those who did not answer these questions were excluded from this secondary analysis.

For the purpose of this secondary analysis women were classified in the following groups, using the information obtained in the follow-up visit one month after randomization:

1) Exercise group, defined as women performing exercise ≥2 days a week for ≥20 min each day.
2) No exercise group, defined as women performing exercise <2 days a week for ≥20 min each day.

Definition of physical exercise, as ≥2 days a week for ≥20 min each day, was definition used in prior trials on exercise in pregnancy [27].

Outcomes

The primary outcome of this secondary analysis was the incidence of PTB < 37 weeks. The secondary outcomes were incidence of PTB < 34, <32, and <28 weeks. The neonatal outcomes were admission to a neonatal intensive care unit, neonatal death (death of a live-born infant within the first 28 days of life), and a composite of adverse perinatal outcomes defined as at least 1 of the following: necrotizing enterocolitis, intraventricular hemorrhage grade 3 or 4, respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity requiring therapy, blood-culture proven sepsis, and neonatal death.

Data analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc., Armonk, NY, USA).

Data are shown as means ± standard deviation (SD), or as number (percentage). Univariate comparisons of dichotomous data were performed with the use of the chi-square test with continuity correction. Comparisons between groups were performed with the use of the *t*-test to test group means with SD by assuming within-group variances.

Logistic regression, presented as unadjusted odds ratio (crude OR) or adjusted odds ratio (aOR) with the 95% confidence interval (CI) was performed for primary and secondary outcomes. Adjusted analysis was performed to correct data for relevant baseline characteristics. Two adjusted analyses were performed, one in which covariates were included if they statistically differed between the two studied groups, and one in which all potentially relevant baseline characteristics were added to the model as covariates. The latter analysis was performed to show robustness of our results. All results presented in the abstract and text refer to the second adjusted analysis. Relevant baseline characteristics to be considered as covariates were: maternal age, ethnicity, body mass index (BMI), smoking during pregnancy, parity, prior cervical surgery (either LEEP or cone biopsy), CL at the time of randomization, use of vaginal progesterone, and use of cervical pessary.

A 2-sided P value less than 0.05 was considered significant.

Results

300 asymptomatic singleton pregnancies without prior SPTB but with TVU CL ≤ 25 mm at 18 0/6–23 6/7 weeks agreed to take part in the trial [30], underwent randomization, and were enrolled and followed up. No women were lost or excluded after randomization and at follow-up. All of them responded to the questions regarding activity at the time of randomization and one month after the randomization, and were included in this secondary analysis.

Characteristics of the study population

Out of them 300 women analyzed, none of them was prescribed any form of activity restriction from the research staff. 99 women (33.0%) performed exercise during pregnancy ≥2 days a week for ≥20 min each day one month after the diagnosis of short TVU CL and were included in the exercise group. 201 (67.0%) were included in the no exercise group.

Of the 201 women in the no exercise group, 90 (44.8%) affirmed that they had reduced their activity after the diagnosis of short cervix despite the research staff recommendations, while the other 111 (55.2%) women performed a sedentary life style even before the diagnosis of short cervix.

Of the 99 women in the exercise group, 82 (82.8%) performed aerobic exercise, including running/jogging, swimming, cycling, and walking, while 17 (17.2%) performed anaerobic exercise, including powerlifting and sprinting (Table 1). Table 1 shows the baseline demographic and clinical characteristics for each group. 81 (81.8%) women in the exercise group, and 177 (88.1%) in the no exercise group were found to have TVU CL ≤ 20 mm and were prescribed vaginal progesterone 200 mg daily.

Outcomes

Tables 2 and 3 show the primary and secondary outcomes. PTB < 37 weeks occurred in 22 women (22.2%) in the exercise group, and 66 women (32.8%) in the no exercise group (aOR 0.65, 95% CI 0.33–1.03). There were no significant differences in the incidence of PTB < 34, <32, and <28 weeks, and in the neonatal outcomes.

Discussion

Main findings

This planned secondary analysis of the Italian Pessary Trial evaluated harms and benefits of exercise during pregnancy in asymptomatic singleton pregnancies without prior SPTB and with TVU CL ≤ 25 mm. Per trial protocol we recommended all women to continue their routine exercise as before the randomization. Despite this recommendation, 90 women (30.0%) their activity after the diagnosis of short cervix. The vast majority of the included women (210 women, 70.0%) continued they activity as before the diagnosis of short cervix. 111 (37.0%) women performed a sedentary life style as before the diagnosis of short cervix, and 99 women (33.0%) continued to exercise ≥2 days a week for ≥20 min.

We found that performing exercise ≥2 days a week for ≥20 min each day was associated with a non-significant reduction in PTB < 37 weeks by 32%. Notably, incidences of PTB at all cut-offs were less common (Table 2), in the exercise group compared to the non-exercise group. However, none of the outcomes reached the statistical significance.

Table 1
Characteristics of the included women for exercise and no exercise group.

	Exercise N = 99	No exercise N = 201	*p-value*
Running/Jogging n (%)	20 (20.2%)	–	–
Swimming n (%)	31 (31.3%)	–	–
Cycling n (%)	8 (8.1%)	–	–
Walking n (%)	23 (23.2%)	–	–
Powerlifting n (%)	15 (15.2%)	–	–
Sprinting n (%)	2 (2.0%)	–	–
Age	29.7 ± 5.6	28.2 ± 6.5	0.06
mean ± SD (years)			
Ethnicity	89 (89.9%)	179 (89.1%)	0.98
Caucasian n (%)	10 (10.1%)	22 (10.9%)	
Other n (%)			
BMI	26.5 ± 6.2	26.5 ± 6.2	0.95
mean ± SD (Kg/m^2)			
Smoking n (%)	9 (9.1%)	30 (14.9%)	0.21
Nulliparous n (%)	70 (70.7%)	139 (69.2%)	0.89
Prior cervical surgery	2 (2.0%)	7 (3.5%)	0.74
LEEP n (%)	0 (0%)	3 (1.5%)	0.55
Cone biopsy n (%)			
CL	12.0 ± 6.6	12.0 ± 5.4	0.94
mean ± SD	81 (81.8%)	177 (88.1%)	0.20
≤20 mm n (%)			
Reduced activity*	–	90 (44.8%)	–

LEEP, loop excision of transformation zone; SD, standard deviation; CL, cervical length.
* Women who reduced their activity after the diagnosis of short cervix.

Strengths and limitations

Our study has several strengths. This is a secondary analysis of a large and high-quality prospective randomized controlled trial. To best of our knowledge, there are limited data from randomized trials on the effect of exercise in women with short cervix [31]. However, even if this is a secondary analysis of a randomized trial, this study was limited by the nonrandomized approach. In the original trial women were randomized into 1:1 ratio into either pessary or no pessary group. In this study, women were divided into two groups according to the exercise activity. Therefore findings from this study can be biased from unbalanced variables between the two groups. The open label study design of the trial can be a source of bias. This study was not powered for the reported outcomes. For the purpose of this secondary analysis, women were classified in exercise and non-exercise groups using the information obtained in the follow-up visit one month after randomization. The mean gestational age at randomization was 22.4 weeks. Therefore this study assessed the effects of exercise performed before ~24 weeks of gestation on the risk of preterm birth. There is no information on the effects of exercise performed after ~24 weeks of gestation on the risk of preterm birth. We used a definition of physical exercise used in prior trials on exercise in pregnancy [27]. Different definitions may lead to different results. For example, performing higher frequency exercise, in women with short cervix may increase the risk of PTB. In the no-exercise group we included both women who reduced their activity after the

Table 2
Incidence of preterm birth in the exercise and in the no exercise group.

	Exercise N = 99	No exercise N = 201	*Crude OR (95% CI)*	*aOR* (95% CI)*
PTB < 37 week n (%)	22 (22.2%)	66 (32.8%)	0.58 (0.33 to 1.02)	0.65 (0.33 to 1.03)
PTB < 34 week n (%)	9 (9.1%)	31 (31.8%)	0.55 (0.25 to 1.20)	0.64 (0.88 to 2.28)
PTB <32 week n (%)	7 (7.1%)	19 (9.5%)	0.73 (0.30 to 1.80)	2.58 (0.34 to 19.33)
PTB <28 week n (%)	4 (4.0%)	12 (6.0%)	0.66 (0.21 to 2.11)	0.78 (0.13 to 4.53)

RR, relative risk; CI, confidence interval; PTB, preterm birth.
* Adjuster for all variables reported in Table 1.

Table 3
Neonatal outcomes in the exercise and in the no exercise group.

	Exercise N = 99	No exercise N = 201	*Crude OR (95% CI)*	*aOR[*] (95% CI)*
Admission to NICU	12 (12.1%)	31 (15.4%)	0.76 (0.37 to 1.55)	0.78 (0.27 to 2.21)
Neonatal death	1 (1.0%)	3 (1.5%)	0.67 (0.07 to 6.56)	0.80 (0.77 to 8.17)
Composite perinatal outcome[*]	21 (21.2%)	49 (24.4%)	0.84 (0.47 to 1.49)	0.98 (0.42 to 2.30)

RR, relative risk; CI, confidence interval; NICU, neonatal intensive care unit.
Composite perinatal outcome defined as at least 1 of the following: necrotizing enterocolitis, intraventricular hemorrhage grade 3 or 4, respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity requiring therapy, blood-culture proven sepsis, and neonatal death.
[*] Adjuster for all variables reported in Table 1.

diagnosis of short cervix, and those who performed a sedentary life style even before the diagnosis of short cervix. These two groups may have a different baseline risk of PTB. The original trial found that spontaneous PTB at less than 34 weeks of gestation was significantly less common in the women who received cervical pessary. Therefore, in this cohort, pessary placement is an important modifier of the risk of PTB, and was more common in the exercise group, even if with no statistically significant differences.

Comparison with prior literature

Different strategies have been studies for prevention of PTB, including cerclage, progesterone, pessary, diet, supplements and life style modification [5,11–14,16,17,31–44]. Grobman et al. found that some form of activity restriction was prescribed for more than one in every three nulliparous women who were diagnosed with a short CL [28]. About 70% of women who had activity restricted were recommended to refrain from work, or sexual activity. They found that activity restriction did not reduce the rate of PTB, but they did not assess the effect of exercise on the incidence of PTB. In our trial we explicitly recommended to the women not to change their activity, and bed rest or any form of activity restriction, including sexual activity, were not recommended. Despite these recommendations, a good number of enrolled women reduced their activity. Our findings also concurred with prior level-1 data that showed that exercise during pregnancy may be beneficial, and does not increase the risk of PTB [24–26].

Conclusion

In summary, in asymptomatic singleton pregnancies with short cervix, performing exercise $\geq$2 days a week for $\geq$20 min each day does not increase the risk of PTB.

Disclosure

The authors report no conflict of interest

Contribution to authorship

All authors fulfilled the journal's definition of authorship
PM is the guarantor of the manuscript and the lead authors. PM affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no aspects of the study have been omitted; that any discrepancies from the study as planned have been explained; and that the manuscript's contents are not misleading.

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Ethical approval

The trial was approved by the local IRB (Comitato Etico Università degli Studi di Napoli Federico II, protocol number #213/15) on November 27, 2015

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