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The Effect of a Supervised Exercise Program Throughout Pregnancy on Longitudinal Lipid Profile Changes: A Randomized Clinical Trial

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Abstract

Objective: To investigate whether a supervised exercise program during pregnancy induces modifications in the maternal lipid profile.

Methods: This unplanned secondary analysis of a multicenter randomized controlled trial (March 2021–June 2023) was conducted at Hospital Universitario de Torrejón, the only participating center with routine lipid profiling during all three trimesters and postpartum. Eligible women had a singleton pregnancy < 14^{+3} weeks without complications. Participants were randomized (1:1) to a supervised exercise program (three 55–60 min sessions/week, virtual or onsite) or control (usual activity). Exercise adherence was defined as ≥ 80% session attendance. Maternal characteristics, blood pressure, and weight were recorded at baseline and follow-up visits in the second and third trimesters and 6–12 months postpartum. Venous blood samples were collected for lipid profiling, including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Between-group differences were tested with Wilcoxon signed-rank tests, and repeated measures were analyzed with generalized estimating equations including gestational age, intervention group, delivery status, and obesity interaction. Both intention-to-treat and per-protocol analyses were performed. Statistical significance was considered at $P < 0.05$.

Results: A total of 202 pregnant women were enrolled, and 182 were included in the final analysis (90 in the control group and 92 in the intervention group). No significant between-group differences were observed in lipid profiles at the second trimester, third trimester, or postpartum. Longitudinal analysis showed higher HDL-C levels in the IG (+3.24 mg/dl; 95% confidence interval (*CI*): 0.13–6.35, $P = 0.041$), persisting postpartum, and a nonsignificant trend toward lower LDL-C (–6.02 mg/dl; 95% *CI*: −13.18 to 1.14, $P = 0.099$). These effects were not confirmed in the per-protocol analysis, and no interaction with obesity was observed.

Conclusion: A supervised exercise program throughout pregnancy may increase HDL-C levels and potentially reduce LDL-C, thereby improving the maternal lipid profile. Further studies are needed to confirm and expand upon these findings.

Registration: No. NCT04563065 (Randomized Controlled Clinical Trial).

Keywords: Pregnancy; Exercise; Lipids; Lipoproteins

Introduction

Lipids and lipoproteins are very important for fetal development and maternal health. Cholesterol is essential for cell membrane formation maintaining membrane integrity, and preserving cholesterol-rich domains, which are fundamental for most membrane-associated signaling cascades.[1] It is also the precursor for many important hormones, such as steroids, vitamin D, and bile acids.[2] During pregnancy, maternal blood cholesterol and triglycerides (TG) increase, with a peak at the end of the third trimester, near term.[3] After delivery, lipid and lipoprotein levels rapidly return to normal. Although the nutritional environment can interfere, it has been proven that they arise even under

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different nutritional conditions.[4] Regardless of dietary differences, by late pregnancy, plasma cholesterol levels are approximately 50% higher than those routinely seen before pregnancy, while TG levels are increased 2-3 times.[3,5,6]

In the mother, evidence suggests that a failure to appropriately modify the lipid profile during pregnancy may increase the risk of hypertensive disorders, spontaneous preterm delivery, long-term cardiovascular risk and even maternal mental disorders.[7–11] Although the literature is contradictory, this failure may also affect the fetus and newborn development, including a higher risk for increased birth weight, large for gestational age and macrosomia, lipid levels, and adiposity at two years of age. In the Framingham study,[12–15] adult low-density lipoprotein (LDL) levels of the newborn were related to maternal LDL levels before pregnancy.

In non-pregnant populations, physical exercise decreases total cholesterol (TC), LDL, and TG, and increases high-density lipoprotein (HDL) levels.[16,17] Although most guidelines recommend pregnant women to engage in at least 150 min of moderate intensity exercise per week,[18–20] little is known about its effects on maternal lipids throughout pregnancy. Some studies have found no differences between women who are more physically active and those who are inactive.[21–23] Other studies have found lower levels of TC and TG during pregnancy in more active women.[24,25] To the best of our knowledge, there are no studies evaluating the effects of exercise during pregnancy on the lipid profile in the postpartum period.

The aim of this study was to assess the effect of a supervised physical exercise program during pregnancy on the lipid profile during pregnancy and postpartum.

Materials and methods

Study design and population

This is an unplanned secondary analysis of a multi-center randomized, non-blinded controlled trial (RCT) conducted between March 2021 and June 2023. The original multicenter clinical trial was carried out through a collaborative effort between the departments of Obstetrics and Gynecology at four maternity units across Spain and the Universidad Politécnica de Madrid. For this present secondary analysis, data were exclusively derived from Hospital Universitario de Torrejón, as it was the only participating center where lipid profile assessments were routinely performed across all three trimesters of pregnancy (once per trimester), as well as during the postpartum period.

All consecutive pregnant women who attendeded their first-trimester prenatal visit were invited to participate in the study. Eligibility criteria were a single live fetus, gestational age at recruitment less than 14 weeks and 3 days, no obstetric complications at the time of recruitment based on the guidelines of the American College of Obstetricians and Gynecologists[19], and not being enrolled in any other supervised exercise program during pregnancy.

Randomization, intervention group and control group

A computer-generated sequence provided simple random allocation (1:1) to intervention group (IG) or the control group (CG). After stratification based on the recruiting center, randomization was implemented in Research Electronic Data Capture, which also served as the electronic data-capture platform. Participants were assigned between 12^{+0} and 14^{+3} weeks of gestation.[26]

Pregnant women assigned to the IG followed a virtual or onsite supervised exercise program throughout pregnancy, after randomization. The exercise program comprised three 55–60 minutes sessions per week, structured into seven components according to the Barakat model, developed by our research group.[27] The original hybrid delivery (two online sessions via Zoom and one onsite session in the hospital gym) was converted entirely to online delivery between March 2021 to March 2022 owing to COVID-19 restrictions. Exercise adherence was defined as the proportion of sessions attended divided by the total number of planned sessions over the individual gestational period.[28] Participants were classified as "exercise adherent" when attendance was ≥ 80%.[29]

Pregnant women in the CG were advised to maintain their usual daily activity and to refrain from enrolling in any structured educational exercise program exceeding 30 minutes per session at least three days per week.

Follow-up

After randomization, both groups followed the same pregnancy care and study follow-up appointments, with study visits at 19^{+0} to 21^{+6}, 27^{+0} to 28^{+6} and 35^{+0} to 36^{+6} weeks of gestation and a postpartum visit 6 to 12 months after delivery. Maternal blood pressure and maternal weight were recorded at every visit. Measurements obtained at 12^{+0} to 13^{+6} weeks (selection visit) were considered baseline measurements.

Maternal characteristics, blood sampling and lipid profiling

Data collected at randomization included maternal age, weight, height, pre-pregnancy body mass index (BMI), parity (nulliparous or multiparous ≥ 24 weeks), mode of conception (spontaneous or assisted conception), cigarette smoking before pregnancy (yes or no), gestational age based on first trimester ultrasound, and pre-pregnancy physical-activity level (none, occasional, acrive (2× week), very active (3-4× week), athlete (daily)). Maternal BMI categories were: underweight < 18.5 kg/m^2, normal ≥ 18.5 to < 25 kg/m^2, overweight ≥ 25 to < 30 kg/m^2, and obese ≥ 30 kg/m^2.

Maternal venous blood was obtained non-fasting at 24^{+4} to 26^{+6} weeks, and fasting at 34^{+0} to 36^{+4} weeks and 6 to 12 months postpartum. Lipid profiles were measured using the following procedures: TC, TG, and HDL were tested using a direct colorimetric method on an automated spectrophotometer (Biosystems®, Spain). LDL was calculated using the Friedewald equations.[30]

Statistical analysis

Descriptive data were expressed as medians with interquartile range or as counts and percentages. Between-groups comparisons at the second trimester, third trimester, and postpartum visits employed the Wilcoxon signed rank test. Repeated measurements of each lipid marker were analyzed with generalized estimating equations assuming an autoregressive correlation structure. In these models, we included gestational age at the time of measurement, randomization group (IG *vs*. CG) evaluating the effect of the intervention, a time-dependent variable indicating whether delivery had occurred, and the interaction of gestational age and delivery to capture different trajectories before and after birth.

We tested the interaction between gestational age and randomization to explore a possible differential effect of the intervention on the markers at different times. In addition, the effect of obesity was studied, including it in the model and interacting it with the randomization, to test if the randomization had a different effect on the biomarker in obese women compared to non-obese ones. Estimates, 95% confidence intervals (*CI*) and *P* values were reported. Statistical significance was considered at $P < 0.05$.

Sample-size calculations for the original trial were published.[31] For this study, both intention-to-treat and per protocol analysis (attendance ≥ 80% in the IG) were performed. All statistics were performed in R version 4.2.2[32] using the *geepack*[33], *ggplot2*[34], *sjplot*[35] and *table1*[36] packages.

Ethical approval

The trial coordinators regularly conducted quality control procedures to ensure proper data handling and adherence to the study protocol. Ethical approval was obtained from the Local Research Ethics Committee, and written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with the principles outlined in the *Declaration of Helsinki*. This randomized controlled clinical trial was registered under the identifier NCT04563065.

Results

From March 2021 to June 2023, a total of 202 pregnant women were recruited. Ninety-eight women were randomized to the CG and 104 to the IG. After applying the appropriate exclusion criteria, 182 participants were included in the final analysis (90 in the CG and 92 in the IG, Fig. 1). Maternal and pregnancy characteristics of the study population are presented in Table 1. The lipid profiles of the study groups during the second trimester, third trimester, and postpartum period are summarized in Table 2. No statistically significant differences were observed at these time points.

In the analysis of longitudinal changes in the lipid profile, significantly higher HDL levels were observed in the IG compared to the CG (mean difference: +3.24 mg/dl; 95% *CI* 0.13–6.35, $P = 0.041$), and this difference persisted into the postpartum period (Table 3, Fig. 2). However, not statistically significant, lower LDL levels were observed in the IG compared to the CG (mean difference: −6.02 mg/dl; 95% *CI* −13.18 to 1.14, $P = 0.099$), with the *CI* suggesting a potentially clinically relevant effect (Table 3, Fig. 3). These findings were not found in the per-protocol analysis.

The interaction between obesity and the randomization group was not significant (Supplementary Table 1, http://links.lww.com/MFM/A105).

Discussion

First, lipid levels undergo significant changes throughout pregnancy consistent with previously reported patterns. Second, no statistically significant differences in lipid profile were observed between women in the supervised exercise program (IG) and those who did not participate (CG) during the second and third trimesters or the postpartum period. However, when repeated measurements were taken into account, statistically significantly higher HDL levels and not significantly lower LDL levels were found in the IG compared to the CG and these changes remained

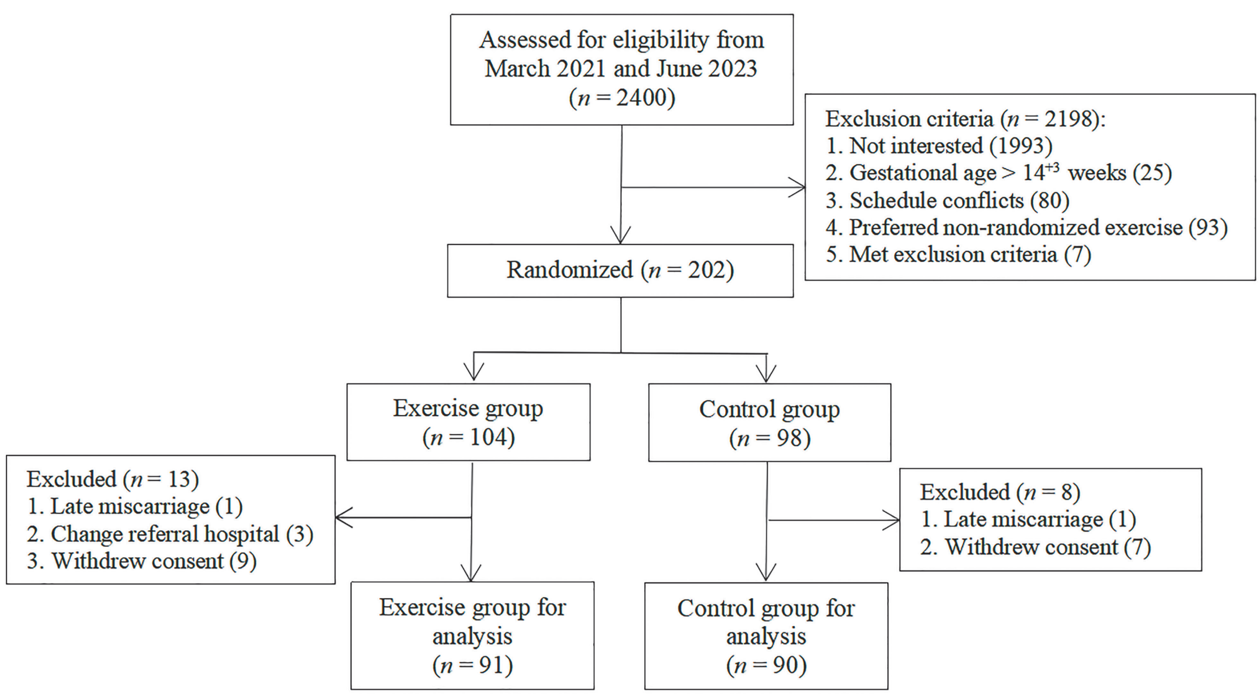

Figure 1. Patient's flow diagram.

Table 1

Maternal and pregnancy characteristics of the study population.

Characteristics	Control ($n = 90$)	Intervention (ITT analysis) ($n = 91$)	Intervention (PP analysis) ($n = 37$)
Age (years)	33.60 ± 4.30	33.19 ± 4.25	33.95 ± 3.51
Maternal BMI (kg/m^2)	24.04 ± 4.52	24.83 ± 4.64	24.07 ± 5.08
Normal weight (< 25)	60 (66.67)	56 (61.54)	28 (75.68)
Overweight (25-30)	22 (24.44)	21 (23.08)	4 (10.81)
Obesity (> 30)	8 (8.89)	14 (15.38)	5 (13.51)
Concepcion method			
Assisted	8 (8.89)	10 (10.99)	6 (16.22)
Natural	82 (91.11)	81 (89.01)	31 (83.78)
Ethnicity			
Caucasian	85 (94.44)	86 (94.51)	33 (89.19)
Latin-American	5 (5.56)	5 (5.49)	4 (10.81)
Parity			
Nulliparous	52 (57.77)	53 (58.24)	26 (70.27)
Multiparous	38 (42.70)	38 (41.76)	11 (29.73)
Smoking before pregnancy			
No	71 (78.89)	77 (84.62)	31 (83.78)
Yes	19 (21.11)	14 (15.38)	6 (16.22)
Alcohol before pregnancy			
No	46 (51.11)	46 (50.55)	20 (54.05)
Yes	44 (48.89)	45 (49.45)	17 (45.95)
Previous preterm delivery			
No	84 (97.67)	81 (96.43)	33 (97.06)
Yes	2 (2.33)	3 (3.57)	1 (2.94)
Missing data	4	7	3
Previous maternal disease			
No	63 (70.00)	67 (73.63)	29 (78.38)
Yes	27 (30.00)	24 (26.37)	8 (21.62)
Exercise adherence > 80%*			
No	—	39 (51.32)	0
Yes	—	37 (48.68)	37 (100.00)

Results are presented as mean ± standard deviation or as n (%) as appropriate. BMI: Body mass index.
*Missing data $n = 15$.

during the postpartum period. Third, these patterns were similar in obese and non-obese women.

In recent years, numerous studies have investigated the benefits of physical exercise during pregnancy for maternal, fetal, and neonatal health. Exercise has been shown to improve maternal health during pregnancy, reduce gestational weight gain, and lower the risk of gestational diabetes and hypertensive disorders[45–47]. Several results from this RCT have been published in this context[31,38,39]. Changes in the lipid profile of patients who exercise during pregnancy may contribute to the protective effect of physical activity against such pregnancy-related complications. However, few studies have specifically explored the biochemical alterations, particularly lipid profile changes, that occur as a result of exercise during pregnancy.

Some studies using questionnaires or objective measures to assess physical activity in pregnant women have found no association between physical activity and changes in lipid profile.[21–23] In contrast, one study involving 234 pregnant women classified into high versus low physical activity (based on average daily step count during pregnancy) suggested that physical activity was associated with lower TC and TG levels, regardless of maternal weight.[24] Another large observational study including 925 pregnant women assessed physical activity using questionnaires in the first trimester of pregnancy and measured lipid profiles at the end of the first trimester.[25] That study found that women who spent more time being physically active had lower TG and TC concentrations compared to inactive women; however, unlike our findings, they found no association with HDL cholesterol.

Several RCTs have investigated the impact of physical exercise programs during pregnancy on maternal lipid profiles; however, these studies have used different types of interventions and durations. For instance, Kim *et al*.[40] investigated the effect of an online Pilates program on the lipid profile of 16 pregnant women, 8 participating in the program and 8 controls. The lipid profile was measured in both groups before and after the intervention took place, showing significantly lower levels of TC, TG, and LDL in the IG compared to the CG. Strom *et al*.[28] randomized 20 women to the IG and 11 to the CG and observed higher HDL levels in the IG during the third trimester; although they reported no statistically significant differences in the HDL levels overall.

Ramirez-Velez *et al*.[41] randomized 24 women to the IG and 26 to the CG, who underwent 12 weeks of supervised exercise. This study demonstrated that supervised exercise led to a decrease in TG and TC, but within normal ranges. In contrast to our study, participants in the IG also received individualized dietary guidance. Similarly, a pilot study involving 16 diabetic pregnant women with diabetes reported significantly lower LDL levels in the IG compared to the CG[42].

In contrast, three other RCTs did not find any differences in the lipid profiles between the IG and the CG.[43–45] Among these, the UPBEAT trial was the largest. randomizing 1158 obese pregnant women to an intervention designed to increase physical activity and improve dietary habits. Secondarily analysis of the lipid profile in this trial revealed that the intervention mitigated the rise in LDL levels and also reduced the increase in various lipoprotein particle subtypes, specifically, extremely large, very large, large, medium, and very low-density lipoprotein particles, especially those containing TG.[45]

Study strengths and limitations

The main strength of our study lies in its RCT design, which included several check-ups at different timepoints and prospectively collected and analyzed samples. Another strength is that the intervention was homogeneous among all participants, following a standardized and structured protocol under international recommendations[46], which allows comparisons with other studies and allows future pooling of data. Finally, to our knowledge, this is the first RCT investigating the effect of exercise during pregnancy on the postpartum period.

Our study also has some limitations. The main one inevitably relates to the small sample size, which may have limited our ability to detect statistically significant differences between groups. Nonetheless, the use of repeated measures partially diminished this limitation by enhancing the study's statistical power, leading to the identification

Table 2

Lipid profile during pregnancy and postpartum in the control and intervention groups: intention-to-treat and per-protocol analyses

	Intention to treat analysis (n = 181)			Per protocol analysis (n = 127)		
Lipid parameter	CG (n = 90)	IG (n = 91)	P	CG (n = 90)	IG (n = 37)	P
TC (mg/dl)						
2º trimester	251 ± 48.1	249 ± 44.2	0.946	251 ± 48.1	251 ± 48.3	0.849
3º trimester	272 ± 56.8	266 ± 48.0	0.344	272 ± 56.8	268 ± 43.6	0.626
Postpartum	177 ± 28.2	184 ± 35	0.458	177 ± 28.2	180 ± 37.2	0.959
HDL (mg/dl)						
2º trimester	79.8 ± 16.8	83.5 ± 17.7	0.101	79.8 ± 16.8	84.0 ± 16.8	0.256
3º trimester	75.5 ± 16.1	77.7 ± 10.2	0.510	75.5 ± 16.1	75.5 ± 19.0	0.715
Postpartum	62.8 ± 12.9	67.0 ± 17.3	0.187	62.8 ± 12.9	64.4 ± 18.1	0.985
LDL (mg/dl)						
2º trimester	140 ± 41.9	134 ± 38.2	0.416	140 ± 41.9	138 ± 38.5	0.946
3º trimester	159 ± 45.4	149 ± 40.3	0.205	159 ± 45.4	151 ± 34.0	0.426
Postpartum	101 ± 26.7	102 ± 28.8	0.832	101 ± 26.7	102 ± 23.0	0.969
TG (mg/dl)						
2º trimester	163 ± 56.8	159 ± 54.6	0.791	163 ± 56.8	153 ± 44.0	0.626
3º trimester	203 ± 56.0	208 ± 67.9	0.560	203 ± 56.0	215 ± 60.2	0.319
Postpartum	64.5 ± 30.5	78.5 ± 60.2	0.345	64.5 ± 30.5	83.6 ± 74.5	0.524

Data were presented as mean ± standard deviation. Comparisons between were performed using the Wilcoxon signed rank test. CG: Control group; IG: Intervention group; TC: Total cholesterol; HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: Triglycerides.

Table 3

Generalized Estimating Equations with an autoregressive correlation structure generated from the repeat measurements analysis of each component of the lipid profile according to gestational age and for each protocol analysis.

	Intention-to-treat analysis (n = 181)		Per protocol analysis (n = 127)	
Lipid parameter	Estimates (95% *CI*)	P	Estimates (95% *CI*)	P
Total cholesterol				
Intercept	185.32 (147.34, 223.30)	< 0.001	181.51 (135.43, 227.59)	< 0.001
Intervention	–1.35 (–9.61, 6.90)	0.748	0.11 (–10.86, 11.08)	0.985
GA	2.36 (1.18, 3.55)	< 0.001	2.51 (1.07, 3.95)	0.001
Postpartum	–12.13 (–101.70, 77.44)	0.790	–19.41 (–133.70, 94.89)	0.739
Weeks after delivery	–2.25 (–3.89, –0.61)	0.007	–2.27 (–4.34, –0.21)	0.031
HDL				
Intercept	96.53 (82.30, 110.75)	< 0.001	98.95 (82.52, 115.38)	< 0.001
Intervention	3.24 (0.13, 6.35)	0.041	2.17 (–1.78, 6.12)	0.28
GA	–0.6 (–1.05, –0.16)	0.008	–0.68 (–1.19, –0.16)	0.01
Postpartum	–31.12 (–69.59, 7.34)	0.113	–34.31 (–83.97, 15.36)	0.175
Weeks after delivery	0.57 (–0.10, 1.24)	0.094	0.65 (–0.19, 1.49)	0.130
LDL				
Intercept	80.54 (47.78, 113.30)	< 0.001	77.79 (39.05, 116.52)	< 0.001
Intervention	–6.02 (–13.18, 1.14)	0.099	–2.84 (–12.21, 6.52)	0.551
GA	2.15 (1.13, 3.17)	< 0.001	2.26 (1.05, 3.47)	< 0.001
Postpartum	20.75 (–67.29, 108.79)	0.643	2.00 (–113.87, 117.87)	0.973
Weeks after delivery	–2.12 (–3.66, –0.58)	0.007	–1.94 (–3.91, 0.03)	0.053
Triglycerides				
Intercept	14.86 (–30.73, 60.45)	0.522	9.54 (–41.20, 60.28)	0.712
Intervention	2.52 (–7.38, 12.42)	0.617	1.11 (–10.95, 13.17)	0.857
GA	5.26 (3.84, 6.69)	< 0.001	5.45 (3.86, 7.04)	< 0.001
Postpartum	51.83 (–55.53, 159.18)	0.343	97.79 (–27.81, 223.39)	0.127
Weeks after delivery	–5.24 (–7.20, –3.27)	< 0.001	–6.02 (–8.29, –3.75)	< 0.001

For each lipid parameter, the listed rows represent predictors included in the generalized estimating equations models. Number of observations for each lipid parameter (sum of repeated measurements across second trimester, third trimester, and postpartum): Total cholesterol ITT = 469, PP = 331; HDL ITT = 458, PP = 332; LDL ITT = 447, PP = 316; Triglycerides ITT = 468, PP = 330.
CI: Confidence intervals; GA: Gestational age; HLD: High density lipoprotein; ITT: intention-to-treat analysis; LDL: Low density lipoprotein; PP: Per-protocol analysis.

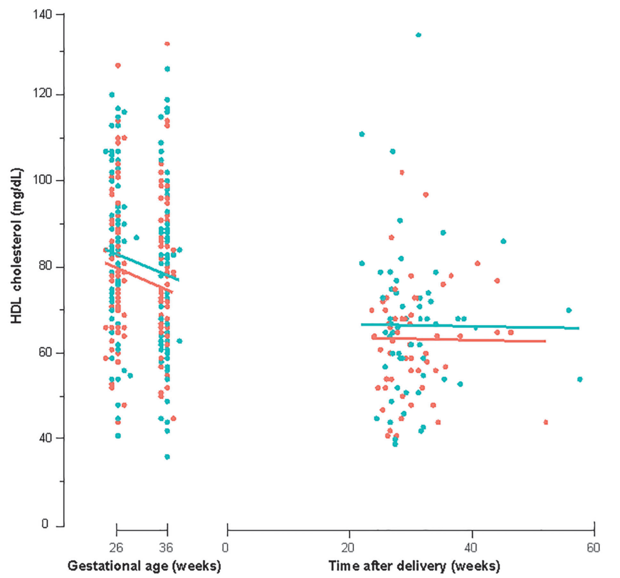

Figure 2. Evolution of high-density lipoprotein cholesterol levels during pregnancy and postpartum in the intention-to-treat analysis, modeled using generalized estimating equations with an autoregressive correlation structure. The blue line represents the intervention group, and the red line represents the control group.

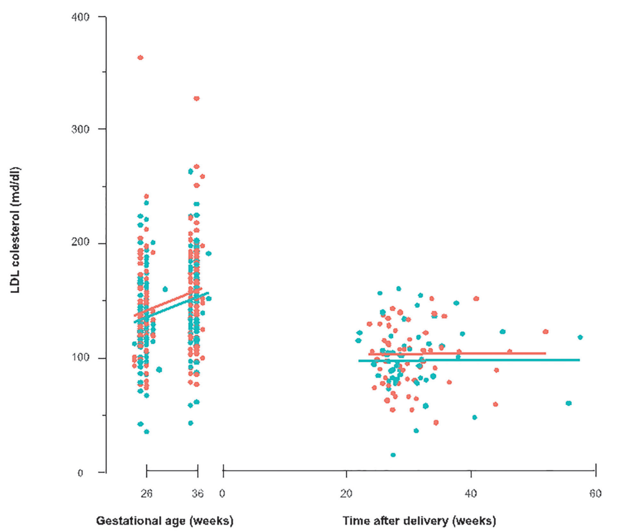

Figure 3. Evolution of low-density lipoprotein cholesterol levels during pregnancy and postpartum in the intention-to-treat analysis, modeled using generalized estimating equations with an autoregressive correlation structure. The blue line represents the intervention group, and the red line represents the control group.

of some significant associations. In this sense, the low adherence to exercise in the IG has significantly reduced our sample. Since this analysis was not originally planned, another important limitation relates to the limited assessment of confounders such as patients' diet or health habits, which may also have influenced the lipid profile.

Clinical and research implications

It has been widely demonstrated that physical exercise has a modulating effect on the lipid profile in the non-pregnant population, resulting in a decrease in total and LDL and an increase in Remove the period after HDL.[47] which has a cardiovascular risk reduction effect.[48,49] Our findings regarding increased postpartum maternal HDL levels in patients who exercised during pregnancy may suggest a reduction in future cardiovascular risk in these women.

Moreover, maternal HDL has been linked to neonatal outcomes, particularly birth weight. Previously studies have reported an inverse relationship between HDL levels and the risk of large-for-gestational-age infants and macrosomia.[14,50] Additional evidence has linked maternal lipid profiles during pregnancy with adiposity in offspring during the first two years of life.[51] To better understand the implications of these findings and to evaluate the potential cardiovascular protective effects for both mother and child, larger-scale prospective studies with extended follow-up periods are warranted.

Conclusion

In low-risk pregnant women, a supervised exercise program may improve the lipid profile during pregnancy by potentially increasing HDL and decreasing LDL levels. These changes seem to remain after delivery but long-term follow-up studies are necessary to confirm our findings and to evaluate their impact on the mother's cardiovascular health and the newborn's health.

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Author Contributions

Aránzazu Martín-Arias served as the principal investigator. Aránzazu Martín-Arias, Maria M Gil, and Irene Fernandez-Buhigas were responsible for study conceptualization, design, manuscript preparation, and final submission. Miguel Sánchez-Polan and Cristina Silva-Jose designed and implemented the exercise program. Aránzazu Martín-Arias, Adriana Aquise, and Cristina Aramburu were involved in data collection and curation. Aránzazu Martín-Arias, Belén Santacruz, and Maria M Gil contributed to securing funding and financial support. Rebeca Bustos and Valeria Rolle were responsible for data curation and statistical analysis. All authors contributed to the interpretation of results and reviewed and approved the final manuscript.

Conflicts of Interest

None.

Editor Note

Maria M Gil is the editorial board members of *Maternal-Fetal Medicine*. The article was subject to the journal's standard procedures, with peer review handled independently of this editor and the associated research groups.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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