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Original Article

Fetal Growth and Adiposity of Infants Born Large for Gestational Age in Three Harmonized Randomized Trials

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Abstract

Objective Infants born large for gestational age (LGA) are at an increased risk of short- and longer-term adverse outcomes. Understanding fetal growth and adiposity and their trajectories may help inform interventions to prevent birth of LGA infants. We aimed to compare fetal growth and adiposity measures of infants born LGA with those born not LGA, to determine whether the discrepancy at birth was primarily due to larger size throughout gestation, or instead to different trajectories of fetal growth.

Study Design This was a secondary analysis of secondary outcomes of fetal growth and adiposity from three harmonized randomized trials—the LIMIT, GRoW, and Optimise randomized trials. These trials recruited women in early pregnancy, and a singleton gestation, from three major public metropolitan Adelaide maternity hospitals. Maternal body mass index (BMI) ranged from 18.5 to $\geq$40.0 kg/m^2. Data were obtained from enrolled women who underwent research ultrasounds at 28 and 36 weeks' gestation. Outcome measures were ultrasound measures of fetal biometry and adiposity.

Results Infants born LGA had larger fetal biometry measures, and higher growth trajectories, from 20 weeks' gestation. Fetal adiposity measures were consistently larger among infants born LGA and these differences increased over time. We did not find evidence that the differences in biometry and adiposity measurements varied according to maternal BMI.

Conclusion Infants born LGA had larger fetal biometry measures at all time points from 20 weeks' gestation, compared with infants born not LGA suggesting any interventions to prevent LGA likely need to commence earlier in pregnancy or prior to conception.

Keywords
- large for gestational age
- fetal growth
- fetal adiposity
- maternal overweight and obesity

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Key Points

- Infants born LGA had larger fetal biometry measures from 20 weeks' gestation.
- Infants born LGA had larger fetal adiposity measures.
- Interventions to prevent LGA need to start earlier in pregnancy or prior to conception.

Large for gestational age (LGA) infants are variably defined as those with a birth weight greater than the 90th, 95th, or 99th percentile for gestational age and sex. Most commonly, LGA infants are defined as those with a birth weight greater than the 90th percentile for gestational age and sex, when compared with a reference population. The incidence of infants born LGA is increasing, with some hypothesizing that this increase is driven by increasing rates of maternal overweight and obesity.[1–5] Infants born LGA are at increased risk of shoulder dystocia,[6,7] neonatal hypoglycemia,[7,8] and admission to the nursery.[7,8] Women who deliver an LGA infant are at an increased risk of cesarean birth[6,7] and postpartum hemorrhage.[7,8] Longer-term infants born LGA are at increased risk of abnormal infant and childhood growth patterns and obesity.[9–12]

Maternal overweight and obesity, defined as a body mass index (BMI) $\geq$ 25 and $\geq$30 kg/m^2, respectively, represents an independent risk factor for birth of an LGA infant.[3,13–15] Across developed nations, rates of maternal overweight and obesity are rapidly increasing, doubling over the past 20 years.[16,17] In Australia, approximately 50% of women entering pregnancy are overweight or obese.[18,19]

An understanding of fetal growth patterns of infants born LGA may facilitate targeted interventions to prevent aberrant growth. However, while fetal growth has been studied in infants born LGA to women with diabetes,[20–22] there is little published work on fetal growth of infants born LGA to women who do not have diabetes or among women who are overweight or obese.

This secondary analysis compared fetal growth and adiposity measures of infants born LGA to those born not LGA, in order to determine whether the discrepancy at birth was primarily due to a larger size throughout gestation or instead to different trajectories of growth. Additionally, the potential for these patterns to differ by maternal BMI was explored.

Methods

The Clinical Cohort

This analysis reports data from research ultrasounds of participants who underwent one or more ultrasounds in three harmonized randomized controlled trials (RCTs), the LIMIT,[23] GRoW,[24] and Optimise[25] RCTs. These three studies, from our research group, were designed using similar protocols with consistent definitions for baseline characteristics and pregnancy and birth outcomes. All trials enrolled women less than 20 weeks' gestation with singleton pregnancies. The LIMIT and GRoW RCTs included women with early pregnancy BMI of 25 kg/m^2 or more, and the Optimise RCT included women with early pregnancy BMI between 18.5 and 24.9 kg/m^2 inclusive. Maternal height and weight was measured, and BMI calculated, between 10$^{0/7}$ and 20$^{0/7}$ weeks' gestation in the three included trials. Data from women randomized to both standard care and intervention groups were combined from all three trials. The relationship between fetal growth and adiposity and LGA did not differ with respect to the effect of the trial interventions; thus, it was considered appropriate to use participants from both groups.

Briefly, women were recruited to one of the three harmonized RCTs between June 2008 and April 2017 in metropolitan Adelaide, South Australia. Study protocols were purposefully designed so that they were sufficiently similar to allow valid comparisons between them and data from the studies to be combined.

Over the time of recruitment of the three RCTs, local hospital and state guidelines for routine pregnancy care remained consistent,[26] with the exception of screening and diagnosis of gestational diabetes mellitus (GDM).[27] Prior to 2015, the local diagnostic criterion for GDM were a positive 75-g oral glucose tolerance test at 28 weeks' gestation with fasting blood glucose >5.5 mmol/L or 2 hours $\geq$ 7.8 mmol/L.[27] From 2015, Australian Diabetes in Pregnancy Society recommendations changed,[28] revised 75-g oral glucose tolerance test diagnostic criteria became one or more of fasting blood glucose $\geq$ 5.1 mmol/L, 1 hour $\geq$ 10.0 mmol/L, or 2 hours $\geq$ 8.5 mmol/L.[27,28] This change impacted women recruited to the GRoW and Optimise RCTs. Women diagnosed with GDM remained in the studies and were treated as per their treating hospital guidelines.[27] This did not include advice regarding gestational weight gain.

In all three trials, women were invited to attend for a research ultrasound at 28 (range: 26$^{0/7}$–29$^{6/7}$) and 36 (range: 34$^{0/7}$–37$^{6/7}$) weeks' gestation, with fetal measures obtained as described below. All research ultrasounds were performed by a medical practitioner with specialist or subspecialist training in obstetric ultrasound, blinded to the participant's allocated treatment group. A small number of women who underwent a clinical ultrasound during these gestational windows consented to provide their fetal biometry measurements and did not have a research ultrasound.

Antenatal Dietary and Lifestyle Intervention and Control

Women participating in the Lifestyle Advice group of the LIMIT and Optimise RCTs[25,29] received a comprehensive, tailored dietary and lifestyle intervention over the course of their pregnancy, administered by a research dietitian and trained research assistants. The dietary and lifestyle intervention has been described in detail elsewhere.[29,30]

Antenatal Metformin as an Adjuvant to Dietary and Lifestyle Intervention

All women participating in the GRoW RCT[24] received the dietary and lifestyle intervention referenced above.[23,30] Women in the study received either oral metformin tablets (500 mg) (Metformin group) or a placebo tablet (Placebo group), identical in taste and appearance. Women in both groups were instructed to take one tablet per day for the first week, increasing to a maximum of two tablets twice daily (maximum 2,000 mg daily) over 4 weeks as tolerated and continued throughout pregnancy.

Fetal Ultrasound Measures

An accurate gestational age and estimated date of confinement was calculated for each woman based on early pregnancy ultrasound and last menstrual period. Pregnant women are offered an early ultrasound at 11 to 14 weeks' gestation at which dating and nuchal translucency are done followed by a routine fetal anomaly scan at 18 to 20 weeks' gestation, in keeping with South Australian Perinatal Practice Guidelines,[26] and consented to providing results to the researchers. All women were invited for a research ultrasound at 28 (range: $26^{0/7}$–$29^{6/7}$) and 36 (range: $34^{0/7}$–$37^{6/7}$) weeks' gestation. A medical practitioner with specialist training in obstetric ultrasound performed all research ultrasounds and was blinded to the woman's allocated treatment group.

Fetal Biometry Measures

Fetal biometry measures collected from the routine fetal anomaly scan and the later research ultrasounds included standard measurements of head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL) in accordance with national and international standards of practice.[31] Biometry measures obtained from the research ultrasounds were converted into z-scores to allow for variation in gestational age and fetal sex, using recognized Australian population standards.[31–33] Estimated fetal weight (EFW) was calculated using the Hadlock C formula.[34]

Fetal Growth Velocities

Fetal growth velocities are presented as the difference between 28 and 36 weeks' measures, calculated as total change/actual number of days between measurements. Velocity z-scores were likewise calculated using recognized Australian population standards where available.[35]

Fetal Adiposity Measures

Fetal subcutaneous fat thickness measurements were obtained at both research ultrasounds. These measurements included mid-thigh lean mass (MTLM), mid-thigh fat mass (MTFM), abdominal fat mass (AFM), and subscapular fat mass (SSFM) and were obtained by methods described previously.[36–42] Mid-thigh total, lean and fat mass were obtained by taking a longitudinal view of the femur, then rotating the transducer through 90 degrees to obtain a cross-sectional view of the mid-thigh.[37,38] MTFM was measured by taking the total cross-sectional limb area (MTTM) and subtracting MTLM (consisting of the central lean area comprising muscle and bone). Fetal AFM was measured at the level of the AC, between fetal mid-axillary lines and anterior to the margins of the ribs.[36,37] This was measured in millimeters using magnification. The SSFM was obtained by a sagittal view of the fetal trunk, to view the entire longitudinal section of the scapula. The subcutaneous fat tissue measurement was taken at the level of the end of the scapula.[37] We have previously shown good interobserver variability for these measurements in a subset of women who participated in the LIMIT study.[41]

Definition of Large for Gestational Age

Infants were considered LGA if their birth weight was $>90^{th}$ percentile for gestational age and infant sex.[43]

Statistical Analysis

Baseline characteristics of women included in this secondary analysis were described for the combined cohort. Continuous variables were reported as means and standard deviations (SDs) or as medians and interquartile ranges if not normally distributed. Categorical variables were reported as frequencies and percentages.

Detectable Effect Calculation

The available sample size of 3,260 women comprised participants from all three studies with at least one a fetal ultrasound measure. The overall rate of LGA was 17.58%; 2,700 independent ultrasound measures participants would give 80% power (with two-sided alpha 0.05) to detect a difference of approximately 0.12 SD in fetal biometry and adiposity measures between LGA and non-LGA infants.

For combined LGA and time effects, simulation was used to determine the detectable difference in fetal measures at a single time point and change in this difference over time. With 2,700 observations, two time points, and an LGA rate of 17.58%, the simulations showed that there was >80% power to detect >0.1 SD between LGA and non-LGA and interaction effects between 0.5× and 0.75× those of the LGA effect.

Analysis 1: Two-Way Interaction Models

Differences in fetal biometry measures between LGA and non-LGA infants were investigated using linear regression models, with LGA, time, and their interaction. Generalized estimating equations (GEEs) were used to account for correlation due to repeated measures, and models were adjusted for maternal BMI, parity, age, intervention group, smoking status, and quintile of socioeconomic disadvantage. Results are presented as difference in means (LGA – non-LGA) and 95% confidence interval (CI) at each time point, as well as the *p*-value for the LGA-by-time interaction term.

Analysis 2: Three-Way Interaction Models

Based on the results of the two-way interaction analyses, three-way interaction analyses were performed to investigate whether the difference in fetal growth patterns between LGA and non-LGA infants varied according to maternal BMI. These analyses incorporated a three-way interaction between LGA status, time, and maternal BMI (as a continuous variable). The estimated difference between LGA and non-LGA, along with a test of LGA-by-time interaction, was derived at three different

levels of maternal BMI (22.0, 27.0, and 35.0 kg/m^2) and a test of the three-way interaction term was also performed.

Results

Participant Characteristics

We included data from 3,260 women, with baseline characteristics described in ►Table 1 and the number of women with available ultrasound data at each time point is presented in ►Supplementary Table S1 (available in the online version). The overall mean BMI at trial entry was 30.71 kg/m^2 (SD: 6.92 kg/m^2). The majority of women were in their second or subsequent pregnancy, were non-smokers, and were of Caucasian ethnicity. More than half of women were from two of the most socioeconomically disadvantaged quintiles of the Index of Relatively Socioeconomic Disadvantage.[44] These baseline demographics were similar to those of the three RCTs included.[24,25,29] There were 573 LGA infants (17.58%) born to women in this combined cohort.

Table 1 Baseline characteristics of women from LIMIT, GRoW, and Optimise randomized controlled trials who contributed research ultrasound data to the analysis of fetal growth

Characteristic	Overall cohort $N = 3,260$
BMI (kg/m^2): mean (SD)	30.71 (6.92)
BMI category: *N* (%)	
18.5–24.9	628 (19.26)
25.0–29.9	1,064 (32.64)
30.0–34.9	772 (23.68)
35.0–39.9	478 (14.66)
≥40.0	318 (9.75)
Age at trial entry: mean (SD)	29.92 (5.41)
Weight at trial entry: mean (SD)	83.58 (19.96)
Height at trial entry: mean (SD)	164.86 (6.68)
Multiparous: *N* (%)	1,849 (56.72)
Smoking status: *N* (%)	
Nonsmoker	2,848 (87.36)
Smoker	363 (11.13)
Missing	49 (1.50)
IRSD quintile: *N* (%)	
Q1	913 (28.01)
Q2	836 (25.64)
Q3	480 (14.72)
Q4	565 (17.33)
Q5	464 (14.23)
Ethnicity: *N* (%)	
Caucasian	2,770 (84.97)
Non-Caucasian	490 (15.03)
LGA: *N* (%)	573 (17.58)

Abbreviations: BMI, body mass index; IRSD, Index of Relative Socioeconomic Disadvantage[44]; LGA, large for gestational age; SD, standard deviation.

Fetal Biometry Measures

Results of the two-way interaction of LGA and timing of ultrasound analysis are presented in ►Table 2 below. Infants born LGA, in comparison to those born not LGA, were larger in all fetal growth measures, at all time points assessed, and these differences increased over time (►Table 2). The greatest differences in fetal biometry measures between infants born LGA, and those born not LGA, were seen for fetal AC measures at all time points (►Table 2). Calculated EFW, which is a function of the fetal biometry measures of BPD, HC, FL, and AC,[45] similarly was greater among infants born LGA, compared with those born not LGA, at both 28 and 36 weeks' gestation.

Fetal Growth z-Scores of Large for Gestational Age versus Not Large for Gestational Age Infants

In keeping with the above, fetal BPD, HC, FL, AC, and EFW z-sores were significantly greater among infants born LGA, compared with those born not LGA, at all time points assessed, and the difference increased over time (►Supplementary Table S2, available in the online version).

With the exception of fetal BPD z-score at 36 weeks' gestation among non-LGA infants [−0.04 [SD 1.15] cm], all z-scores were positive at all time points, indicating that, even among those infants not born LGA, fetuses were larger, on average, than the reference population[33] (data not shown), likely because of the comparatively disproportionate number of women included in this cohort who were overweight or obese. We have previously shown that these women consistently have mean fetal biometry z-scores greater than 0.[41]

Fetal Adiposity Measures of Large for Gestational Age versus Not Large for Gestational Age Infants

With the exception of AFM measures at 28 weeks' gestation (not LGA mean: 3.54 [SD: 1.00] mm vs. LGA mean 3.67 [SD 0.95] mm; estimated mean difference 0.08 [95% CI: −0.05, 0.21] mm; $p = 0.229$], all adiposity measures were statistically significantly greater among infants born LGA, compared with those born not LGA, at all time points, and these differences increased over time (►Table 3). The magnitude of estimated mean differences ranged from 0.12 mm (95% CI: 0.00, 0.24) for SSFM measurements at 28 weeks' gestation, up to 0.98 mm (95% CI: 0.68, 1.27) for MTLM measurements at 28 weeks' gestation (►Table 3).

Impact of Maternal Body Mass Index on Fetal Growth and Adiposity Measures among Infants Born Large for Gestational, versus Those born non-Large for Gestational Age

Fetal Biometry Measures and Fetal Biometry Measure z-Scores

Maternal BMI was not associated with further difference between fetal biometry measures or fetal biometry measures z-scores in infants born LGA, compared with those born not

Table 2 Fetal biometry measures of infants born large for gestational age versus those born not large for gestational age, at 20, 28, and 36 weeks' gestation

Measure (wk)	Not LGA mean (SD) cm	LGA mean (SD) cm	Estimate mean difference (95% CI)	*p*-Value
BPD				<0.001[a]
20	4.60 (0.33)	4.67 (0.34)	0.06 (0.03, 0.09)	<0.001
28	7.18 (0.42)	7.35 (0.43)	0.16 (0.12, 0.20)	<0.001
36	8.87 (0.39)	9.15 (0.35)	0.27 (0.23, 0.30)	<0.001
HC				<0.001[a]
20	17.09 (1.13)	17.38 (1.17)	0.25 (0.15, 0.36)	<0.001
28	26.43 (1.33)	27.02 (1.39)	0.55 (0.41, 0.68)	<0.001
36	32.02 (1.22)	32.84 (1.09)	0.78 (0.67, 0.89)	<0.001
FL				<0.001[a]
20	3.19 (0.29)	3.26 (0.28)	0.06 (0.03, 0.08)	<0.001
28	5.28 (0.32)	5.40 (0.34)	0.11 (0.08, 0.14)	<0.001
36	6.85 (0.32)	7.05 (0.30)	0.19 (0.16, 0.22)	<0.001
AC				<0.001[a]
20	15.14 (1.23)	15.57 (1.28)	0.35 (0.23, 0.47)	<0.001
28	24.36 (1.58)	25.49 (1.72)	1.05 (0.88, 1.21)	<0.001
36	32.28 (1.70)	34.39 (1.91)	2.02 (1.83, 2.20)	<0.001
EFW				<0.001[a]
28	1248.15 (215.33)	1390.21 (253.48)	131.99 (107.78, 156.20)	<0.001
36	2813.16 (355.66)	3258.66 (399.93)	435.44 (396.66, 474.22)	<0.001

Abbreviations: AC, abdominal circumference; BPD, biparietal diameter; CI, confidence interval; EFW, estimated fetal weight; FL, femur length; HC, head circumference; LGA, large for gestational age; SD, standard deviation.
[a]*p*-Value for the interaction term.

Table 3 Fetal adiposity measures in infants born large for gestational age versus those born not large for gestational age

Measure (wk)	Not LGA mean (SD) mm	LGA mean (SD) mm	Estimate mean difference (95% CI)	*p*-Value
MTLM (cm^2)				0.003[a]
28	4.82 (1.04)	5.34 (1.07)	0.50 (0.36, 0.64)	<0.001
36	8.80 (1.93)	9.79 (2.07)	0.98 (0.68, 1.27)	<0.001
MTFM (cm^2)				<0.001[a]
28	4.46 (1.19)	5.06 (1.35)	0.58 (0.41, 0.75)	<0.001
36	10.74 (2.74)	12.76 (3.42)	2.01 (1.53, 2.48)	<0.001
AFM (mm)				<0.001[a]
28	3.54 (1.00)	3.67 (0.95)	0.08 (-0.05, 0.21)	0.229
36	5.46 (1.58)	6.32 (1.72)	0.80 (0.57, 1.04)	<0.001
SSFM (mm)				<0.001[a]
28	3.16 (0.85)	3.36 (0.95)	0.12 (0.00, 0.24)	0.047
36	4.89 (1.38)	5.55 (1.60)	0.59 (0.38, 0.79)	<0.001

Abbreviations: AFM, abdominal fat mass; CI, confidence interval; LGA, large for gestational age; MTFM, mid-thigh fat mass; MTLM, mid-thigh lean mass; SD, standard deviation; SSFM, subscapular fat mass.
[a]*p*-Value for the interaction term.

LGA (►**Supplementary Table S3**, available in the online version)

Fetal Adiposity Measures

Again, increasing maternal BMI was not associated with further differences seen between fetuses born LGA, compared with those born not LGA, with regard to fetal adiposity measures shown (►**Supplementary Table S4**, available in the online version).

Discussion

Main Findings

Our findings suggest infants born LGA have larger fetal biometry measures, and higher growth trajectories, evident from 20 weeks' gestation. Similarly, fetal adiposity measures are consistently larger among infants born LGA and these differences increase over time. We did not find evidence that the differences in biometry and adiposity measurements, including changes in magnitude over time, varied according to maternal BMI.

Strengths and Limitations

There are many strengths to our work. These results come from a large, prospectively collected cohort of women. While the included women were from multiple trials, they represent a cohort of women whose pregnancies were managed similarly, allowing for such cross-study work to be carried out. Additionally, our work allows consideration of the effect of maternal BMI on fetal growth and fetal growth trajectories, across the BMI spectrum. We acknowledge, however, that this is a secondary analysis only, and the results should be considered with caution.

Interpretation

These findings add to the growing body of evidence that fetal growth and growth trajectories are "set" from early in pregnancy, and that infants born LGA exhibit differences early. Wong et al showed that fetal AC z-scores of infants born LGA were larger on average than those of infants not born LGA, from as early as 18 weeks' gestation.[46] Higher fetal growth rate between the first and second trimester has been associated with an increased risk of infant birth weight greater than 4,500 g or greater than 2 SDs above the mean.[47] Taken together, these findings suggest differences in fetal growth may be evident from as early as the first trimester of pregnancy.

Previous work investigating altered fetal growth and fetal growth trajectories among infants born LGA have focused on fetal AC measurements. Madendag et al showed that infants born LGA had greater mean AC, and thus EFW, measurements at 26 to 28 weeks' gestation.[48] Similarly, Caradeux et al have shown both fetal AC z-score and AC z-score velocity are predictive of risk of birth of LGA infants.[49] However, the analyses presented here considered all fetal biometry measures and have shown significant differences in all measures of fetal growth from as early as 20 weeks' gestation, suggesting fetal skeletal, organ, and adipose tissue growth is impacted by factors contributing to LGA.

These data represent the largest cohort of women who have had longitudinal scans assessing fetal adiposity measures. Interestingly, these results are in agreement with smaller research cohorts. Among a group of 702 Chinese women who had fetal biometry and adiposity measures performed at 28 and 36 weeks' gestation, Chen et al defined population and ethnicity-specific reference ranges for AFM and SSFM measures.[50] The mean AFM measurements among both LGA and not LGA infants in these analyses were significantly larger than the mean AFM measurements in the Chinese population at both 28 and 36 weeks' gestation.[50] The SSFM measurements among infants born not LGA in these analyses were closer to the population mean SFMM presented by Chen et al; however, the mean SSFM measurements among infants born LGA in our population were larger than the population mean's presented by Chen et al at 28 and 36 weeks' gestation.[50] The differences in our findings compared the study by Chen et al[50] are likely explained by differences in the populations providing data. Women in our study were predominantly Caucasian ($n = 2{,}770$; 84.97%), and mean maternal BMI was 30.71 kg/m^2. In comparison, the population recruited by Chen et al were women of Asian ethnicity, all with a normal BMI (18.5–24.9 kg/m^2).[50]

With regard to fetal subcutaneous tissue thickness measurements, most interest in the literature has focused on AFM measurements and the utility of this measurement in predicting birth weight and risk of LGA infants.[36,51–53] AFM measures taken during the third trimester have only variably been associated with birth weight and neonatal adiposity.[54–56] This suggests that fetal AFM measurements may not be the most reliable fetal subcutaneous tissue measurement for defining a fetal population at increased risk of being born LGA, and additional work on other fetal subcutaneous tissue measurements, and overall fetal body composition, are required.

Being born LGA represents an independent risk factor for childhood obesity[57] and may lie on the causal pathway of the intergenerational cycle of obesity.[58] There has been significant interest in the published literature on prevention of LGA birth by antenatal interventions, usually commenced after the first trimester.[24,25,29,59,60] The findings of this current study, that is accelerated growth trajectories of infants born LGA were observed as early as 20 weeks' gestation, provides insight into why antenatal interventions have thus far been ineffective at preventing LGA.

Conclusions and Future Work

Infants born LGA show increased fetal biometry and adiposity measures and increased growth trajectories, from as early as 20 weeks' gestation. Antenatal interventions to prevent LGA have potentially started too late to alter fetal growth and growth trajectories. Preconception interventions are an important next step.

Authors' Contribution

Each author fulfills the requirements for authorship. J.M. D. and A.R.D. were involved in the study concept and design of the trials, supervision of conduct of the trial, and acquisition of data. A.J.P developed the concept of this

exploratory analysis. A.J.P., J.L., A.R.D., and J.M.D. were involved equally in the analysis and interpretation of data, critical review of the manuscript, and provided approval of the final submitted version. JL was responsible for conducting the statistical analysis. A.J.P. drafted the manuscript, had full access to all of the study data, and takes responsibility for the integrity of the data, and the accuracy of the data analysis.

Ethics Approval

The study protocols were approved by the Women's and Children's Health Network Human Research and Ethics Committee (LIMIT randomised trial—REC numbers 1839 [main study] and 2051 [ancillary studies including ultrasound]; GRoW randomised trial—HREC/12/WCHN/114; Optimise randomised trial—HREC/13/WCHN/152) with local institutional approval at each site. The trials are registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12607000161426, ACTRN12612001277831, ACTRN12614000583640).

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Clinical Trials Registrations

Australian and New Zealand Clinical Trials Registry: LIMIT—ACTRN12607000161426; GRoW—ACTRN12612001277831; Optimise—ACTRN12614000583640.

Conflict of Interest

None declared.

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