Repeat Antenatal Betamethasone and Cardiometabolic Outcomes

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abstract

BACKGROUND: Repeat dose(s) of antenatal betamethasone are recommended for women at <32 weeks with ongoing risk of preterm birth. However, there is concern that use of repeat dose(s) in fetal growth restriction (FGR) may increase the risk of later cardiometabolic disease.

METHODS: We undertook secondary analysis of data from the Australasian Collaborative Trial of Repeat Doses of Corticosteroids Midchildhood Outcome Study to determine if FGR influences the effect of repeat betamethasone on growth and cardiometabolic function. At 6 to 8 years, children underwent anthropometry, dual energy x-ray absorptiometry, intravenous glucose tolerance testing, ambulatory blood pressure monitoring, and spirometry. FGR was defined as severe FGR at entry, cesarean delivery for FGR, or customized birth weight below the third centile.

RESULTS: Of 266 children assessed, FGR occurred in 43 of 127 (34%) exposed to repeat betamethasone and 44 of 139 (32%) exposed to placebo. There was an interaction between FGR and repeat betamethasone treatment for the effect on height (*z* score mean difference [95% confidence interval]; FGR: 0.59 [0.01 to 1.17]; non-FGR: −0.29 [−0.69 to 0.10]; P = .01). However, FGR did not influence the effect of repeat betamethasone on cardiometabolic function, which was similar in treatment groups, both in FGR and non-FGR subgroups.

CONCLUSIONS: Repeat antenatal betamethasone treatment had no adverse effects on cardiometabolic function, even in the presence of FGR. It may have a positive effect on height in FGR. Clinicians should use repeat doses of antenatal corticosteroids when indicated before preterm birth, regardless of FGR, in view of the associated neonatal benefits.

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Mr Cartwright conducted the initial analyses and drafted the manuscript; Drs Harding, Crowther, Cutfield, and Battin conceptualized and designed the study, obtained funding, and contributed to the interpretation of data; Dr Dalziel conceptualized and designed the study and contributed to the interpretation of data; Dr McKinlay conceptualized and designed the study, obtained funding, conducted the initial analyses, and drafted the manuscript; and all authors revised the manuscript and approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Repeat dose(s) of antenatal betamethasone are recommended for women at <32 weeks with ongoing risk of preterm birth, but there is concern that use of repeat dose(s) in fetal growth restriction (FGR) may increase the risk of later cardiometabolic disease.

WHAT THIS STUDY ADDS: Repeat antenatal betamethasone treatment had no adverse effects on cardiometabolic function in midchildhood, even in FGR, but may have a positive effect on height in FGR. Repeat dose(s) are recommended for preterm birth, when indicated, regardless of FGR.

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Antenatal corticosteroid therapy is one of the most effective interventions for preterm birth, resulting in rapid maturation of fetal organ systems.[1] The Australasian Collaborative Trial of Repeat Doses of Corticosteroids (ACTORDS) revealed that neonatal benefit is greatest when antenatal corticosteroids are administered in repeat doses,[2] a finding supported by authors of systematic reviews[3] and animal studies.[4,5] Repeat doses can be used to reduce the incidence and severity of preterm lung disease and other serious neonatal morbidity, with absolute benefits similar to that of an initial course of antenatal corticosteroids.[2] Detailed follow-up of children in the ACTORDS at 2 and 6 to 8 years of age has revealed that repeat dose(s) of betamethasone given at intervals 7 days or more if there is ongoing risk of preterm birth within the next week are safe with no adverse effects on growth, neurodevelopment, behavior, learning, general health, lung function, bone mass, blood pressure, body composition, renal function, and glucose homeostasis.[6–9]

However, concern remains about whether it is safe to expose fetuses with growth restriction to repeat doses of corticosteroids, particularly because fetal growth restriction (FGR) is associated with an increased risk of cardiometabolic disease,[10] and increased exposure to maternal corticosteroids has been postulated as an underlying mechanism.[11] In addition, animal studies have revealed adverse effects of repeat antenatal corticosteroids on later cardiometabolic and lung function (effects that were most apparent in animals with FGR).[12–15] Further, in an observational study, antenatal corticosteroid exposure in early FGR was associated with an increased risk of short stature in childhood.[16]

No randomized trials have specifically evaluated the efficacy and safety of repeat antenatal corticosteroid therapy in FGR. Therefore, we undertook a secondary analysis of the ACTORDS data to determine the influence of FGR on the effects of repeat doses of antenatal betamethasone on growth and cardiometabolic function in midchildhood.

METHODS

ACTORDS

The ACTORDS (international standard randomized controlled trial number 48656428) was a placebo-controlled, double-blind, randomized trial of repeat antenatal betamethasone treatment conducted at 23 collaborating hospitals across Australia and New Zealand.[2] Women with a single, twin, or triplet pregnancy were eligible if they were <32 weeks' gestation, had ongoing risk of preterm birth, and had received a single course of antenatal corticosteroids ≥7 days before trial entry. Exclusion criteria included chorioamnionitis requiring urgent delivery, labor at the second stage, mature fetal lung development, or further corticosteroid therapy that was considered essential.

A total of 982 women (1146 fetuses) were randomly assigned, via a central telephone service, to either the repeat betamethasone (Celestone Chronodose, comprising 7.8 mg betamethasone sodium phosphate and 6 mg betamethasone acetate; Schering-Plough, Sydney, Australia) or the masked saline placebo. Treatment was repeated each week if a woman was judged to be at continued risk of preterm birth, up to 32 weeks' gestation.

Repeat antenatal betamethasone therapy was associated with neonatal benefit, including clinically important reductions in respiratory distress syndrome (RDS), severe lung disease, and other combined serious morbidity.[2] At the 2 years' corrected age, neurodevelopment, growth and general health were similar between groups.[6] Before the completion of the 2-year follow-up, midchildhood follow-up was planned because of concerns of the potential for long-term adverse effects of fetal corticosteroid exposure.

Midchildhood Outcomes Study

All surviving children of mothers who had participated in and remained in the ACTORDS were invited to partake in a study of neurocognitive function, growth, and general health, including spirometry (EasyOne 2001; New Diagnostic Designs Technologies, Zurich, Switzerland), at 6 to 8 years' corrected age.[7] In addition, children who were assessed in New Zealand were also invited to participate in a more detailed study of cardiometabolic function, as previously described.[8,9] This included the measurement of body composition by whole-body dual energy radiograph absorptiometry (DXA), glucose and insulin function by a frequently sampled intravenous glucose tolerance test with Minimal Modeling (MinimalModel, version 6.02), renal function by estimated creatinine clearance, and 24-hour ambulatory blood pressure (AMBP) monitoring (Spacelabs 90217; Spacelabs Healthcare Co, Issaquah, WA). These assessments were conducted throughout New Zealand by a single team of investigators, blinded to treatment allocation. Children with severe disability or who could not assent to testing were excluded from the cardiometabolic studies. Assessment of body composition was limited to 2 centers (Auckland and Christchurch) so that DXA measurements could be performed on identical instruments (Lunar Prodigy; General Electric Healthcare, Madison, WI). Ethical approval was obtained from the New Zealand Multicentre Ethics Committee. Written informed consent was obtained from

caregivers at follow-up, and assent was sought from the children.

In this study, we hypothesized that exposure to repeat antenatal corticosteroids, compared with a single dose, would have an adverse effect on growth, cardiometabolic risk factors, bone mass, and lung function at 6 to 8 years' corrected age in children with FGR but not children with normal prenatal growth.

Statistical Analysis

Children who underwent 1 or more tests of cardiometabolic function at 6 to 8 years' corrected age were included in this secondary analysis of data from the New Zealand ACTORDS Midchildhood Outcomes Study. The prespecified outcomes for this analysis were age- and sex-specific *z* scores for height, weight, and BMI; whole-body fat and lean mass, regional fat mass (android and gynoid), and limb lean mass; whole-body bone mineral content and area; fasting plasma glucose and insulin concentrations, and Minimal Model estimates of insulin sensitivity, acute insulin release, and disposition index; height-specific *z* scores for daytime and nighttime systolic and diastolic AMBP and percentage diurnal dip; plasma creatinine concentration and estimated glomerular filtration rate; and height- and sex-specific *z* scores for forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio, and mean forced expiratory flow at 25% to 75% of FVC (FEF25-75).

FGR was defined a priori as 1 or more of the following: obstetric diagnosis of FGR at trial entry, cesarean delivery for FGR, or having a customized birth weight less than the third centile (version 6.7.8.3; Perinatal Institute, Birmingham, United Kingdom). Although this definition includes postrandomization factors, we felt that this was important because antenatal diagnosis of FGR substantially underrepresents the true incidence of FGR in the preterm population.[17,18] Customized birth weight centiles, which are based on fetal growth curves, were used because these have been shown to improve detection of FGR.[19,20] Although infants exposed to repeat doses in the ACTORDS had slightly lower birth weight *z* scores, meta-analysis has revealed that repeat doses do not increase the risk of being small for gestational age.[3]

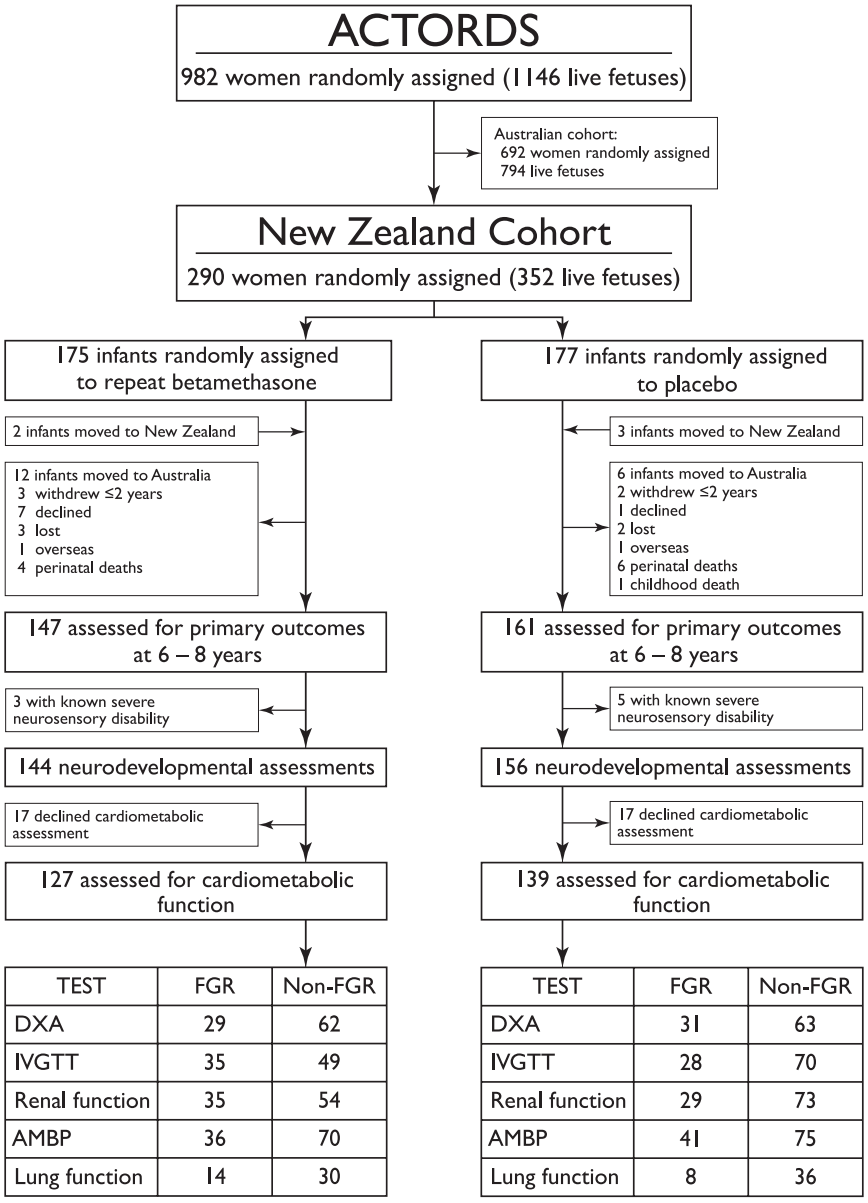
Analysis was performed by using SAS (version 9.4; SAS Institute, Inc, Cary, NC). Data are presented as number (percent), mean (SD), or median (interquartile range). Treatment groups were compared for the prespecified outcomes by using generalized linear models with adjustment for sex and gestational age at trial entry and clustering of children from multiple pregnancy by generalized estimating equations. Body composition data were additionally adjusted for current height. The influence of FGR on treatment effect was assessed by an interaction test. Treatment effects within subgroups (FGR and non-FGR) are reported as either mean difference (MD) for normally distributed data or ratio of geometric means (RGM) for positively skewed data, with 95% confidence intervals (CIs).

RESULTS

Of the 323 surviving children eligible for follow-up in New Zealand, 308 were assessed at 6 to 8 years' corrected age, of whom 266 underwent 1 or more tests of cardiometabolic function (repeat betamethasone 127; placebo 139; Fig 1). Children who did not complete any tests of cardiometabolic function, compared with those who were assessed, had lower birth weight *z* scores, and their mothers were more likely to be multiparous but were similar for other baseline characteristics (Supplemental Table 5).

Of the 266 children included in this analysis, the rate of FGR was similar between those exposed to repeat betamethasone (34%) and placebo (32%). In the FGR subgroup, those randomly exposed to repeat betamethasone were more likely than those exposed to placebo to have received ≥4 trial treatments (repeat betamethasone 10 of 43 [27.0%]; placebo 1 of 44 [2.9%]; $P = .007$) and had a longer gestation (repeat betamethasone mean [SD]: 31.8 [2.7] weeks; placebo mean [SD]: 30.6 [2.7] weeks; $P = .03$). Repeat betamethasone therapy reduced the severity of neonatal lung disease and the need for surfactant therapy (Table 1). In the non-FGR subgroup, there were no differences in baseline characteristics between children randomly exposed to repeat betamethasone or placebo, and, again, repeat betamethasone therapy reduced the incidence of RDS and severity of neonatal lung disease (Table 1).

The FGR subgroup, compared with non-FGR, was characterized by older maternal age (FGR mean [SD]: 32.4 [5.4] years; non-FGR mean [SD]: 30.7 [5.6] years; $P = .03$), higher maternal BMI (FGR mean [SD]: 28.7 [6.9]; non-FGR mean [SD]: 25.8 [5.7]; $P = .004$), later gestational age at trial entry (FGR mean [SD]: 28.9 [2.0] weeks; non-FGR mean [SD]: 28.2 [2.3] weeks; $P = .02$), and increased rates of multiple pregnancy (FGR: 25 of 72 [35.0%]; non-FGR: 28 of 159 [18.0%]; $P = .007$) and preeclampsia (FGR: 31 of 72 [43.0%]; non-FGR: 18 of 159 [11.0%]; $P \leq .001$) (Table 1). The FGR subgroup, compared with non-FGR, had a shorter gestation (FGR mean [SD]: 31.2 [2.7] weeks; non-FGR mean [SD]: 32.1 [3.9] weeks; $P = .03$), lower birth weight *z* score (FGR mean [SD]: −1.1 [0.8]; non-FGR mean [SD]: 0.1 [0.8]; $P \leq .001$), and an increased rate of serious neonatal morbidity (FGR: 28 of 87 [32.0%]; non-FGR: 36 of 179 [20.0%]; $P = .03$) (Table 1).



TEST	FGR	Non-FGR
DXA	29	62
IVGTT	35	49
Renal function	35	54
AMBP	36	70
Lung function	14	30

TEST	FGR	Non-FGR
DXA	31	63
IVGTT	28	70
Renal function	29	73
AMBP	41	75
Lung function	8	36

FIGURE 1
Profile of participants assessed for cardiometabolic function at midchildhood. IVGTT, intravenous glucose tolerance test.

For childhood height, there was a significant interaction between repeat antenatal betamethasone therapy and FGR. In the FGR subgroup, children exposed to repeat betamethasone had larger height *z* scores than children exposed to placebo; no significant difference was seen between treatment groups in the non-FGR subgroup (FGR height *z* score MD: 0.59; 95% CI: 0.01 to 1.17; non-FGR MD: −0.29; 95% CI: −0.69 to 0.10; $P = .01$ for interaction). In post hoc analysis, this interaction remained significant after adjustment for ethnicity and maternal height (Table 2).

For all other cardiometabolic outcomes, treatment groups were similar, both in the FGR and non-FGR subgroups, with no evidence of an interaction effect. This included fat mass (whole body, android, gynoid), lean mass (whole-body, limb), bone mass (whole body bone mineral content and bone area) (Table 2); fasting glucose and insulin concentrations, and Minimal Model estimates for glucose and insulin kinetics (insulin sensitivity, acute insulin release, and disposition index) (Table 3); plasma creatinine concentration, estimated glomerular filtration rate, and AMBP (daytime systolic and diastolic and nighttime systolic and diastolic *z* scores and diurnal systolic and diastolic percentage dip) (Table 3); and lung function (FEV1, FEV1/FVC, and FEF25-75 *z* scores) (Table 4).

In post hoc analysis, additional adjustment for maternal smoking during pregnancy and the number of trial treatments administered did not alter results.

DISCUSSION

In this secondary analysis of data from the New Zealand ACTORDS Midchildhood Outcomes Study, we found that among children with FGR, exposure to repeat antenatal betamethasone was associated with increased height at midchildhood by ~0.5 SD, an effect not seen in children without FGR. Exposure to repeat antenatal betamethasone did not alter any other measures of cardiometabolic function in those with and without FGR.

FGR is associated with reduced height in childhood and adulthood, both in preterm- and term-born subjects.[21] This was particularly evident in the placebo group, in which children with FGR were >1 SD shorter in midchildhood than children without FGR. Contrary to our hypothesis, repeat betamethasone treatment appeared to have a positive effect on midchildhood height in children with FGR. Although we cannot exclude the possibility of a type 1 error, authors of previous studies have suggested that antenatal corticosteroid treatment may influence skeletal growth.[22,23] In the Auckland Steroid Trial, a single course of antenatal betamethasone compared with placebo was

TABLE 1 Characteristics of Children, Assessed for Cardiometabolic Function at Midchildhood, and Their Mothers

	FGR Subgroup			Non-FGR Subgroup		
	Total	Repeat Betamethasone Trial Intervention	Placebo Trial Intervention	Total	Repeat Betamethasone Trial Intervention	Placebo Trial Intervention
Maternal characteristics	*n* = 72	*n* = 37	*n* = 35	*n* = 159	*n* = 75	*n* = 84
Age, y	32.4 (5.4)[a]	32.3 (5.9)	32.5 (4.8)	30.7 (5.6)	30 (5.5)	31.3 (5.7)
Height, cm	162.9 (6.5)	163.8 (6.9)	161.8 (5.9)	164.5 (6.8)	164.4 (6.9)	164.5 (6.8)
BMI	28.7 (6.9)[a]	28.5 (7.4)	28.9 (6.4)	25.8 (5.7)	26.1 (5.6)	25.5 (5.9)
Parity						
0	36.1% (26)	40.5% (15)	31.4% (11)	37.1% (59)	42.7% (32)	32.1% (27)
1–3	48.6% (35)	43.2% (16)	54.3% (19)	54.1% (86)	50.7% (38)	57.1% (48)
≥4	15.3% (11)	16.2% (6)	14.3% (5)	8.8% (14)	6.7% (5)	10.7% (9)
Multiple pregnancy	34.7% (25)[a]	27.0% (10)	42.9% (15)	17.6% (28)	16.0% (12)	19.0% (16)
Smoking during pregnancy	22.2% (16)	27.0% (10)	17.1% (6)	34.0% (54)	28.0% (21)	39.3% (33)
Gestational age at trial entry, wk	28.9 (2)[a]	28.9 (1.9)	28.9 (2.1)	28.2 (2.3)	28.2 (2.3)	28.2 (2.3)
Main reasons for risk of preterm birth[b]						
Preterm prelabor rupture of membranes	13.9% (10)	16.2% (6)	11.4% (4)	35.2% (56)	33.3% (25)	36.9% (31)
Preterm labor	6.9% (5)[a]	8.1% (3)	5.7% (2)	20.8% (33)	24.0% (18)	17.9% (15)
Severe FGR	36.1% (26)[a]	35.1% (13)	37.1% (13)	0.0% (0)	0.0% (0)	0.0% (0)
Preeclampsia	43.1% (31)[a]	40.5% (15)	45.7% (16)	11.3% (18)	12.0% (9)	10.7% (9)
Cervical incompetence	4.2% (3)	2.7% (1)	5.7% (2)	8.8% (14)	10.7% (8)	7.1% (6)
Antepartum hemorrhage	5.6% (4)[a]	8.1% (3)	2.9% (1)	29.6% (47)	32.0% (24)	27.4% (23)
Multiple pregnancy	4.2% (3)	2.7% (1)	5.7% (2)	5.0% (8)	8.0% (6)	2.4% (2)
Other	26.4% (19)[a]	24.3% (9)	28.6% (10)	12.6% (20)	6.7% (5)	17.9% (15)
No. trial treatments						
1	52.8% (38)	45.9% (17)	60.0% (21)	44.0% (70)	41.3% (31)	46.4% (39)
2 or 3	31.9% (23)	27.0% (10)	37.1% (13)	39.0% (62)	41.3% (31)	36.9% (31)
≥4	15.3% (11)	27.0% (10)[c]	2.9% (1)	17.0% (27)	17.3% (13)	16.7% (14)
Infant baseline characteristics	*n* = 87	*n* = 43	*n* = 44	*n* = 179	*n* = 84	*n* = 95
Sex, female	44.8% (39)	51.2% (22)	38.6% (17)	44.1% (79)	44.0% (37)	44.2% (42)
Ethnicity[d]						
Māori	29.9% (26)	30.2% (13)	29.5% (13)	27.9% (50)	28.6% (24)	27.4% (26)
Pacific peoples	14.9% (13)	23.3% (10)	6.8% (3)	10.6% (19)	9.5% (8)	11.6% (11)
Other non-European	6.9% (6)	9.3% (4)	4.5% (2)	5.6% (10)	7.1% (6)	4.2% (4)
European	48.3% (42)	37.2% (16)	59.1% (26)	55.9% (100)	54.8% (46)	56.8% (54)
Main neonatal outcomes						
Gestational age at birth, wk	31.2 (2.7)[a]	31.8 (2.6)[c]	30.6 (2.7)	32.1 (3.9)	31.9 (4.0)	32.2 (3.8)
Birth weight, g	1354 (454)[a]	1450 (446)	1260 (447)	1926 (813)	1905 (887)	1945 (745)
Birth weight *z* score	−1.1 (0.8)[a]	−1.0 (0.8)	−1.1 (0.9)	0.1 (0.8)	0.1 (0.9)	0.2 (0.7)
RDS[e]	43.7% (38)	34.9% (15)	52.3% (23)	40.2% (72)	29.8% (25)[c]	49.5% (47)
Severity of neonatal lung disease[f]		[c]			[c]	
Severe	12.6% (11)	4.7% (2)	20.5% (9)	12.8% (23)	7.1% (6)	17.9% (17)
Moderate	18.4% (16)	23.3% (10)	13.6% (6)	16.8% (30)	10.7% (9)	22.1% (21)
Mild	41.4% (36)	34.9% (15)	47.7% (21)	36.9% (66)	47.6% (40)	27.4% (26)
None	27.6% (24)	37.2% (16)	18.2% (8)	33.5% (60)	34.5% (29)	32.6% (31)
Mechanical ventilation	71.3% (62)	62.8% (27)	79.5% (35)	64.2% (115)	61.9% (52)	65.3% (62)
Oxygen therapy	60.9% (53)	55.8% (24)	65.9% (29)	55.9% (100)	50.0% (42)	61.1% (58)
Surfactant	27.6% (24)	16.3% (7)[c]	38.6% (17)	26.3% (47)	21.4% (18)	30.5% (29)
Serious neonatal morbidity[g]	32.2% (28)[a]	25.6% (11)	38.6% (17)	20.1% (36)	14.3% (12)	25.3% (24)

Data are percent (number) and mean (SD).

[a] $P < .05$ for comparison between subgroups (Fisher's exact test or *t* test).

[b] At trial entry; not mutually exclusive.

[c] $P < .05$ for comparison between trial intervention groups within subgroup (Fisher's exact test or *t* test).

[d] Ethnicity prioritized in order of Maori, Pacific, other non-European, and European.

[e] Defined as clinical signs of RDS and a ground glass appearance on chest radiograph.

[f] Defined as mild (mean airway pressure <7 cm water or fractional inspired oxygen <0.4), moderate (mean airway pressure 7 to <10 cm water or fractional inspired oxygen 0.40–0.79), or severe (mean airway pressure ≥10 cm water or fractional inspired oxygen ≥0.80).

[g] Defined as 1 or more of air leak syndrome, patent ductus arteriosus, need for oxygen at 36 wk postmenstrual age, severe intraventricular hemorrhage (grade 3 or 4), periventricular leukomalacia, proven necrotizing enterocolitis, or retinopathy of prematurity.

TABLE 2 Anthropometry and Body Composition at Midchildhood of Children Exposed to Repeat Betamethasone or Placebo

Outcome	Subgroup	Repeat Betamethasone	*n*	Placebo	*n*	Treatment Effect: MD or RGM[a] (95% CI)	*P*
Anthropometry, mean (SD)							
Height *z* score	FGR	0.16 (1.15)	42	−0.45 (1.40)	44	0.59 (0.01 to 1.17)	.01
	Non-FGR	0.28 (1.26)	84	0.57 (1.23)	95	−0.29 (−0.69 to 0.10)	
Wt *z* score	FGR	−0.04 (1.30)	43	−0.39 (1.73)	44	0.30 (−0.35 to 0.96)	.16
	Non-FGR	0.33 (1.39)	84	0.57 (1.12)	95	−0.23 (−0.63 to 0.17)	
BMI *z* score	FGR	−0.18 (1.27)	42	−0.06 (1.39)	44	−0.18 (−0.77 to 0.96)	.76
	Non-FGR	0.29 (1.28)	84	0.35 (1.10)	95	−0.06 (−0.43 to 0.30)	
DXA body composition, median (interquartile range)							
Fat mass, whole body, kg	FGR	3.65 (2.60–6.22)	29	3.34 (1.72–5.14)	31	0.82 (0.64 to 1.05)[a]	.22
	Non-FGR	3.84 (2.44–6.33)	62	4.09 (2.77–7.16)	63	1.05 (0.88 to 1.25)[a]	
Fat mass, android, kg	FGR	200.1 (175.5–402.9)	29	194.1 (118.3–492.3)	31	0.84 (0.62 to 1.13)[a]	.33
	Non-FGR	228.0 (156.5–399.4)	62	244.8 (170.2–578.4)	63	1.04 (0.83 to 1.30)[a]	
Fat mass, gynoid, kg	FGR	963.2 (678.5–1419.4)	29	830.6 (509.5–1225.9)	31	0.86 (0.71 to 1.05)[a]	.19
	Non-FGR	949.6 (667.2–1459.0)	62	983.1 (696.6–1592.3)	63	1.06 (0.92 to 1.21)[a]	
Lean mass, whole body, kg	FGR	19.3 (16.4–20.8)	29	17.4 (15.6–20.2)	31	0.95 (0.91 to 1.00)[a]	.27
	Non-FGR	19.1 (16.5–22.4)	62	20.5 (17.8–23.6)	63	0.99 (0.96 to 1.01)[a]	
Lean mass, limbs, kg	FGR	7.14 (5.94–8.59)	29	6.47 (5.35–7.81)	31	0.95 (0.89 to 1.01)[a]	.23
	Non-FGR	7.10 (5.84–8.61)	62	7.71 (6.40–9.37)	63	1.00 (0.95 to 1.04)[a]	
Bone mineral content, whole body, g	FGR	876 (762–1025)	29	791 (661–1011)	31	0.94 (0.88 to 1.01)[a]	.41
	Non-FGR	843 (702–1018)	62	897 (792–1142)	63	0.98 (0.94 to 1.03)[a]	
Bone area, whole body, cm^2	FGR	1058 (934–1192)	29	969 (853–1116)	31	0.97 (0.92 to 1.01)[a]	.44
	Non-FGR	1039 (894–1168)	62	1085 (946–1261)	63	1.00 (0.97 to 1.03)[a]	

[a] Adjusted for gestational age at trial entry and sex. Body composition comparisons were also adjusted for height. *P* value is for the test of interaction.

associated with a greater proportion of adult stature in the lower body segment,[24] although, in this trial and in a similar observational study of moderate-to-late preterm birth, antenatal corticosteroid exposure was not associated with altered final height.[25] Nevertheless, in a cohort study of adolescents with very low birth weight, adolescents exposed to antenatal corticosteroids were ∼0.3 SD taller, even after adjustment for confounding factors.[26]

Delayed onset of puberty, leading to a prolonged period of accelerated appendicular growth, has been proposed as 1 possible explanation for these changes,[8] as suggested in 1 trial.[27] However, with our study, we aimed to assess children before pubarche.[9] Premature adrenarche, which is more common in children born small for gestation age, could lead to an increase in linear growth velocity, but all children were carefully examined, and none had confirmatory signs, apart from several who had also commenced puberty (Tanner stage 1).[9] Childhood obesity may also accelerate linear growth,[28] but, in this cohort, FGR was associated with lower rather than increased BMI and fat mass.

There is ongoing debate about the long-term health effects of catch-up growth in preterm infants. Infants with growth restriction who do not exhibit catch-up growth during the neonatal period are more likely to have permanent short stature[21] and subnormal cognitive function in adulthood.[29] Conversely, human and animal studies have revealed an association between rapid catch-up growth during infancy and increased risk of cardiometabolic disease in later life.[30–34] Infants with FGR are predisposed to insulin resistance and central obesity, and these changes may be exacerbated by rapid catch-up growth, possibly because of altered epigenetic profiles.[35,36] However, in this study, FGR did not appear to be associated with increased adiposity or insulin resistance, either in children exposed to repeat betamethasone or those exposed to placebo. In addition, in the FGR subgroup, repeat antenatal betamethasone therapy was not associated with any adverse effects on cardiometabolic function. Thus, it seems unlikely that the catch-up in height seen with repeat betamethasone in the FGR subgroup, if true, poses any risk to cardiometabolic health. We do not know the mechanism underlying this catch-up growth, although authors of an ovine study found that repeat doses of betamethasone reduced postnatal concentrations of insulin-like growth factor binding protein 3, which may potentiate the effects of insulin-like growth factor 1 on linear growth.[37] Investigation of the effect of repeat antenatal corticosteroids on linear growth in meta-analysis of individual patient data, including assessment of dose-response effects, may be used to help quantify this association and interaction with FGR and elucidate possible mechanisms.[38]

A challenging issue for this study was the definition of FGR, which is conceptually straightforward but much more difficult to identify in practice. Although subgroup analysis should strictly only involve factors

TABLE 3 Glucose, Renal, and Vascular Function at Midchildhood of Children Exposed to Repeat Betamethasone or Placebo

Outcome	Subgroup	Repeat Betamethasone	*n*	Placebo	*n*	Treatment Effect: MD or RGM[a] (95% CI)	*P*
Fasting plasma concentrations							
Glucose, mmol/L	FGR	4.7 (0.4)	35	4.7 (0.4)	28	0.1 (−0.1 to 0.2)	.39
	Non-FGR	4.7 (0.3)	49	4.8 (0.3)	70	−0.1 (−0.2 to 0.0)	
Insulin, mIU/L	FGR	4.8 (3.7–7.2)	35	4.5 (3.0–6.3)	28	1.19 (0.88 to 1.59)[a]	.68
	Non-FGR	5.2 (3.6–7.5)	49	4.9 (3.5–6.2)	70	1.05 (0.85 to 1.30)[a]	
Minimal model							
Insulin sensitivity, $\times 10^{-4}$ min^{-1} mIU^{-1} L	FGR	6.82 (4.49–12.91)	35	9.43 (6.94–14.26)	28	0.79 (0.57 to 1.09)[a]	.68
	Non-FGR	7.99 (4.91–11.02)	49	9.67 (5.58–13.81)	70	0.87 (0.70 to 1.08)[a]	
Acute insulin release, mIU L^{-1} min	FGR	341 (200–752)	35	293 (174–563)	28	1.21 (0.78 to 1.86)[a]	.79
	Non-FGR	278 (185–504)	49	235 (171–442)	70	1.08 (0.83 to 1.41)[a]	
Disposition index	FGR	2723 (1902–4402)	35	3323 (1930–5226)	28	0.96 (0.64 to 1.44)[a]	.88
	Non-FGR	2219 (1302–3402)	49	2262 (1487–4764)	70	0.89 (0.68 to 1.16)[a]	
Renal function							
Plasma creatinine concentration, μmol/L	FGR	36.9 (5.3)	35	36.4 (4.1)	29	0.5 (−2.1 to 3.1)	.31
	Non-FGR	37.4 (4.7)	54	38.4 (5.8)	73	−1.0 (−2.8 to 0.9)	
Estimated glomerular filtration rate, mL per min/1.73 m^2	FGR	108.0 (17.0)	35	105.3 (13.4)	29	3.1 (−5.2 to 11.5)	.70
	Non-FGR	106.1 (12.6)	54	105.3 (15.3)	73	0.8 (−4.1 to 5.7)	
AMBP							
Daytime systolic *z* score	FGR	−0.51 (1.05)	36	−0.53 (1.20)	41	0.04 (−0.47 to 0.54)	.45
	Non-FGR	−0.47 (0.99)	70	−0.24 (1.28)	75	−0.22 (−0.60 to 0.16)	
Daytime diastolic *z* score	FGR	−0.58 (1.03)	36	−0.75 (1.05)	41	0.19 (−0.30 to 0.68)	.15
	Non-FGR	−0.76 (0.89)	70	−0.52 (1.03)	75	−0.24 (−0.56 to 0.08)	
Nighttime systolic *z* score	FGR	0.06 (0.93)	36	0.01 (1.11)	41	0.05 (−0.44 to 0.53)	.75
	Non-FGR	−0.20 (0.92)	70	−0.15 (1.08)	75	−0.05 (−0.38 to 0.29)	
Nighttime diastolic *z* score	FGR	0.27 (0.92)	36	0.22 (1.04)	41	0.04 (−0.41 to 0.49)	.61
	Non-FGR	0.03 (0.95)	70	0.12 (0.94)	75	−0.09 (−0.40 to 0.22)	
Diurnal systolic % dip	FGR	10.7 (6.9)	36	12.1 (5.9)	41	−1.2 (−4.0 to 1.6)	.80
	Non-FGR	12.5 (5.2)	70	13.4 (5.0)	75	−0.9 (−2.5 to 0.7)	
Diurnal diastolic % dip	FGR	17.5 (8.4)	36	17.8 (8.3)	41	0.0 (−4.0 to 3.9)	.83
	Non-FGR	18.4 (6.5)	70	19.1 (7.1)	75	−0.7 (−2.8 to 1.5)	

Data are mean (SD) and median (interquartile range).
[a] Adjusted for gestational age at trial entry and sex. *P* value is for the test of interaction.

TABLE 4 Lung Function at Midchildhood of New Zealand Children Exposed to Repeat Betamethasone or Placebo

Outcome	Subgroup	Repeat Betamethasone	*n*	Placebo	*n*	Treatment Effect: MD (95% CI)	*P*
FVC *z* score	FGR	−0.13 (0.78)	14	−0.26 (0.85)	8	0.39 (−0.33 to 1.10)	.32
	Non-FGR	−0.13 (0.82)	30	0.05 (0.85)	36	−0.26 (−0.66 to 0.15)	
FEV1 *z* score	FGR	−0.75 (0.79)	14	−1.01 (1.15)	8	0.66 (−0.18 to 1.50)	.35
	Non-FGR	−1.00 (1.00)	30	−0.77 (0.91)	36	−0.20 (−0.65 to 0.25)	
FEV1/FVC *z* score	FGR	−1.28 (0.67)	14	−1.41 (0.87)	8	0.41 (−0.19 to 1.02)	.81
	Non-FGR	−1.52 (1.08)	30	−1.47 (0.93)	36	−0.01 (−0.47 to 0.45)	
FEF25-75 *z* score	FGR	−1.34 (0.92)	14	−1.37 (1.37)	8	0.62 (−0.31 to 1.56)	.74
	Non-FGR	−1.55 (1.25)	30	−1.39 (1.18)	36	−0.10 (−0.65 to 0.45)	

Data are mean (SD). Adjusted for gestational age at trial entry and sex. *P* value is for the test of interaction.

identified before randomization, we were concerned that the rate of FGR reported at trial entry (10%) underrepresented the actual degree of FGR in this high-risk cohort and could potentially obscure the influence of FGR on outcomes. Authors of studies have estimated that <25% of infants who are small for gestational age are identified antenatally as having a potential growth problem, even in pregnancies known to be at risk, and detection rates are even lower in those not considered at risk.[39,40] We took a conservative approach, defining FGR as a birth weight less than the third centile, rather than the more commonly used 10th centile. Customized rather than population centiles were used because of the strong association between preterm birth and FGR.[18,41] Despite this narrower definition, FGR was identified in a third of the cohort, which is consistent with other reports.[18] As expected, the rate of serious neonatal morbidity was 60%

higher in the FGR subgroup, although the rate of severe neonatal lung disease did not differ between infants with and without FGR.

Our findings are perhaps somewhat surprising, given the number of animal studies in which authors have linked fetal corticosteroid exposure to both reduced fetal growth and cardiometabolic disease.[12,42–45] In addition, animal studies have suggested that maternal betamethasone administration may exacerbate fetal cardiovascular dysfunction in FGR.[12,46] However, human trials have consistently demonstrated that antenatal corticosteroid treatment is safe in the long-term.[1,3] The reason for this discrepancy has not been fully explained but may be due to the use of physiologic doses of corticosteroids, shorter durations of exposure in clinical studies, and interspecies differences in the timing of organ development.[47]

Authors of some studies have suggested that antenatal corticosteroid treatment may be less effective in FGR because of increased endogenous corticosteroid production and reduced clearance of corticosteroids from the fetal compartment.[48,49] However, in preterm lambs with FGR induced by single uterine artery ligation, maternal antenatal betamethasone continued to induce lung structural maturation and expression of surfactant proteins, although fetuses with growth restriction had increased endogenous corticosteroid concentrations.[50] In a large population study of preterm infants who were small for gestational age, those exposed to a single course of antenatal corticosteroids had reduced rates of death and intraventricular hemorrhage but not respiratory morbidity.[51] Our study has revealed that, in FGR, repeat doses of antenatal betamethasone reduced the severity of neonatal lung disease and use of surfactant, suggesting that repeat doses may be required for pulmonary maturation in FGR in humans.

This study has some important limitations, including the limited size of the New Zealand ACTORDS cohort and the inherent risk of bias in subgroup analysis. However, we felt that it was important to undertake this exploratory analysis given the high rates of FGR among preterm infants and the ongoing concerns around efficacy and safety of repeat corticosteroid exposure in this subgroup. In addition, the ACTORDS is the only trial of repeat antenatal corticosteroids in which researchers have undertaken detailed follow-up of participants in midchildhood, at an age when cardiometabolic parameters become predictive of later risk of chronic disease.[9] We did not have access to paternal height, but given that maternal height was similar in randomized treatment groups, we would not expect any imbalance in midparental height.

CONCLUSIONS

Repeat antenatal betamethasone treatment had no adverse effects on later cardiometabolic function, even in the presence of FGR. It may have a positive effect on childhood height in FGR. Clinicians should use repeat doses of antenatal corticosteroids when indicated before preterm birth, regardless of FGR, in view of the associated neonatal benefits and absence of later adverse effects.

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APPENDIX: COLLABORATORS

The following ACTORDS Follow-up Steering Group members are nonauthor contributors:

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ABBREVIATIONS

ACTORDS: Australasian Collaborative Trial of Repeat Doses of Corticosteroids
AMBP: ambulatory blood pressure
CI: confidence interval
DXA: dual energy radiograph absorptiometry
FEF25-75: mean forced expiratory flow at 25% to 75% of forced vital capacity
FEV1: forced expiratory volume in 1 second
FGR: fetal growth restriction
FVC: forced vital capacity
MD: mean difference
RDS: respiratory distress syndrome
RGM: ratio of geometric means

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Repeat Antenatal Betamethasone and Cardiometabolic Outcomes

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