Short-Term Effects of Dexamethasone versus Betamethasone on Ultrasonic Measures of Fetal Well-Being: Cohort from a Blinded, Randomized Trial

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Keywords

Antenatal corticosteroids · Doppler ultrasound · Dexamethasone · Betamethasone · Cardiotocograph

Abstract

Introduction: Maternal corticosteroid administration for anticipated preterm birth is common; however, the corticosteroid effect on fetal ultrasound and cardiotocograph (CTG) remains contested. This study aimed to evaluate short-term ultrasound and CTG impact of (a) dexamethasone versus betamethasone (b) pooled corticosteroid effect. **Methods:** Substudy of blinded randomized trial of dexamethasone versus betamethasone (given <34 weeks). Umbilical artery (UA), middle cerebral artery (MCA), ductus venosus (DV), and uterine artery Doppler, myocardial performance index (MPI), biophysical profile (BPP), and CTG measured pre-corticosteroid then 1, 2, 4, and 7 days post-corticosteroid. **Results:** Of 47 fetuses (39 singleton; 4 dichorionic, diamniotic twins; and

4 monochorionic, diamniotic twins) in the February 2012–2013 period, 24 received dexamethasone and 23 betamethasone at average gestation 29.8 ± 2.9 weeks. Thirteen pregnancies (30%) had pre-corticosteroid fetal concerns (estimated weight <10th centile and/or abnormal UA/MCA Doppler). Few significant differences were seen post-corticosteroid: DV pulsatility index and right MPI initially decreased 15–20%, and average BPP decreased slightly on days 1–2. There were no major differential effects of dexamethasone versus betamethasone. **Discussion/Conclusion:** No substantive post-corticosteroid effects were seen for most ultrasound/CTG measures in fetuses with heightened preterm birth risk but predominantly normal pre-corticosteroid measures. Clinically, this suggests avoiding overreliance on individual measures for delivery decisions post-corticosteroid; equally, multiple/marked ultrasound changes suggest true pathology and not corticosteroid effect.

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Introduction

Antenatal corticosteroids are routinely prescribed to women at high risk of preterm birth <34 weeks' gestation; they reduce the risk of neonatal death, respiratory distress syndrome, and intraventricular hemorrhage [1]. Corticosteroid administration is extremely common in pregnancy, as 3–4% of births occur at 24–34 weeks [2]. Many women receive corticosteroids but give birth beyond 34 weeks [3]. Effect of maternal corticosteroids on fetal Doppler and other fetal assessment such as biophysical profile (BPP) and cardiotocograph (CTG) is of considerable clinical interest, since almost all women receiving corticosteroids will undergo such fetal well-being assessments, and they may be used to determine timing of preterm birth [4]. Particularly, interpretation of measures could be problematic if they are affected in a large and/or inconsistent fashion after corticosteroids, or by 1 type of corticosteroid compared to another.

Corticosteroids have widespread pharmacological effects mediated via gene transcription and protein expression effects in many organ systems, with effects noted within hours of administration [5]. This leads to both desired fetal effects such as increased protein production in the lungs with resulting phospholipid biosynthesis and the appearance of surfactant [5], potentially less desirable effects such as increased fetal blood pressure [6], and effects such as decreased cerebral blood flow that are associated with decreased intraventricular hemorrhage short term but could also be linked to adverse neurodevelopment in the longer term [7]. Regarding how these effects manifest short term in commonly used measures of fetal well-being, existing data suggest little corticosteroid effect on Doppler measures if baseline umbilical artery end-diastolic velocities are normal, except possibly decreased middle cerebral artery (MCA) pulsatility index (PI) for several days [8, 9]. Temporary reductions in BPP score, particularly fetal movements and breathing, and CTG variability are also reported [10, 11]. When baseline umbilical artery (UA) end-diastolic velocities are abnormal, most studies show temporary improvement post-corticosteroid; however, effect, degree, and duration are inconsistent [8, 12]. It is also uncertain to what degree the 2 commonly used corticosteroid preparations (dexamethasone and betamethasone) differ in their effects. Both betamethasone and dexamethasone cross the placenta in their active form and have comparable properties, including virtually identical chemical composition (although preservative preparations may differ) [13]. However, prior clinical studies have suggested that dexamethasone

might be associated with a lower risk of neonatal intraventricular hemorrhage but a greater risk of neurosensory impairment and chorioamnionitis [14]. Regarding short-term effects, prior reviews of betamethasone and dexamethasone (with heterogeneous study designs, included antenatal populations, and regimens) suggest a greater reduction in fetal body movements, breathing, and heart rate variability 2–3 days after betamethasone, but are inconclusive regarding Doppler ultrasound effects [8, 11].

The A*STEROID-blinded randomized controlled trial compared outcomes of mothers given intramuscular dexamethasone versus betamethasone for preterm birth risk 24–34 weeks' gestation [14]. We performed a substudy (SUPER-A*STEROID) to determine short-term ultrasound and CTG effects of dexamethasone versus betamethasone on fetal well-being.

The objectives were to:

1. evaluate effects of either dexamethasone or betamethasone (pooled corticosteroid effect) on fetal cardiovascular and behavioral status in the first 7–10 days after administration, as assessed ultrasonically by UA Doppler, MCA Doppler, ductus venosus (DV) Doppler, uterine artery (UtA) Doppler, myocardial performance index (MPI), amniotic fluid index (AFI), BPP, and CTG;
2. evaluate any differential effects of dexamethasone or betamethasone on the Doppler measures, BPP, or CTG;
3. evaluate any differential dexamethasone versus betamethasone effects, in fetuses with suspected fetal compromise versus no suspected fetal compromise at baseline.

Materials and Methods

We conducted a prospective substudy of women participating in the multicenter, randomized, double-blind trial of antenatal intramuscular dexamethasone versus betamethasone for women at risk of preterm birth <34 weeks' gestation, the A*STEROID trial (ACTRN12608000631303). Women gave written informed consent to participate and were randomized to receive 2 intramuscular injections of either 12 mg dexamethasone or 11.4 mg betamethasone, 24 h apart. Inclusion criteria for the A*STEROID trial were women with a singleton or twin pregnancy, considered by their treating clinicians to be at risk of preterm birth <34 weeks' gestation, and exclusion criteria were chorioamnionitis requiring urgent delivery, higher order multiple pregnancy, antenatal corticosteroids already given, and known fetal lung maturation, in the second stage of labor [15]. Additional exclusion criteria for SUPER-A*STEROID were suspicion of abnormal fetal cardiac morphology and maternal medication with potential major fetal car-

diovascular effect (e.g., digoxin). SUPER-A*STEROID participants were recruited from 2 Metropolitan Sydney Hospitals participating in A*STEROID, the Royal Hospital for Women (RHW), and St. George Hospital (SGH) at the time of or soon after recruitment to the main study. Participants were only recruited to SUPER-A*STEROID if the clinical team felt delay of corticosteroids for 1–2 h to allow for pre-corticosteroid ultrasound would not compromise clinical care, and if the woman gave informed consent for the additional study participation. Ethical approval was received from the South-Eastern Sydney Local Health District Human Research Ethics Committee (SESLHD HREC reference number: 11/202).

Conduct of Study

All women underwent baseline examination using curvilinear transducers of Voluson E8 Expert (GE Medical Systems, Sydney, NSW, Australia), Voluson 730 (GE Medical Systems, Sydney, NSW, Australia), or Philips iU22 (Philips Healthcare, Macquarie Park, NSW, Australia) <4 h prior to corticosteroid administration. This included assessment of fetal biometry [16, 17], AFI (deepest vertical pocket for twin pregnancy) [18], BPP (measured over at least 30 min ultrasound duration) [19], and UA [20], MCA [20–22], cerebroplacental ratio (CPR) [23], DV [24], and UtA Doppler [20] using existing reference intervals/scoring methods. Doppler traces were acquired using ISUOG-recommended techniques [25], with 3 readings taken and averaged for each vessel. Measurement of Myocardial Performance Index using our group's modified-MPI [26], in both right and left fetal cardiac ventricles, with the calculation of "peak" left, right, and delta MPI (LMPI, RMPI, and DMPI, respectively) [27] was performed when a suitable machine and a sonographer experienced in MPI acquisition were available. A pre-corticosteroid CTG (if ≥ 26 weeks) was performed and classified according to local guidelines [28] and variability assessment as per prior publications, with maximal short-term variability (STV) visually estimated using the difference between the highest and lowest fetal heart rates in the best 1-min epoch of the tracing, excluding during accelerations and decelerations, and overall variability estimated using the average difference in beats per minute between the highest peak and the lowest trough of the fluctuation throughout the CTG [29, 30]. As this estimate could not achieve the precision of computerized CTG, it was classified into 5 beats-per-minute segments (<5, 5–9, 10–14, 15–19).

All women who remained undelivered had these measurements (except fetal biometry) repeated at 24 h after corticosteroid administration (acceptable range 18–30 h), 48 h (range 42–54 h), 96 h (range 3–5 days), and 7 days (acceptable range 6–10 days). Ninety percent of studies were performed by a single experienced operator (AH), the remainder by the maternal-fetal medicine team (RHW), or experienced sonographers (SGH).

Maternal demographic data, pregnancy, labor, and neonatal data were abstracted from case notes for correlation with data obtained from the clinical examinations (see online suppl. Appendix; see www.karger.com/doi/10.1159/000517623 for all online suppl. material: datasheet). Australian birthweight centiles by gender and gestation at birth were used for the calculation of birth weight centiles [31, 32].

Data Analysis

Data were analyzed using SPSS Version 22.0 (SPSS Inc., Chicago, IL, USA). All data were collected and entered prior to un-

blinding, and MPI analysis was also performed prior to unblinding. Prior to CTG analysis, to blind the observer to the corticosteroid status at the time of the CTG, identifying details were removed and CTGs labeled using a random number sequence (<https://www.random.org>).

Demographic data, outcome data, reason for corticosteroid use, and baseline fetal status are presented for the total cohort and for the 2 corticosteroid groups. Continuous variables were compared between groups using parametric (independent samples *t*-test or ANOVA) or nonparametric analysis (Mann-Whitney U or Kruskal-Wallis test) based on their distribution. Proportional distributions of categorical outcome variables were related to CTG and Doppler results using χ^2 and Fisher's exact tests.

For analysis of repeated measures (ultrasound and CTG measurements at baseline, 24 h, 48 h, 96 h, and 7–10 days), the repeated-measures analysis-of-variance technique was used for parametric data. Mauchly's test of sphericity was used to assess sphericity of data, and if nonsignificant, sphericity-assumed significance results are reported, otherwise Greenhouse-Geisser-corrected significance values are reported [33]. The Bonferroni method was used to minimize type I error for multiple comparisons [33]. Repeated-measures analysis of variance with between-subjects factors was used to analyze repeated measures by (1) corticosteroid received (dexamethasone or betamethasone); (2) singleton or multiple pregnancy; and (3) suspected fetal compromise at baseline (estimated fetal weight <10th centile for gestational age [34], and/or umbilical artery PI >95th centile for gestation, and/or absent to reversed UA end-diastolic flow, and/or MCA PI <5th centile for gestation). Friedman's ANOVA was used for repeated-measures analysis of nonparametric data [35], allowing for within-subjects but not between-subjects analysis as this is a limitation of nonparametric data [33]. Relationships between CTG, Doppler parameters, indication for corticosteroid use (fetal concerns vs. not), and pregnancy outcome were examined using Pearson correlation testing or Spearman's correlation testing as appropriate for parametric and nonparametric data.

After initial data analysis, it was noted that for many variables, particularly MPI and CTG, the number of subjects available for the prespecified 5-time point repeated-measures analysis was small, due either to birth prior to 1-week follow-up, or to participants being discharged and not having all follow-up tests performed. To enable more complete use of data, a post hoc repeated-measures analysis as described above but only including 3 time points (baseline, 24 h, and 48 h) was performed.

Sample Size Calculation

Power calculations were based on (a) parameters most often reported to change after corticosteroid administration even in fetuses with normal baseline Doppler studies, that is, MCA PI and CTG variability; (b) ability to detect a change in MPI values pre- and post-corticosteroid administration. Mean gestational age at entry of 31 weeks was used to allow incorporation of assumptions regarding likely population parameter means and standard deviations (SDs) from previous studies. Calculations were performed using G*Power3, Universität Düsseldorf [36].

Regarding the whole-group comparisons of pre- and post-corticosteroid measurements (pooled corticosteroid effect), a sample size of 50 was proposed to enable detections of: (a) a decrease in the proportion of normal variability CTGs from 90% pre-corticosteroid to 70% 48 h after corticosteroid administration, with 95%

Fig. 1. Participant flow diagram.

power; (b) a decrease in MCA PI of 0.2 between pre-corticosteroid administration values and values 48 h later (allowing for a standard error in MCA PI measurement of 0.4, and at 90% power). A smaller sample size of 20 women was required to detect, with 80% power, a change in the “peak” LMPI value pre- and post-corticosteroid administration of 10% (0.04), assuming a normal measurement of 0.42 ± 0.06 at 31 weeks as per our group’s LMPI reference interval [37]. Regarding dexamethasone versus betamethasone comparisons, a sample size of 40 was calculated as sufficient to detect with 80% power a difference in MCA PI of 0.3 post-corticosteroid administration between the groups (assuming SD of 0.3).

Results

As shown in Figure 1, of the 47 fetuses: 39 were singleton; 4 were dichorionic, diamniotic twin fetuses; and 4 were monochorionic, diamniotic twin fetuses from February 2012 to 2013 (at which time enrollment ceased as A*STEROID recruitment closed). Twelve women (14 fetuses) gave birth before 1-week follow-up, leaving 17 fetuses post-dexamethasone and 16 post-betamethasone potentially eligible for a repeated-measures analysis. Of 188 ultrasounds performed, 187 (99%) were performed within protocol time frames. Performance of CTGs was more variable (online suppl. Fig. 1).

Baseline participant characteristics (Table 1) found groups well-matched at baseline apart from all 4 twin pairs (8 fetuses) being randomized to dexamethasone ($p = 0.04$). Approximately half of the women were nulliparous, born in Australia, and Caucasian. Antepartum hemorrhage (42%) was the most common reason for corticosteroid administration, followed by threatened preterm labor or preterm prelabor rupture of membranes, growth restriction/fetal concerns, and preeclampsia. In 13 women (30%), there were baseline fetal concerns identified; however, only 5 fetuses had baseline UA abnormality (UA PI >95th centile for gestation and/or absent/reversed end-diastolic flow).

Regarding pregnancy outcome data (Table 2), 17 babies (36%) were born <34 weeks and 18 (38%) were born at term (≥ 37 weeks). Consistent with the parent A*STEROID trial, there were no significant differences between dexamethasone and betamethasone groups for perinatal outcomes including gestation at birth, birth weight centile, and neonatal morbidities.

Baseline ultrasound data for the total cohort and by corticosteroid given are shown in Table 3. These were normal in most fetuses: 5 (11%), 3 (6%), and 10 (21%) of 47 fetuses had abnormal UA Doppler, abnormal MCA Doppler, and abnormal CPR for gestation, respectively,

Table 1. Baseline demographic and obstetric characteristics of total corticosteroid cohort and by corticosteroid administered

	Total cohort (<i>n</i> = 43 women, 47 babies) (mean ± SD)	Dexamethasone (<i>n</i> = 20 women, 24 babies) (mean ± SD)	Betamethasone (<i>n</i> = 23 women, 23 babies) (mean ± SD)	<i>p</i> value, D versus B
Maternal age, years	33.0±5.3	33.8±5.1	32.3±5.5	0.37
Body mass index, kg/m ²	24.8±5.9	24.2±5.8	25.4±6.0	0.53
Gestation at entry, weeks	29.8±2.9	29.9±3.1	29.8±2.8	0.97
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	
Nulliparous	20 (47)	11 (55)	9 (39)	0.30
Born Australia	22 (51)	11 (55)	11 (48)	0.64
Ethnicity				
Caucasian	24 (56)	12 (60)	12 (52)	
Asian	12 (28)	6 (30)	6 (26)	
Maori/Islander	5 (12)	2 (10)	3 (13)	0.61
Other	2 (5)	0 (0)	2 (9)	
Smoker	1 (2)	0 (20)	1 (4)	1.0
Concurrent maternal medical conditions	19 (44)	11 (55)	8 (35)	
Hypertension	12 (28)	5 (25)	7 (30)	
Diabetes	3 (7)	3 (15)	0 (0)	0.18
Other	4 (9)	3 (15)	1 (4)	
Primary pathology				
APH	18 (42)	8 (40)	10 (43)	0.82
TPL/PPROM	5 (12)	2 (10)	3 (13)	1.0
FGR/fetal concerns	7 (16)	5 (25)	2 (9)	0.22
Preeclampsia	7 (16)	2 (10)	5 (22)	0.22
Short cervix	4 (9)	2 (10)	2 (9)	1.0
Other*	2 (5)	1 (5)	1 (4)	1.0
Twin pregnancy	4 (9)	4 (20)	0 (0)	
DCDA	2 (5)	2 (10)	0 (0)	0.04
MCDA	2 (5)	2 (10)	0 (0)	
Recruited STG	24 (56)	10 (50)	14 (61)	0.47
Recruited RHW	19 (44)	10 (50)	9 (39)	
Fetal concerns [†]	13 (30): 11 singleton, 2 sIUGR twins	7 (35): 5 singleton, 2 sIUGR twins	6 (26): 6 singleton	0.53

D, dexamethasone; B, betamethasone; SD, standard deviation; APH, antepartum hemorrhage (with or without placenta previa); TPL/PPROM, threatened premature labor ± preterm premature rupture of membranes; FGR/fetal concerns, growth restricted fetus/anticipated need for preterm birth on fetal grounds; DCDA, dichorionic, diamniotic; MCDA, monochorionic, diamniotic; STG, St. George Hospital; RHW, Royal Hospital for Women; sIUGR, selective intrauterine growth restriction; EFW, estimated fetal weight. * The 2 patients, in whom “other” was the primary pathology/reason for corticosteroid administration, had a history of multiple prior spontaneous preterm births and were given corticosteroids 1 week prior to the earliest gestation that their previous preterm births had occurred. [†]At the time of study entry, any of EFW <10th centile for gestational age, umbilical artery PI >95th centile for gestation, absent to reversed umbilical artery end-diastolic flow, MCA PI <5th centile for gestation.

with no significant differences between groups. MPI values were within reference intervals in all except 2 cases. Baseline CTG was non-reassuring in approximately 50% of fetuses in both groups, predominantly due to preterm contractions.

Tables 4 and 5 and online suppl. Tables 1–5 show the repeated measure results for Doppler, MPI, AFI, BPP,

and CTGs, including within- and between-subjects effects. Overall, minimal differences from a pre-corticosteroid baseline to a final follow-up, between dexamethasone and betamethasone at each of the 5 time points, or on within- and between-subjects effects testing, were noted. Specifically,

Table 2. Pregnancy outcome of total corticosteroid cohort and by corticosteroid administered

	Total cohort (<i>n</i> = 43 women, 47 babies) (mean ± SD)	Dexamethasone (<i>n</i> = 20 women, 24 babies) (mean ± SD)	Betamethasone (<i>n</i> = 23 women, 23 babies) (mean ± SD)	<i>p</i> value D versus B
Gestation at birth, weeks	35.4±3.8	35.5±4.0	35.2±3.7	0.83
GA entry to birth, weeks	5.5±4.9	5.6±4.9	5.4±4.9	0.89
Timing of birth*	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	
Birth <48 h	47	24	23	
Birth 48 hours-7 days	2 (4)	1 (4)	1 (4)	1.0
Birth 7+ days	13 (27.7)	6 (25)	7 (30)	0.78
Birth <34 wk	31 (66)	17 (71)	14 (61)	0.47
Birth <37 wk	17 (36)	8 (33)	9 (39)	0.68
Live birth	29 (62)	15 (63)	14 (61)	0.91
Mean BW, kg±SD	47 (100)	24 (100)	23 (100)	1.0
BW centile	2.5±1.0	2.4±1.0	2.5±1.0	0.86
<10th	11 (23)	7 (29)	4 (17)	0.34
10th–50th	15 (32)	8 (33)	7 (30)	0.76
50th–90th	15 (32)	6 (25)	9 (39)	0.30
>90th	6 (13)	3 (13)	3 (13)	0.96
Male infant	26 (55)	16 (67)	10 (44)	0.11
Mode of birth				
Vaginal	20 (43)	11 (46)	9 (39)	0.64
Caesarean	27 (57)	13 (54)	14 (61)	
5-min Apgar <6	1 (2)	0 (0)	1 (4)	0.49
	<i>n</i> = 32	<i>n</i> = 20	<i>n</i> = 12	
Cord ABG pH (mean ± SD)	7.27±0.08	7.26±0.08	7.27±0.08	0.77
Cord ABG BE (mean ± SD)	−2.4±4.7	−2.9±5.1	−1.7±4.0	0.49
Highest neonatal care				
Ward	17 (36)	8 (33)	9 (39)	0.68
Special care	21 (45)	9 (38)	12 (52)	0.31
NICU	9 (19)	7 (29)	2 (9)	0.14
Neonatal complications†	24 (51)	14 (58)	10 (43)	0.31
RDS/HMD/TTN	12 (26)	8 (33)	4 (17)	
Infection	1 (2)	0 (0)	1 (4)	
Congenital anomaly	7 (15)	5 (21)	2 (9)	
Jaundice	6 (13)	3 (13)	3 (13)	
Other	7 (15)	5 (21)	2 (9)	
Discharged alive	46	24 (100)	22 (96)‡	0.49
Neonatal length of stay, days: Median (IQR)	5.0 (4.0–23.0)	10.5 (4.0–27.3)	5.0 (4.0–23.0)	0.51

D, dexamethasone; B, betamethasone; SD, standard deviation; GA, gestational age; BW, birth weight; ABG, arterial blood gas; BE, base excess; VBG, venous blood gas; NICU, neonatal intensive care unit; RDS/HMD/TTN, respiratory distress syndrome, hyaline membrane disease, transient tachypnea of newborn; IQR, interquartile range. * Timing of birth, birth <48 h = birth <48 h after first dose of corticosteroids; birth 48 h–7 days = birth between 48 h and 7 days after first dose of corticosteroids; birth 7+ days = birth 7 or more days after first dose of corticosteroids; birth <34 weeks = birth at <34 completed weeks' gestation; birth <37 weeks = birth at <37 completed weeks' gestation. † Subgroups add to >100% as some babies had multiple neonatal complications. "Other" includes feed intolerance, 1× intraventricular hemorrhage. Congenital anomalies were hypospadias (*n* = 1), webbed 2nd–3rd toes (*n* = 1), unilateral cleft lip and palate (*n* = 1), arm lymphedema (*n* = 1), inguinal hernia (*n* = 2), and hemivertebra (*n* = 1). ‡ Neonatal death of baby born at 25 weeks' gestation whose parents decided against active resuscitation.

Table 3. Baseline ultrasound and CTG data by total corticosteroid cohort and corticosteroid given

	Total cohort (<i>n</i> = 43 women, 47 babies) (mean ± SD)	Dexamethasone (<i>n</i> = 20 women, 24 babies) (mean ± SD)	Betamethasone (<i>n</i> = 23 women, 23 babies) (mean ± SD)	<i>p</i> value D versus B
Gestation at first ultrasound, weeks	29.8±2.9	29.9±3.1	29.8±2.8	0.97
EFW, kg	1.5±0.6	1.4±0.6	1.5±0.6	0.85
EFW Z-score	−0.2±1.3	−0.4±1.3	−0.1±1.3	0.48
UA PI	1.05±0.20	1.05±0.21	1.05±0.20	0.99
MCA PI	1.84±0.32	1.89±0.32	1.80±0.33	0.37
MCA PSV, cm/s	41.0±9.5	41.1±10.2	41.1±9.0	0.99
CPR	1.81±0.42	1.9±0.5	1.7±0.4	0.20
DV PI (<i>n</i> = 41), median (IQR)	0.56 (0.50–0.64)	0.56 (0.49–0.66)	0.54 (0.50–0.62)	0.80
LMPI	(Total <i>n</i> = 25) 0.47±0.06	(Total <i>n</i> = 17) 0.47±0.05	(Total <i>n</i> = 8) 0.46±0.07	0.56
ICT, ms	31.5±5.0	32.4±5.3	29.6±3.7	0.20
IRT, ms	44.9±6.3	45.5±5.3	43.7±8.3	0.51
ET, ms	163.9±10.8	165.5±11.7	160.4±8.1	0.28
RMPI	(Total <i>n</i> = 21) 0.49±0.07	(Total <i>n</i> = 13) 0.51±0.07	(Total <i>n</i> = 8) 0.46±0.07	0.10
“a” interval, ms	242.6±12.6	246.5±12.8	236.2±9.7	0.07
“b” interval, ms	162.9±7.3	163.2±6.8	162.4±8.5	0.82
UtA PI, median (IQR)	(Total <i>n</i> = 37)			
RUtA	0.92 (0.74–1.14)	0.90 (0.83–1.13)	0.96 (0.73–1.25)	0.48
LUtA	0.93 (0.89–1.11)	0.79 (0.58–1.03)	0.88 (0.73–1.18)	0.46
AFI, cm (singletons)	13.1±4.3	12.1±2.7	13.7±5.0	0.24
BPP	6.7±1.1	6.8±1.2	6.6±0.9	0.48
CTG maximum STV, bpm1	(Total <i>n</i> = 37) 18.4±3.1	(Total <i>n</i> = 18) 18.2±3.7	(Total <i>n</i> = 19) 18.6±2.6	0.75
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	
UA PI > p95 ²	5 (11)	4 (17)	1 (4)	0.35
MCA PI < p5/PSV > p95 ³	3 (6)	1 (4)	2 (9)	0.61
CPR < p5 ⁴	10 (21)	5 (21)	5 (22)	1.0
DV > p95 ⁵	6 (13)	3 (13)	3 (13)	1.0
LMPI >95th centile for GA	2/25 (8)	1/17 (6)	1/8 (13)	1.0
RMPI >95th centile for GA	2/21 (10)	2/13 (15)	0/8 (0)	0.51
DMPI >95th centile for GA	2/21 (10)	2/13 (15)	0/8 (0)	0.51
Amniotic fluid ⁶				
Oligohydramnios	4 (9)	1 (4)	3 (13)	0.35
Normal	41 (87)	23 (96)	18 (78)	0.10
Polyhydramnios	2 (4)	0 (0)	2 (9)	0.51
BPP <6	1 (2)	1 (4)	0 (0)	1.0
CTG non-reassuring or abnormal: ⁷	19 (51)	10 (56)	9 (50)*	0.74
Due to contractions only	11/19 (58)	6/10 (60)	5/9 (56)	1.0
Average STV <5 ⁸	1/19 (5)	1/10 (30)	0/9 (0)	1.0
Other/additional features	7/19 (37)	3/10 (30)	4/9 (44)	1.0

Key (continues overleaf). D, dexamethasone; B, betamethasone; SD, standard deviation; EFW, estimated fetal weight; UA, umbilical artery; PI, pulsatility index; MCA, middle cerebral artery; PSV, peak systolic velocity; CPR, cerebroplacental ratio; DV, ductus venosus; LMPI, left myocardial performance index; ICT, isovolumetric contraction time; IRT, isovolumetric relaxation time; ET, ejection time; RMPI, right myocardial performance index; DMPI, delta myocardial performance index; UtA, uterine artery; AFI, cm, amniotic fluid index in centimeters; BPP, biophysical profile; CTG, cardiotocograph; STV, short-term variability; bpm, beats per minute. ¹ By visual analysis as described in Materials and Methods. ² Defined as UAPI >95th centile for gestation and/or absent to reversed end-diastolic flow. ³ Defined as MCA PI <5th centile for gestation and/or PSV >95th centile for gestation. ⁴ Defined as CPR <5th centile for gestation. ⁵ Defined as DV PIV >95th centile for gestation and/or absent to reversed “a” wave. ⁶ Oligohydramnios defined as <5th centile for gestation (or for twins DVP <2 cm), normal 5th–95th centile (DVP 2–8 cm), and polyhydramnios >95th centile for gestation (DVP >8 cm). ⁷ By NSW Health Guidelines as described in Materials and Methods. ⁸ By visual analysis as described in Materials and Methods. * 1 baseline CTG in Betamethasone group unable to be classified.

Table 4. Doppler studies pre- and post-corticosteroid administration, dexamethasone versus betamethasone

(a) UA PI	Individual time points									
	All			Dexamethasone			Betamethasone			<i>p</i> value
	<i>N</i>	mean	SD	<i>N</i>	mean	SD	<i>N</i>	mean	SD	
Baseline	45	1.05	0.20	22	1.05	0.21	23	1.05	0.20	0.99
24 h	46	1.01	0.23	23	1.02	0.28	23	1.01	0.18	0.98
48 h	43	1.04	0.26	23	1.04	0.28	20	1.05	0.23	0.92
96 h	35	1.03	0.21	19	1.02	0.23	16	1.04	0.19	0.84
1 week	32	1.02	0.18	16	1.02	0.18	16	1.03	0.18	0.83
	Within-subjects (<i>n</i> = 30)*					Between-subjects effects				
	Mean	95% CI	<i>p</i> value			Dexamethasone (<i>n</i> = 16)		Betamethasone (<i>n</i> = 14)		<i>p</i> value
						mean	SD	mean	SD	
Baseline	1.03	0.96–1.10	0.87			1.01	0.17	1.05	0.19	
24 h	1.00	0.94–1.06				0.99	0.19	1.01	0.14	
48 h	1.02	0.94–1.09				0.99	0.24	1.04	0.16	0.60
96 h	1.03	0.95–1.10				1.02	0.22	1.04	0.20	
1 week	1.03	0.96–1.09				1.02	0.18	1.04	0.19	
(b) MCA PI	Individual time points									
	All			Dexamethasone			Betamethasone			<i>p</i> value
	<i>N</i>	mean	SD	<i>N</i>	mean	SD	<i>N</i>	mean	SD	
Baseline	43	1.84	0.32	21	1.89	0.32	22	1.80	0.33	0.37
24 h	43	1.80	0.35	21	1.82	0.34	22	1.78	0.35	0.70
48 h	42	1.81	0.38	23	1.84	0.37	19	1.77	0.40	0.56
96 h	34	1.81	0.31	17	1.89	0.37	17	1.76	0.21	0.28
1 week	30	1.88	0.23	14	1.91	0.25	16	1.85	0.22	0.52
	Within-subjects effects (<i>n</i> = 27)*					Between-subjects effects				
	mean	95% CI	<i>p</i> value			Dexamethasone (<i>n</i> = 13)		Betamethasone (<i>n</i> = 14)		<i>p</i> value
						mean	SD	mean	SD	
Baseline	1.96	1.86–2.07	0.44			2.00	0.25	1.92	0.26	
24 h	1.96	1.84–2.08				1.97	0.34	1.96	0.26	
48 h	1.95	1.85–2.05				1.93	0.26	1.96	0.25	0.45
96 h	1.88	1.77–1.99				1.96	0.35	1.80	0.18	
1 week	1.90	1.81–1.99				1.92	0.25	1.87	0.20	

Table 4 (continued)**(c) MCA PSV, cm/s Individual time points**

	Dexamethasone			Betamethasone			<i>p</i> value
	<i>N</i>	mean	SD	<i>N</i>	mean	SD	
Baseline	43	41.0	9.5	21	41.0	10.1	
24 h	43	39.7	8.6	21	40.6	8.9	0.99
48 h	42	41.7	8.6	23	43.8	9.2	0.53
96 h	34	40.3	8.6	17	41.4	7.1	0.08
1 week	30	44.7	9.2	15	42.6	9.8	0.47
						8.3	0.23
Between-subjects effects							
Within-subjects effects (<i>n</i> = 28)*				Dexamethasone (<i>n</i> = 15)			
	mean	95% CI	<i>p</i> value		mean	SD	<i>p</i> value
Baseline	39.6	36.6–42.6	0.003		mean	SD	
24 h	39.4	36.4–42.4			39.7	8.6	
48 h	40.3	37.5–43.0			36.9	6.4	
96 h	40.5	37.5–43.6			39.4	7.2	0.75
1 week	45.1	41.5–48.7			39.4	8.2	
					47.6	8.6	

(d) DV PI Individual time points

	Dexamethasone			Betamethasone			<i>p</i> value
	<i>N</i>	mean	IQR	<i>N</i>	median	IQR	
Baseline	41	0.56	0.50–0.64	21	0.56	0.49–0.66	
24 h	41	0.50	0.43–0.59	21	0.55	0.41–0.59	0.80
48 h	38	0.52	0.44–0.62	22	0.47	0.40–0.58	0.71
96 h	29	0.54	0.49–0.65	14	0.56	0.48–0.63	0.17
1 week	29	0.56	0.46–0.62	15	0.50	0.44–0.61	0.68
						0.49–0.68	0.08
Within-subjects effects (<i>n</i> = 20)*							
	Median	IQR	<i>p</i> value				
Baseline	0.55	0.50–0.62					
24 h	0.46	0.38–0.55					
48 h	0.52	0.52–0.66	0.006				
96 h	0.59	0.45–0.66					
1 week	0.55	0.45–0.61					

DV, ductus venosus; PI, pulsatility index; UA PI, umbilical artery; MCA, middle cerebral artery; PSV, peak systolic velocity; IQR, interquartile range. * (a) 30 fetuses with UA PI recorded at all 5 time points. 95% CI, 95% confidence interval of mean. * (b) 27 fetuses with MCA PI recorded at all 5 time points. 95% CI, 95% confidence interval of mean. * (c) 28 fetuses with MCA PSV recorded at all 5 time points. 95% CI, 95% confidence interval of mean. * (d) 20 fetuses with DV PI recorded at all 5 time points.

Table 5. Biophysical profile and CTG STV pre- and post-corticosteroid administration, dexamethasone versus betamethasone**(a) Biophysical Profile**

	Individual time points				Dexamethasone				Betamethasone				<i>p</i> value
	All				N	mean	SD		N	Mean	SD		
Baseline	47	6.7	1.1		24	6.8	1.2		23	6.6	0.9		0.47
24 h	46	6.6	0.9		23	6.5	0.9		23	6.6	0.9		0.75
48 h	43	6.4	1.1		23	6.4	1.3		20	6.5	0.9		0.66
96 h	35	6.7	1.1		18	6.9	1.0		17	6.5	1.1		0.26
1 week	31	7.2	1.0		16	7.0	1.0		15	7.5	0.9		0.20
Between-subjects effects													
Within-subjects effects (<i>n</i> = 27)*													
	mean	95% CI	<i>p</i> value		Dexamethasone (<i>n</i> = 14)				Betamethasone (<i>n</i> = 13)				<i>p</i> value
					mean		SD		mean		SD		
Baseline	6.7	6.3–7.1	0.02		6.7		1.0		6.6		1.0		
24 h	6.5	6.2–6.9			6.3		0.7		6.8		1.0		
48 h	6.4	5.9–6.9			6.1		1.5		6.6		1.0		0.25
96 h	6.9	6.5–7.3			7.0		1.0		6.8		1.0		
1 week	7.2	6.8–7.6			6.9		1.0		7.5		0.9		

(b) Maximum STV, beats per minute

	Individual time points				Dexamethasone				Betamethasone				<i>p</i> value
	All				N	mean	SD		N	Mean	SD		
Baseline	33	18.4	3.1		15	18.2	3.7		18	18.6	2.6		0.75
24 h	33	18.6	3.4		15	19.6	3.5		18	17.8	3.3		0.14
48 h	33	17.9	3.5		17	18.4	3.6		16	17.4	3.6		0.44
96 h	16	19.4	1.6		7	19.4	2.0		9	19.4	1.4		0.99
1 week	17	19.5	3.2		9	19.3	3.0		8	19.6	3.6		0.86
Between-subjects effects													
Within-subjects effects (<i>n</i> = 10) [†]													
	Mean	95% CI	<i>p</i> value		Dexamethasone (<i>n</i> = 4)				Betamethasone (<i>n</i> = 6)				<i>p</i> value
					Mean		SD		Mean		SD		
Baseline	19.4	17.8–20.9	0.24		19.8		2.2		19.0		2.0		
24 h	20.4	17.9–23.0			22.0		3.5		18.8		3.4		
48 h	17.4	15.1–19.8			18.3		3.4		16.7		2.9		0.29
96 h	19.4	18.6–20.1			18.8		1.0		20.0		1.1		
1 week	19.8	16.9–22.7			20.3		3.6		19.3		4.1		

CTG, cardiotocograph; STV, short-term variability. * 27 fetuses with biophysical profile score recorded at all 5 time points; 95% CI, 95% confidence interval of mean. [†] 10 fetuses for which maximum STV is recorded at all 5 time points; 95% CI, 95% CI, of mean.

1. No significant differences for UA PI, MCA PI, or CPR from pre-corticosteroid to final follow-up, within or between groups.
2. No significant differences between dexamethasone and betamethasone average MCA peak systolic velocity (PSV) at any time-point, or on between-subjects effects testing across time points. There was a significant difference in overall MCA PSV across the 5-time point subjects ($n = 28$) for within-subjects effects testing ($p = 0.003$), due to a significant difference between the 1-week follow-up result and the other 4 time intervals.
3. No significant differences between dexamethasone and betamethasone median DVPI values at any time-point. There was however a significant difference in overall within-subjects effects testing ($n = 20$, $p = 0.006$) due to a decrease from baseline (0.56) to 24 h median DVPI (0.50) (Table 3).
4. Apart from significantly lower median LUtA PI at 96 h post-dexamethasone, there were no significant differences in RUtA or LUtA PI between the 2 corticosteroids at each individual time-point, or in within-subjects testing.
5. AFI (singletons only) showed no significant differences between dexamethasone and betamethasone in average AFI at any of the 5 time points or on between-subjects effects testing. Overall, AFI differed across the 5-time point subjects ($n = 26$) for within-subjects effects testing, ($p = 0.03$) due to a slightly lower average AFI at 1 week follow-up (12.4) compared to other time points (12.9–14.0).
6. For BPP, there was a significant difference in overall BPP across the 5-time point subjects ($n = 27$) for within-subjects effects testing ($p = 0.02$), due to changes in no fetal breathing observed post-corticosteroid (57% at baseline, 67% at 24 h, 72% at 48 h, 60% at 96 h, and 29% at 1 week: $p = 0.003$). There were no significant BPP differences between dexamethasone and betamethasone.
7. For CTGs, there were no significant differences between maximum STV (visually estimated) overall from baseline through to final follow-up, or between dexamethasone versus betamethasone at any time-point. CTGs visually estimated as having normal variability at baseline (35/35, 100%) did not differ significantly to the proportion at 48 h (32/36, 89%, $p = 0.12$). The proportion of reactive CTGs (84% vs. 81%, $p = 0.72$) was similar at baseline and 48 h. No differential CTG effect of dexamethasone vs. betamethasone was observed. Overall, the proportion of CTGs classified as non-reassuring or abnormal ranged from 25 to 47%, with most non-reassuring classifications due to the presence of preterm contractions.
8. For LMPI (online suppl. Table 4), there were no significant differences from baseline to final follow-up, or between dexamethasone and betamethasone at each of the 5 time points. Although LMPI subcomponents did show some differences (ICT decreased from baseline at 24–28 h, before returning toward pre-corticosteroid values by a 1-week follow-up, with dexamethasone, showing a more marked decrease than betamethasone, while ET initially increased after corticosteroids), a change in absolute terms was modest (7–13%). For RMPI and its constituent “a” and “b” time intervals (online suppl. Table 5), there were no significant differences between RMPI overall from baseline through to final follow-up, or between dexamethasone and betamethasone at each of the 5 time points. However, there was a significant difference ($n = 7$, $p = 0.04$) in within-subjects testing due to a lower average RMPI from baseline to a 24-h follow-up (from 0.52 to 0.43), driven by a higher “b” interval measurement. No differences were noted for DMPI between time points or corticosteroids (data not shown).

Comparisons of fetuses with normal fetal welfare versus suspected fetal compromise at baseline were limited by a small subgroup sample size. Of the 13 pregnancies with baseline concerns, 8 gave birth before 1-week follow-up, including all 4 with absent or reversed baseline UA end-diastolic flow. As expected, there were significant baseline differences between UA PI, MCA PI, and AFI for the group with fetal concerns versus not. Post hoc between-subjects comparison testing of the participants with all of baseline, 24, and 48 h measures (3 time point comparisons) did find some significant differences (online suppl. Tables 6–7) of (1) a decrease in UA PI from baseline to 24 and 48 h in the no fetal concerns group, while the PI in the fetal concerns group remained essentially unchanged; (2) a slight decrease in MCA PI at 24 h in the fetal concerns group (then returning toward baseline at 48 h), while MCA PI remained essentially unchanged in the no concerns group. However, the absolute difference of the change in values of UA PI and MCA PI remained small (less than 1SD from mean values). The only between-subject differences noted between singletons and twins were a greater variation in DV PI values in twin fetuses ($p = 0.02$).

Correlations

Correlation testing was performed to examine the relationship between those with fetal concerns at baseline with: Doppler measures from baseline to 1-week follow-up, CTG maximum variability from baseline to follow-up, and pregnancy outcome (weeks' gestation at birth, latency from corticosteroid administration to birth, birth weight, and length of neonatal stay). The presence of fetal concerns at baseline was significantly correlated with increasing UA PI for all time points except 1-week follow-up ($r = 0.40$ – 0.53 , $p < 0.02$ for all) and with decreasing MCA PI at baseline ($r = 0.45$, $p = 0.003$), 24 h ($r = 0.50$, $p = 0.001$), and 48 h ($r = 0.46$, $p = 0.002$). The presence of fetal concerns at baseline was also significantly correlated with RUtA and LUtA PI at 0, 24, and 48 h, and negatively correlated with AFI at baseline. No major correlations between fetal status and MPI values, BPP, or maximum STV on CTG were noted. The presence of fetal concerns at baseline was negatively correlated with gestation at birth ($r = -0.55$, $p < 0.001$), latency between corticosteroid administration and birth ($r = -0.40$, $p = 0.006$), and birthweight ($r = -0.67$, $p < 0.001$), and positively correlated with length of hospital stay ($r = 0.65$, $p < 0.001$).

Discussion

In this prospective cohort of women receiving corticosteroids for fetal lung maturation, mostly not for fetal concerns, few post-corticosteroid differences were noted in fetal or maternal Doppler studies, BPP, or CTG, none likely to alter clinical management. The only statistically significant differences noted post-corticosteroid administration in within-subjects repeated-measures testing were an increase in MCA PSV on 5-time point testing; a decrease in median DVPI at 24 h of 16% from baseline (then returning to within 10% of baseline); a decrease in average RMPI of 17% from baseline to 24 h (then returning to within 10% of baseline); a decrease in AFI 5-time point testing (mean AFI lower at 1-week follow-up); and fall in average BPP from baseline to 48 h (primarily due to more fetuses not displaying fetal breathing movements). There was no evidence of a different effect of dexamethasone compared to betamethasone on fetal or maternal Doppler studies, BPP, or CTG.

Of these few differences, the changes in MCA PSV and AFI are not clinically significant, being modest and only occurring between baseline and 7–10 days. The DVPI and RMPI findings are more likely to be relevant, being due to a change in values immediately post-corticosteroid.

RMPI and DVPI both reflect aspects of right heart function [38], decreasing at the 24 h time-point making the finding more likely to be real rather than a chance result. It has been previously suggested that glucocorticoid-induced vasodilation reduces afterload and increases cardiac output, accounting for DVPI and MPI changes [39]. Transient DVPI reductions post-corticosteroid have been noted by some authors [40, 41] but not others [42–45]. Hodges et al. [46] noted an improvement in cardiac function with MPI 24 h after betamethasone administration in FGR fetuses, while a tissue Doppler (MPI) study of 17 FGR fetuses found a decrease in RMPI after corticosteroid administration but not LMPI, further suggesting the current findings to be real [39]. However, both the RMPI and DVPI falls averaged $<20\%$ (only modestly higher than normal Doppler biological variability) and were transient, making it unlikely that such differences would, in isolation, alter clinical management.

Last, the BPP findings were consistent with some prior studies [11] and due to increased absence of fetal breathing movements 24–48 h post-corticosteroid. Although the cause of fetal breathing alteration is uncertain, it has been postulated to be due to glucocorticoid receptor-mediated processes in the fetal brain [47]. This suggests that measuring fetal breathing as part of BPP immediately post-corticosteroid administration should be approached with caution. Unlike prior studies, including studies of 60 and 46 women, respectively, randomized to betamethasone or dexamethasone [48, 49], we did not note substantial decreases in fetal movements or any differential corticosteroid effect [11]: this may reflect that BPP was being performed as 1 component only of study ultrasounds and more subtle changes from prolonged specific fetal movement observation were not noted. However, given the overall reassuring movement findings, we do not believe this has negative practice implications.

For the smaller subgroup with fetal concerns at baseline, as expected, there were significant differences between UA and MCA Doppler values at baseline, 24-h follow-up, and 48 h. These were no longer statistically significant at the later follow-up times, likely due to diminishing subgroup numbers. The between-subjects 5-time point testing did not suggest any differential effect of corticosteroids on UA/MCA/MPI Doppler in the fetal concerns group, in contrast to previous work [50]. However, the number of “fetal concerns” fetuses available for the 5-time point repeated-measures analysis was very small (maximum of 4). Post hoc 3-time point repeated measures (with larger subgroup size) found, consistent with some previous work [44, 45], that MCA PI decreased transiently in the fetal-concerns group,

although contrary to expectations not the UA PI [50]. As this 3-time point measure reflected “fetal concerns” fetuses who required birth between 48 h and 7–10 days post-corticosteroid, our findings may simply be reflecting lack of post-corticosteroid UA PI improvement in FGR fetuses destined for earlier delivery [51].

The supplementary analysis, of singletons versus twins, was limited by the small size of this subgroup ($n = 8$, all assigned by chance to dexamethasone). However, there was no evidence of a differing effect of maternal corticosteroid administration on singletons versus twins.

Strengths and Limitations

The strength of the study is its nesting within a blinded RCT, meaning that ultrasound and CTG data on short-term effects of dexamethasone versus betamethasone were collected and analyzed in a blinded fashion. Although this did not eliminate an observer bias for overall pre- versus post-corticosteroid ultrasound measures, it did do so for assessing any differential effects of dexamethasone versus betamethasone (of which no evidence was found). The de-identification and randomization of CTGs prior to visual analysis also helped reduce any observer bias for pre- versus post-corticosteroid interpretation. Another major strength is the high percentage of ultrasound measures that were collected as per-protocol.

The lower proportion of CTGs performed per-protocol, and the CTG analysis comprising conventional visual methods not computerized CTG (cCTG), is however, a limitation [52]. Initial planned cCTGs were not able to be performed, so all CTGs were analyzed visually and data interpreted with caution. However, recent cCTG studies including over 100 patients each (albeit limited by their retrospective nature/variability in cCTG timing) have not suggested major STV changes post-corticosteroids [53, 54]. Consistent with prior studies, there was no difference in the presence (which was very low) of fetal heart rate decelerations post-steroid [11, 48], reinforcing that in clinical practice, decelerations should be assumed to be real and not attributed to the corticosteroid effect. Additionally, due to timing of both initial corticosteroid dose and clinical considerations regarding timing of follow-up CTGs, these were not consistently performed at set times of day. As the transient loss of diurnal changes has previously been found in fetal heart rate variability after betamethasone administration [55], subtle changes (or any differential betamethasone vs. dexamethasone effect) would be less likely to be noted in this study.

Although 90% of ultrasounds were performed by a single operator, the other 10% were performed by a variety

of trained personnel, introducing interobserver variability. Removing the ultrasounds of the additional operators did not substantially change the mean Doppler values, and did reduce the number of patients eligible for repeated-measures analysis, so decision was made to include all ultrasounds by all operators. Given in usual clinical practice that ultrasounds are often done by several different operators, if any post-steroid differences are so subtle as to require the elimination of interobserver variability, it is unlikely that such differences would be of clinical utility.

Another limitation is that the pregnancy characteristics of the participants restrict the conclusions that can be drawn. Although all were considered at high risk of preterm birth <34 weeks, only a minority had fetal growth restriction/compromise, and over half remained undelivered 7–10 days post-corticosteroid. Therefore, the main conclusions that can be drawn are a relative lack of observed short-term corticosteroid effect on the ultrasound and CTG parameters studied in this population. It remains possible that the greater effects, including a difference in dexamethasone versus betamethasone, could be seen in a group with more growth restriction/fetal compromise. Against this, betamethasone effects from the TRUFFLE trial were slight and thought most likely to reflect the worsening pathology of their FGR cohort rather than a corticosteroid effect [53].

The initial calculated sample size of 50 was not reached, secondary to the parent A*STEROID trial reaching its recruitment target. However, given the small differences found for the pre- versus post-corticosteroid measures on which the trial was powered, it is highly unlikely that the extra 3 fetuses would have altered the findings.

Conclusions

There were no major clinically significant effects of corticosteroid administration on the majority of fetal Doppler measurements, in a population of fetuses at risk of preterm birth with mostly normal baseline fetal welfare studies. There was no evidence of any differential effect of dexamethasone versus betamethasone on the study measures. The modest, transient decrease of measures such as DV PI, right MPI, and BPP after corticosteroid administration suggests that it is appropriate to note in clinical practice timing of corticosteroids in relation to assessment of fetal well-being measures and not rely on a single measure for delivery decisions soon after corticosteroids are given.

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Statement of Ethics

The research described was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. As noted in the manuscript, subjects gave their written informed consent to participate, and ethical approval was received from the South-Eastern Sydney Local Health District Human Research Ethics Committee (SESLHD HREC reference number: 11/202).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Amanda Henry: involved in study concept along with C.A.C. and A.W.W.; developed study protocol; obtained ethical approval; principally responsible for study conduct, data entry, and analysis; and wrote the manuscript. Aditi Mahajan: involved in study conduct, data entry and analysis, and manuscript revisions. Caroline A. Crowther: involved in study concept along with A.H. and A.W.W., PI of parent A*STEROID trial, and involved in data analysis and manuscript revisions. Anne Lainchbury: involved in study conduct, data entry and analysis, and manuscript revisions. Lynne Roberts: involved in study conduct, data entry and analysis, and manuscript revisions. Antonia W. Shand: involved in development of study protocol, study conduct, and manuscript revisions. Alec W. Welsh: involved in study concept along with A.H. and C.A.C., involved in development of study protocol, data analysis, and manuscript revisions; a primary PhD supervisor of A.H. All authors have read and approved the final submitted manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could potentially compromise the privacy of the research participants and are however available from the corresponding author A.H. on reasonable request.

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