The short term fetal cardiovascular effects of corticosteroids used in obstetrics

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Abstract

Background: Corticosteroids are widely used in obstetrics due to their striking effect on perinatal morbidity and mortality of premature neonates. Despite this, relatively few studies have explored short term fetal effects of corticosteroids as measured by ultrasound.

Objectives: 1) To present a literature review of short term fetal cardiovascular effects of corticosteroids 2) To describe the protocol of a current observational study (SUPER-A*STEROID) of cardiovascular effects of dexamethasone and betamethasone in the first week after their administration. This trial is nested within the A*STEROID blinded multicentre randomised controlled trial of the two steroid preparations.

Findings: Existing data suggest corticosteroids have little effect on the major measured fetal blood vessels when the baseline ultrasound is normal. In the compromised fetus, where the umbilical artery end-diastolic flow is abnormal prior to maternal corticosteroids, flow is temporarily restored in approximately 50% of cases. Whether such changes are beneficial is uncertain. Very little data exist that directly compare the short-term effects of betamethasone and dexamethasone. The SUPER-A*STEROID study described will help provide this information.

Keywords: antenatal corticosteroids, Doppler ultrasound, Myocardial Performance Index, premature delivery.

Introduction

It is known that antenatal maternal corticosteroid administration greatly reduces neonatal death, respiratory distress syndrome, and intraventricular haemorrhage rates in preterm infants.[1] Steroid administration to mothers at high risk of preterm delivery < 34 weeks gestation is therefore part of routine clinical practice. As 70–80% of developed world pregnancies delivering at 24–34 weeks gestation receive steroids,[2] in Australia alone at least 5000 steroid courses would be expected to be given each year prior to preterm birth. In reality fetal exposure to exogenous corticosteroids may be much higher, as many mothers receive corticosteroids for risk of preterm birth but deliver > 34 weeks. Additionally, many more women may be given steroids at later gestation when elective caesarean section without labour is planned.

Despite the many pregnancies exposed to corticosteroids, short-term effects of maternal steroid administration on fetal cardiovascular status are still uncertain. Whether the effects seen are beneficial, particularly in the growth-restricted fetus, is also controversial.

Interpretation of short-term fetal corticosteroid effects is made more difficult by the varying ways in which they can be studied, for example

- Type of steroid (betamethasone vs. dexamethasone)
- Baseline Doppler measurements (normal vs. abnormal)
- Indication for steroids
- Fetal vessel (UA, DV, MCA)
- Gestation given.

Existing work suggests that baseline umbilical artery end-diastolic velocity has significant impact on ultrasound measures of steroid effects, with type of steroid also potentially important.[3] Table 1 summarises studies (of predominantly or exclusively singleton fetuses) examining corticosteroid effects in fetuses where baseline umbilical artery flows were normal.[4–16] Although the methodologies of the included studies are mixed, cumulatively they show no consistent evidence of changes in velocity waveform patterns after corticosteroid administration in multiple arteries studied. Middle cerebral artery (MCA) pulsatility index is a possible exception, with changes at 48–72 hours noted in a minority of studies.[3]

Table 2 summarises short term data on effect of corticosteroids on fetal vessels in fetuses with abnormal umbilical artery (UA) diastolic blood flow pre-steroids. Most of these studies show a reduction of placental vascular resistance and temporary restoration of umbilical artery end-

Table 1: Studies describing short-term corticosteroid effects on blood flows with positive umbilical artery end-diastolic velocities at baseline.

First author (year)	Regimen (dose: interval-hours)	Study design (measurement interval: hour)	Patients total (% IUGR)	Umbilical artery flow effects	MCA (PI)	DV (PI)	Uterine artery (PI)	Other blood vessels (PI: comments)
Thuring (4) (2011)	Betamethasone 12 mg x 2: 24 hours apart	T0, 48, 96	18 (70)	↓PI 48h, return by 96h	Non-sig ↓	↓PI 48h ret by 96h	°	-
Piazze (5) (2007)	Betamethasone 12 mg x 2: q24hr	T0, 72, 96, 120	84 (0)	°	↓PI 72h	-	-	-
Urban (2005) (6)	Betamethasone 12 mg x 2: q24hr Dexamethasone 6 mg x 4: q12hr	T0, 24, 72 for both	33 (0) 34 (0)	° °	° ↓PI 72h	- -	- -	- -
Kahler (2004) (7)	Betamethasone 8 mg x 2: q24hr	T0, 24, 32, 48, 72, 96	27 (0)	°	°	°	°	-
Wijnberger (2004) (8)	Betamethasone 12 mg x 2: q24hr	T-120-0, T24-120 (variable)	55 (100)	° (NB high PI at baseline)	Non-sig↓	°	-	-
Simchen (2004) (9)	Betamethasone 12 mg x 2: q24hr	T0, 24, 48, 72	6 (0)	°	°	-	-	-
Deren (2001) (10)	Betamethasone 12 mg x 2: q24hr	T0, 24, 48, 72, 96, 120	35 (0)	°	°	-	-	-
Piazze (2001) (11)	Betamethasone 12 mg x 2: q24hr	T -48 to 0, 72, 120	36 (28)	°	↓PI 72hr	-	°	-
Senat (2000) (12)	Betamethasone 6 mg x 4; q12hr Dexamethasone 4 mg x 4; q12hr	T0, 24-48, 96-168 for both	25 incl. 10 twins (92) 15 incl. 7 twins (87)	° °	° °	- -	° °	DAo ° DAo °
Rotmensch (1999) (16)	Betamethasone 12 mg x 2: q24hr	T0, 48, 96	31 (0)	°	°	-	-	-
Cohlen (1996) (13)	Betamethasone 12 mg x 2: q24hr	T0, 48, 96	15 (7)	°	°	-	°	DAo, ICA, RA, CA all °
Meizner (1989) (14)	Betamethasone 12 mg x 2: q24hr	T0, 24, 48, 72	18 (0)	°	-	-	°	
Chitrit (2000) (15)	Dexamethasone 4 mg x 6: q8hr	T0, 48, 96, 168	26 (0)	°	↓PI 96h	-	-	-

° = no change - = not measured in this study
CA = cerebral arteries other than MCA
Dao = Descending Aorta
ICA = Internal carotid artery
RA = Renal artery
PI= pulsatility index
T0= Baseline (pre-steroids)
MCA = Middle cerebral artery
DV = Ductus venosus
IUGR = Intrauterine growth restriction

diastolic velocities (UAEDF) after betamethasone administration. However, the proportion of cases with restored UAEDF ranges widely, from 33 to 100%.[4,9,17–24] If UAEDF is restored this occurs rapidly: as early as 4–8 hours and definitely by 24 hours post-steroid administration.[22] This suggests direct fetoplacental unit circulatory effects of steroids rather than cellular effects on transcription factors. As changes in uterine artery (UtA) flows are not seen post-steroid, the UA changes are most likely from direct steroid action on the fetal cardiovascular system.[4]

There is wide variability in how long the effect of steroids on UAEDF lasts, with up to 7–10 days reported.[23] However the median time at which the baseline abnormality returns is 3 days after the first dose of steroid.[9,22,23] Other effects on the fetal circulation have not been consistently reported for this group, although decreased MCA PI (accentuating the MCA redistribution pattern seen in the growth restricted fetus) is reported by a minority of authors (Table 2).

Data is scant regarding UAEDF effects in multiple pregnancy. However, Barkehall-Thomas and colleagues[25] found 50% rate of return of positive UAEDF after betamethasone administration

Table 2: Studies describing short-term corticosteroid effects on blood flows with abnormal baseline umbilical artery end-diastolic velocities.

First author (year)	Regimen (dose: interval)	Study design (measurement interval: hour)	Patients Total n (% IUGR)	Baseline UA abnormality	Umbilical artery flow effects	MCA (PI)	DV (PI)	Uterine artery (PI)	Other blood vessels (PI: comments)
Piazze (2012) (17)	Betamethasone 12 mg X 2: q24hr	T0, then q24 until delivery	64 (100)	AREDF	+EDF 24hr 21 (33%)	-	24h if still AREDF	-	-
Thuring (2011) (4)	Betamethasone 12 mg x 2: 24 hours apart	T0, T48, T96	15 (70)	AEDF 11 REDF 4	10 +EDF 48hr (2 REDF → AEDF) Return by 96hr	Non-sig ↓	↓PI 48h ret by 96h	°	-
Nozaki (2009) (18)	Betamethasone 12 mg x 2: 24 hours apart	T0, T24, T48	32 (100)	AEDF all	22 (69%) +EDF 24h	°	↓PI 24, 48h	-	-
Robertson (2009) (19)	Betamethasone 11.4 mg x 2:24 hours apart	T0 then variable (retrospective study)	92 (100)	AEDF all	58 (63%) "transient" +EDF post-steroid	-	-	-	-
Simchen (2004) (9)	Betamethasone 12 mg x 2: q24hr	T0, 24, 48, 72	19 (100)	AREDF	10 (53%) +EDF 24h, gone by 72hr	°	-	-	UV velocity D1 if persistent AREDF
Muller (2003) (20)	Betamethasone 8 mg x 1 Dexamethasone 12 mg x 1	T0, 24–48 for both	3 (100) 17 (100)	13 AEDF and 7 REDF of total group (results not grouped by steroid)	9 (45%) improvement at 24–48hr (7 to +ve flow, 2 REDF to AEDF)	↓24h	°	-	-
Edwards (2003) (21)	Betamethasone 11.4 mg x 2: q24h	T0, 12, 24, 48–240	55 (100)*	AEDF all	39 (71%) +EDF 24hr: median return AEDF 72hr	-	-	-	-
Edwards (2002) (22)	Betamethasone 11.4 mg x 2:24 hours apart	T0 and 24 (all), some also T4, 8, 12	12 (100)	AEDF all	12 (100%) +EDF 8–24h	↓24h	°	-	Renal artery °
Wijnberger (1999) (24)	Betamethasone 12 mg x 2: q24hr	T0, 24, 48, 72, 96	45 (100)	"redistribution" UA	°	-	-	-	-
Wallace (1999) (23)	Betamethasone 11.4 mg x 2:24 hours apart	T0, 24, 48, 72, 96	28 (100)	AEDF all	19 (68%) +EDF 24 hrs: median return AEDF 72hr	-	-	-	-

° = no change - = not measured in this study

* Includes 30 prospective patient and 25 singletons from the retrospective 1999 Wallace, *et al.* study: results pooled

UA = Umbilical artery

PI= pulsatility index

T0= Baseline (pre-steroids)

MCA = Middle cerebral artery

DV = Ductus venosus

UV = Umbilical vein

AEDF = Absent end-diastolic flow

EDF = End-diastolic flow

IUGR = Intrauterine growth restriction

in a mixed cohort of DCDA twins, MCDA twins, and triplets, suggesting hemodynamic effects of steroid administration are similar to singletons. More recently however, Chang and colleagues found that in only four of twenty MCDA twin pregnancies with UAEDF in one twin did EDF transiently return after betamethasone administration.[26]

Whether the effects observed by ultrasound on fetal hemodynamics represent a beneficial boost to fetal circulation, or a potential harmful over-riding of compensation mechanisms, remains controversial. Studies of fetal behavioural effects of antenatal corticosteroids (measured by biophysical profile and cardiotocograph) demonstrate up to 50% reduction in fetal movements at 24–48 hours, up to 90% reduction in fetal breathing movement at 48–72 hours, and decreased fetal heart rate variability of 20–30% at 24–72 hours.[3] As these events (normally of clinical concern, particularly in the growth-restricted fetus) are seemingly happening concurrently with a restored UAEDF, it cannot be assumed the UAEDF restoration is beneficial. Additionally, animal studies have found that 1) blood-brain barrier alterations mean IUGR fetuses have longer exposure times to higher steroid concentrations 2) steroids may compromise their maintenance of blood pressure and cerebral blood flow.[27] Clinically, a neonatal network registry study from 1991–96 found that steroids appeared to be equally of benefit to IUGR and non-IUGR fetuses.[28] However, there are no randomised trials, and a more recent meta-analysis of several small case-control and cohort studies (excluding the registry trial) found that steroids did not confer benefits when given in IUGR.[29] Whether or not steroids benefit IUGR fetuses as much as their normally grown counterparts, IUGR fetuses with abnormal UAEDF pre-steroids who do *not* respond to steroids by returning to positive UAEDF may be at increased risk for adverse outcome. Robertson, *et al.* found significantly higher levels of respiratory distress syndrome (RDS), chronic lung disease, and need for ventilation in 29 fetuses with no return of UAEDF post-steroids vs. 49 fetuses with return of UAEDF.[19] Piazze, *et al*., in their study of 64 IUGR fetuses, reported a 67% RDS rate with persistent absent or reversed end diastolic flow (AREDF) after steroids and only a 20% rate if UAEDF returned.[17] The current hypothesis is that fetuses with UAEDF return have sufficiently intact physiological mechanisms to respond to steroid challenge,[17] while those with persistent UAEDF are a group with greater pre-existing compromise. This fits with Robertson *et al.'s* finding of lower cord pH at birth in their persistent AREDF group.[19]

Differential effects of different corticosteroids?

The two most commonly used steroid preparations in clinical practice worldwide are betamethasone and dexamethasone. Current randomised data is inconclusive regarding whether either preparation has a decreased chance of long-term side effects while maintaining beneficial neonatal effects.[30] There is scant published data on dexamethasone effects on fetal cardiovascular status as measured by ultrasound (Table 1), and only one study directly comparing women randomised to dexamethasone or betamethasone.[6] In this study, only women with normal fetal pre-treatment flows were included, and a change in MCA but not UA flows was found with dexamethasone. In the few studies describing dexamethasone behavioural effects, only a minority of studies describe decreased fetal heart rate variability, body movement and breathing at 24–72 hours. This raises the possibility of different secondary (24+ hours after administration) effects of dexamethasone compared to betamethasone.[3] The pharmaco-physiological mechanism behind any difference in effect is uncertain, but might relate either to timing of administration or absorption characteristics of long-acting betamethasone formulations.

The Myocardial Performance Index

An additional technique for ultrasound measurement of fetal cardiovascular status, without the expertise required to perform a full fetal echocardiogram, is the modified myocardial performance index (mod-MPI). In adults, the MPI distinguishes between normal and abnormal ventricular function, and has been extrapolated to evaluation of the fetal heart in both normal and complicated pregnancies.[31] Our group has recently published a number of refinements to improve the repeatability of the mod-MPI,[31,32] as well as producing Australian normal ranges for both left and right-sided mod-MPI.[33,34]

As corticosteroid administration may alter fetal cardiac output, complicating the interpretation of mod-MPI in growth restricted or other complicated pregnancies where its use is currently being researched, it is important to document whether such changes occur. Apart from a small series of 5 IUGR and 5 control fetuses which found baseline cardiac strain in IUGR fetuses and transient improvement after steroids,[35] we are not aware of published work systematically evaluating the effect of maternal corticosteroid administration on fetal mod-MPI.

Research gap and current study

Few studies have comprehensively assessed the short-term effect of antenatal corticosteroids on ultrasound and CTG measures of fetal cardiovascular function. There is likewise little data correlating short term fetal responses on ultrasound and CTG with either neonatal or infant outcome. There is also a research gap regarding effects of dexamethasone versus betamethasone.

The multicentre A*STEROID study (Australasian Antenatal Study To Evaluate the Role of Intramuscular Dexamethasone versus Betamethasone prior to preterm birth to increase survival free of childhood neurosensory disability) is comparing the effects of betamethasone and dexamethasone in infants up to 2 years of age in a blinded, randomised trial.[36] This study enables our group to concurrently assess, in a subgroup of A*STEROID patients, the short-term effects of:

1 Either corticosteroid on fetal and uteroplacental hemodynamics, including cardiac function as measured by mod-MPI
2 Either steroid on fetal behavioural responses as measured by CTG and biophysical profile
3 Differential effects of betamethasone vs. dexamethasone
4 Correlation between short term effects and neonatal and infant outcomes.

Methods

Patients will be prospectively recruited as a sub-study of women participating in the multicentre randomised double-blind trial of antenatal intramuscular Betamethasone vs. Dexamethasone

for women at risk of preterm birth < 34 weeks gestation, the A*STEROID trial. The sub-study acronym adopted is SUPER-A*STEROID (Steroid Ultrasound Parameters Enhancing Routine-A*STEROID). SUPER-A*STEROID patients will be recruited from two metropolitan Sydney hospitals participating in the A*STEROID study, the Royal Hospital for Women and St George Hospital. Ethical approval for conduct of the study has been granted by the local Human Research Ethics Committee (SESLHD HREC 11/202).

Patients will be eligible for inclusion if they fulfil the A*STEROID study entry criteria of being at risk of preterm birth < 34 weeks gestation, having a singleton or twin pregnancy, having no contraindications to the use of antenatal corticosteroids, and having given informed consent to participate in A*STEROID. Additionally, for SUPER-A*STEROID entry, participants are required to be aged 18–50, have had a normal fetal cardiac morphology ultrasound, and give informed consent to participate in SUPER-A*STEROID. Exclusion criteria are any of the A*STEROID exclusion criteria (chorioamnionitis requiring urgent delivery, higher order multiple pregnancy, antenatal corticosteroids already given, known fetal lung maturation, or in the second stage of labour), an abnormal cardiac morphology scan, psychiatric illness precluding informed consent, insufficient English for valid consent, or mothers taking digoxin or pure beta-blocker. Use of maternal medications with minor potential effects on the fetal cardiovascular system such as labetalol, will be recorded but is not a reason for exclusion.

Conduct of study

All women will undergo baseline examination less than four hours prior to steroid administration. This examination includes:

1 Ultrasound assessment of fetal growth parameters (abdominal circumference, biparietal diameter, head circumference and femur length), biophysical profile (assessment of fetal breathing, movement, tone, and amniotic fluid volume) and placental assessment as described by Viero, *et al.*[37]
2 Ultrasound measurement of umbilical artery, middle cerebral artery, ductus venosus, and uterine artery Doppler. The measurements will be performed in the absence of fetal movements with the angle of insonation as close to 0 degrees as possible. Umbilical artery Dopplers are measured on a free-floating loop of umbilical cord. Middle cerebral artery flows are obtained in a transverse view of the fetal head, at the level of its origin from the circle of Willis, with Doppler gate placed in the proximal third of the MCA. Ductus venosus flow is measured in mid-sagittal or transverse section of the fetal abdomen, positioning the Doppler gate at its isthmic portion. All Doppler measurements are taken three times to improve accuracy.
3 Measurement of myocardial perfusion index, in both right and left fetal cardiac ventricles, at the Royal Hospital for Women site, and if available the St George Hospital site, using previously published data for suggested mod-MPI technical settings.[31]
4 Cardiotocograph (CTG).

All women who remain undelivered will have these measurements repeated (with the exception of fetal growth parameters and placental morphology) 24 hours after steroid administration (acceptable range 18–30 hours), 48 hours after steroid administration (acceptable range 42–54 hours), 96 hours after steroid administration (acceptable range 3–5 days), and 7–10 days after steroid administration (if a repeat dose of steroids was to be given, 7–10 day ultrasound was performed prior to the repeat dose). Ultrasound machines used will be Voluson e8 (GE Medical Systems, Australia) at RHW site, and Voluson 730 (GE Medical Systems, Australia) or iU22 (Philips Healthcare, Australia) at STG site. All MPI measurements will be performed on Voluson e8 or Voluson 730 systems. Assessments will be performed using 3.5–7- MHz linear or curved array transducers.

Following delivery, arterial and venous pH samples will be obtained from the umbilical cord to allow correlation of fetal status at delivery with previously noted ultrasound and CTG parameters. Placentas will be sent for histopathological examination. Pregnancy, labour, and neonatal data will be abstracted from case notes.

Data entry and analysis

All data will be entered into an Excel spreadsheet and analysed using SPSS (SPSS Inc, Chicago, IL, USA). As the normal distribution of Doppler measurements changes with gestational age, individual fetal measurements will be normalised prior to analysis to give a Z-score (by expressing the deviation of the individual measurements from the gestational age mean in standard deviations). Mod-MPI values will be compared against our previously published normal range.[33] Analysis techniques for repeated measures will be used to examine changes of Doppler flows, MPI, biophysical profile, and CTG from baseline to the follow-up ultrasounds.

All data will be collected and entered prior to unblinding of investigators (projected to be January 2014) as to which steroid was received. Relationships between Doppler parameters, CTG, indication for steroid use, neonatal outcomes and (after unblinding) type of steroid used will be analysed using Pearson correlation. Continuous variables will be compared using parametric or non-parametric analysis based on their distribution. Proportional distributions of categorical outcome variables will be related to CTG and Doppler results using Chi-squared and Fisher's exact tests.

Power and sample size

Precision of the sample size calculation was limited by lack of clarity regarding both expected effects of steroids in general on fetal cardiovascular parameters, and any differential effect of betamethasone vs. dexamethasone. A mean gestational age at study entry of 31 weeks was used to allow use of assumptions regarding likely population parameter means and standard deviations from previous studies. All calculations of required sample size were two-sided tests with alpha set at 0.05 and power at a minimum of 80%.

Regarding whole group comparisons of pre-steroid and post-steroid measurements, a sample size of 50 fetuses is proposed to enable detections of

1 Decrease in short-term variability from 9 to 6–95% power
2 Decrease in proportion of normal variability traces from 90% to 70%–95% power
3 Decrease in middle cerebral artery pulsatility index of 0.2

with a standard error of 0.4–90% power. Lesser sample size of 40 allows all these outcomes to be detected with at least 80% power. A smaller sample size of 20 is required in order to detect a change in MPI peak value of 10% (.04) from the normal measurement of 0.42 ± 0.06 at 31 weeks, at 80% power.

Regarding betamethasone vs. Dexamethasone comparisons, and allowing for the fact that numbers in each arm cannot be prospectively known and may not be balanced, a sample size of 40 fetuses is proposed to detect with 80% power:

1 A difference in MCA PI of 0.3 between the groups, assuming standard deviation of 0.3
2 A difference of 3 in mean short-term variability on CTG, assuming standard deviation of 3 in both groups.

Discussion

A substantial number of fetuses are exposed to corticosteroids due to their risk of being born prematurely. It is therefore important to understand short-term effects of corticosteroids on the fetus in utero, and whether there are correlations between these effects and neonatal outcomes and/or later outcomes. Also of importance is whether different steroid preparations display different effects on fetal hemodynamics. The A*STEROID trial of betamethasone vs. dexamethasone is providing the opportunity to comprehensively assess both the ultrasound-measured short term fetal hemodynamic and behavioural effects of these steroids in a blinded fashion, and their relationship to neonatal and later infant outcome. A total of 43 women and 47 fetuses were recruited to the SUPER-A*STEROID trial from Feb 2012–Jan 2013. Final results will be presented after unblinding of investigators to steroid group allocation.

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