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Antenatal corticosteroid therapy: short-term effects on fetal behaviour and haemodynamics

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S U M M A R Y

Antenatal corticosteroid therapy to enhance fetal lung maturity in threatened preterm delivery has a number of non-pulmonary side-effects, both beneficial and undesirable. This review focuses on the short-term (transient) effects of betamethasone and dexamethasone on aspects of fetal circulation and behaviour which are used clinically as markers of fetal well-being. We summarise the effects observed, discuss the proposed underlying mechanisms, and emphasise the consequences for clinical decision-making. Recommendations are given to optimise medical care and to minimise the risk of unwarranted iatrogenic preterm delivery.

1. Introduction

Synthetic corticosteroids (betamethasone, dexamethasone) are routinely administered to pregnant women with threatened preterm delivery to prevent or reduce neonatal death and complications of prematurity [respiratory distress syndrome (RDS), cerebrovascular haemorrhage]. A single course of antenatal corticosteroid has been shown to be effective and safe, as no differences in physical and functional development were found between treatment and control survivors until age 30 years.[1] However, follow-up studies and numerous animal experiments have raised concerns about the long-term side-effects of antenatally administered corticosteroids when treatments are repeated or prolonged.[2]

Betamethasone and dexamethasone are potent drugs which are administered in high doses to pregnant women. Since they are not bound to plasma proteins and are only minimally metabolised by the placenta, their concentrations in the fetal compartment are relatively high 2–3 h after treatment.[3] Short-term fetal effects from exposure to exogenous corticosteroids are therefore likely to occur. Indeed, it has been recognised for some time that synthetic corticosteroids exert significant side-effects on the fetal cardiovascular system, hypothalamic–pituitary–adrenal (HPA) axis, and the brain. However, various studies have reported differences in observed effects which, among others, may relate to the timing of drug administration, the rate and interval of subsequent measurements, and the type of drug. The purpose of this review is (a) to provide an overview of the reported effects of betamethasone and dexamethasone on human fetal behaviour, heart rate and its variability, and Doppler velocity waveform patterns; and (b) to highlight the importance of this knowledge for clinicians to optimise decision-making immediately after drug injection. Although the focus will be on human studies, animal studies will be referred to where appropriate.

2. Design and methodology of the human studies considered for review

Computerised literature search of PubMed and manual search of bibliographies of pertinent articles were performed. Relevant articles were included for review and not subjected to predefined selection criteria. Main characteristics are presented in chronological order in Tables 1 and 2.[4–44]

Steroid effects were evaluated between 25 and 35 weeks' gestation (median 30) and the population size across studies ranged between 13 and 180 (median 30) patients. Long-acting betamethasone (suspension of the acetate and phosphate forms) and short-acting dexamethasone phosphate were used uniformly. Studies differed for several reasons, which included their retrospective or prospective character and execution under clinical or research conditions; indications for steroids [heterogeneously composed study groups vs homogeneous groups of fetuses with intrauterine growth restriction (IUGR), appropriate growth for age (AGA) fetuses, preterm contractions, or twins]; steroid regimen, which did not always comply with the National Institutes of Health recommendations of two doses of betamethasone (12 mg) every 24 h or four doses of dexamethasone (6 mg) every 12 h; duration of study period (range 2–7 consecutive days); interval between subsequent measurements (<24 h; 24 h; 48 h); fetal heart rate

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Table 1
Effects of maternal betamethasone and dexamethasone administration on fetal heart rate (FHR), FHR variability, and body and breathing movements as reported in the literature.

Drug; first author	Regimen (dose; interval)	Study design (observation interval; h)	Observed length (min)	FHR	FHR variability	Body movement	Breathing	Remarks
Betamethasone								
Maršál (1975)[4]	3*12 mg; 24 h	d 0, 96, 168	30				=	
Katz (1988)[5]	4*6 mg; 12 h	d 0, 24, 48, 72	60		↓12–72 h	↓ 24 h		F1; M1
Meizner (1989)[6]	4*6 mg; 12 h	d 0, 24, 48, 72	30/60			↓ 24 h; (=)		M1; (M2)
Mulder (1994)[7]	2*12 mg; 24 h	d 0, 24, 48, 72, 96	60	↑ 72 h	↓ 48, 72 h	↓ 24, 48 h	↓ 48, 72 h	F2; M2
Derks (1995)[8]	2*12 mg; 24 h	d 0, (24), 48, (72), 96	60	=	↓ 48, 72 h	↓ 48 h	↓ 48 h	F2; M2
Ville (1995)[9]	4*6 mg; 12 h	d 0, 24–36, 96–168	30	=	↓ 24–36 h	=		F2; M1; twins
Mulder (1997)[10,a]	2*12 mg; 24 h	d 0, 24, 48, 72, 96	60	=	↓ 48, 72 h	↓ 48 h	↓ 48 h	F2; M2
Magee (1997)[11,a]	2*12 mg; 12 h	d 0, 24, 48	60	↓ 24 h	↑ 24 h	↓ 24 h		F2; M1
Multon (1997)[12]	4*6 mg; 12 h	d 0, 24, 48, 96–168	30	↓ 24 h	=	=		F2; M1; IUGR
Senat (1998)[13,a]	4*6 mg; 12 h	d 0, 24–48, 96–168	30	=	↓ 24–48 h			F2; AGA
Rotmensch (1999)[14,a]	2*12 mg; 24 h	d 0, 48, 96	30/60	=	↓ 48 h	↓ 48 h	↓ 48 h	F2; M2
Rotmensch (1999)[15]	2*12 mg; 24 h	d 0, 48, 96	30			↓ 48 h	↓ 48 h	F2; M2; BPS
Kelly (2000)[16]	2*12 mg; 24 h	d 0, 24–48	30		↓ 24–48 h		↓ 24–48 h	F1; M2; BPS
Mushkat (2001)[17,a]	2*12 mg; 12 h	d 0, (6), 12, (18), 36	20/30	=	=	↓ 12, 18, 36 h	↓ 12, 36 h	F1; M1; M2; AGA
Frusca (2001)[18]	2*12 mg; 24 h	d 0, 24, 48, 72, 96, 120	30	=	↓ 72 h	↓ 48, 72 h		F2; M1; IUGR
Deren (2001)[19]	2*12 mg; 24 h	d 0, 24, 48, 72, 96, 120	30		↓ 24, 48, 72 h	↓ 48 h	↓ 24, 48, 72 h	F1; M2; BPS; AGA
Jackson (2003)[20]	2*12 mg; 24 h	d 0, 24, 48	30			↓ 48 h	↓ 48 h	F1; M1; BPS; AGA
Iddekinge (2003)[21]	2*12 mg; 12 h	d 0, 24, 48	30	=	↓ 24, 48 h			F1
Subtil (2003)[22,a]	2*12 mg; 24 h 4*6 mg; 12 h (SA)	d 0, 8, 32, 56, 80, 104	10–60	↓ 32 h; ↑ 80 h	↑ 8, 32 h; ↓ 56, 80 h	↑ 8 h		F2; M1;
Mulder (2004)[23]	2*12 mg; 24 h	d 0, 24, 48, 72, 96	60	↓ 24 h; ↑ 72 h	↓ 48, 72 h	↓ 24, 48 h	↓ 48, 72 h	F2; M2
Mulder (2004)[24]	2*12 mg; 24 h	d 0, (24), 48, (72), 96	40/60	↓ 24 h	↓ 48, 72 h	↓ 48 h	↓ 48 h	F2; M2; twins
Lunshof (2005)[25]	2*12 mg; 24 h	d 0, 0–48 (6 h interval)	90	↓ 6–12 h	↑ 0–6; 6–12 h; ↓ 42–48 h			F2
Rotmensch (2005)[26]	2*12 mg; 24 h	d 0, 24, 48, 72, 96, 120	20	↑ 72, 96 h	↓ 72, 96 h			F1; contractions
Koenen (2005)[27]	2*12 mg; 24 h	d 0, 48, 72	60	=	↓ 48 h	↓ 48 h	↓ 48 h	F2; M2;
de Heus (2008)[28]	2*12 mg; 24 h	d 0, 24, 48, 72, 96 afternoon (A) morning (M)	60	↓ 6–24 h	↑ 6–24 h; ↓ 48 h (A) =(M)	↓ 48 h (A) =(M)	↓ 48 h (A) =(M)	F2; M2
Dexamethasone								
Dawes (1994)[29]	2*12 mg; 12 h	d 0, 24, 48, 72	10–60	=	↑ 24 h	=		F2; M1
Mulder (1997)[10,a]	2*12 mg; 12 h	d 0, 24, 48, 72, 96	60	=	↑ 24 h	=	=	F2; M2
Magee (1997)[11,a]	2*12 mg; 12 h	d 0, 24, 48	60	↓ 24 h	↑ 24 h	↓ 24 h		F2; M1
Multon (1997)[12]	4*4 mg; 12 h	d 0, 24, 48, 96–168	30	=	=	=		F2; M1; IUGR
Senat (1998)[13,a]	4*4 mg; 12 h	d 0, 24–48, 96–168	30	=	=			F2; AGA
Rotmensch (1999)[14,a]	2*12 mg; 24 h	d 0, 48, 96	30/60	=	↓ 48 h (STV)	↓ 48 h	↓ 48 h	F2; M2
Mushkat (2001)[17,a]	2*12 mg; 12 h	d 0, 6, 12, 18, 36	20/30	=	=	=	↓ 36 h	F1; M1; M2; AGA
Subtil (2003)[22,a]	4*6 mg; 12 h	d 0, 8, 32, 56, 80, 104	10–60	↓ 32 h; ↑ 80 h	↑ 8 h; ↓ 56, 80 h	=		F2; M1

The fetal response is indicated relative to the first dose of steroid (d 0);=, no change; ↓, decrease; ↑, increase.
AGA, appropriate growth for age; BPS, biophysical profile score; CTG, cardiotocogram; F1, CTG visual inspection; F2, CTG computerised numerical analysis; IUGR, intrauterine growth retardation; M1, maternally perceived fetal movements; M2, fetal movements registered by observer using ultrasound equipment; SA, short-acting betamethasone; STV, short-term variability.
[a] Randomised controlled trial.

(FHR) analysis (visual inspection or computerised analysis); fetal movement count (by the mother or by an observer using ultrasound); the duration of serial observations (fixed time or variable); and statistical analysis, which did not always account properly for repeated measurements. None of the studies had included serial control measurements in fetuses not exposed to corticosteroids.

Some studies have assessed the fetal response to corticosteroids by using the biophysical profile score (BPS); 0–2 points are assigned for performance on the FHR non-stress test, fetal body movements and tone; breathing movements, and amniotic fluid content.[15,16,19,20]

3. Short-term effects on fetal behaviour and heart rate patterns

Maršál et al. in 1975 with the use of A-mode ultrasonography were the first to study the effect of betamethasone on fetal breathing activity, at the time considered an important predictor of fetal well-being, but found no change.[4] More than 10 years later, Katz, Meizner and colleagues observed prolonged non-reactive FHR tracings, reduction or cessation of fetal body movements as perceived by the mother, and unaltered Doppler blood flow velocity waveforms in the uterine and umbilical arteries following betamethasone administration.[5,6] The reduction in fetal movements, however, was not confirmed by them when using real-time ultrasound.[6] Although unrecognised for some time, their reports laid the foundation of the subsequently performed fetal studies using betamethasone or dexamethasone, including six randomised controlled trials (see Table 1).

Despite the methodological heterogeneity and differences in result between the studies, inspection of Table 1 shows that there are differential fetal responses to corticosteroids between the primary phase (0–24 h) and secondary phase (>24 h) relative to the first dose.

In the primary phase, studies showed either no significant change in FHR parameters or a decrease in basal FHR accompanied by increased FHR variability for both betamethasone and dexamethasone. The latter changes may be secondary to a steroid-induced increase in fetal systemic blood pressure triggered by the baroreceptor reflex and have been described for the fetal sheep, baboon, and the human neonate.[23,45–48]

In the secondary phase, considerable reductions in FHR variability and fetal body and breathing movements were generally observed 2–3 days after the start of betamethasone therapy. The changes were transient as values returned to pre-treatment level thereafter. When quantified, FHR variation was reduced by 20–30% on days 2 and 3. This resulted in a temporary fall below the lower