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CLINICAL ARTICLE

Fetal and neonatal outcomes after term and preterm delivery following betamethasone administration

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ABSTRACT

Objective: To determine the effects of betamethasone on fetal growth and neonatal outcomes. *Methods:* A retrospective cohort study was performed of deliveries that occurred at Charité University Hospital Berlin, Germany, between January 1996 and December 2008. The betamethasone group included women with preterm labor and symptomatic contractions, cervical insufficiency, preterm premature rupture of membranes, or vaginal bleeding. Women in the control group were matched for gestational age at time of delivery and had not received betamethasone. Fetal growth changes and neonatal anthropometry were compared. *Results:* Among 1799 newborns in the betamethasone group and 42 240 in the control group, betamethasone was associated with significantly lower birth weight (154 g lower on average) after adjusting for confounders (e.g. hypertension, smoking, and maternal weight), sex, and gestational age at delivery ($P < 0.05$). The higher the dose, the greater the difference in mean birth weight versus controls in births before 34^{+0} weeks (≤16 mg −444 g; 24 mg −523 g; >24 mg −811 g), without a detectable improvement in neonatal morbidity or mortality. There was a dose-dependent decline in expected fetal weight gain as estimated by serial ultrasonography examinations 6–8 weeks after betamethasone administration ($P < 0.05$). *Conclusion:* Betamethasone exposure reduces fetal weight gain in a dose-dependent manner without improving neonatal morbidity or mortality.

1. Introduction

Prenatal administration of synthetic glucocorticoids is a powerful intervention to reduce the frequency of respiratory distress syndrome, and neonatal morbidity and mortality among women at risk of preterm birth [1]. Until the late 1990s, repeated maternal glucocorticoid treatment was common practice for women who did not deliver within 7 days of the initial course [2]. This practice was mainly based on experimental evidence showing that surfactant production and lung maturation in fetal sheep is maximized after serial doses of glucocorticoids administered over a period of weeks [3]. Although there is evidence against weekly glucocorticoid injections [4], others support the use of repeated doses for women still at risk of preterm delivery at least 7 days after an initial course, quoting a reduced risk of adverse neonatal outcome [5,6]. Discussion is ongoing about the dose, type of steroid, treatment interval, and whether repeated doses of glucocorticoids are beneficial [7–10]. Differences in effects between the sexes, whereby male fetuses benefit less than do female fetuses, have also been suggested in animal and human studies [11].

The aim of the present study was to determine the effects of maternal betamethasone treatment in initially normally grown fetuses on fetal growth, neonatal outcome, and placental weights.

2. Materials and methods

The present retrospective cohort study comprised data collected for 44 039 deliveries at the Clinic of Obstetrics, Charité University Hospital Berlin, Germany, between January 1, 1996, and December 31, 2008 (data stored in database KIM Argus, GMT GmbH, Frankfurt, Germany). The Charité University Hospital ethics review committee approved the retrospective, observational, and anonymized analysis, and deemed that no formal ethical review or written consent from individual patients was needed.

The deliveries were divided on the basis of whether the mothers had received prenatal treatment with betamethasone. Women in the

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betamethasone group had been diagnosed with preterm labor and symptomatic contractions, cervical insufficiency, preterm premature rupture of membranes, or vaginal bleeding, and received betamethasone (Celestan, MSD GmbH, Haar, Germany) between 23 weeks plus 5 days of pregnancy (23^{+5} weeks) and 33^{+6} weeks. Controls were women with gestational-age-matched pregnancies (on the basis of time of delivery) who did not receive betamethasone treatment. The exclusion criteria were multiple gestations, major malformations, pregnancies with incomplete datasets for all variables under investigation, and pregnancies in which a glucocorticoid other than betamethasone was administered.

For women diagnosed with preterm labor, several dose regimens and intervals of betamethasone treatment were used. These regimens varied between two 8-mg doses (≤16 mg) or two 12-mg doses (24 mg) given once during pregnancy, and repetitive doses of betamethasone (8 mg weekly, or two 12-mg doses every second week) when the diagnosis of preterm labor still persisted (collectively grouped as >24 mg). For the present study, the effects of betamethasone dosage on neonatal outcomes were compared among three different total dosages: 16 mg or less, 24 mg, and more than 24 mg. A time variable (year of delivery) was introduced in the multivariate analyses to adjust for secular trends.

The estimated date of delivery was corrected by early prenatal ultrasonography when the difference between the due date by the last menstrual period and that by early sonography was more than 7 days. Fetal weight before betamethasone treatment and during follow-up ultrasonography was calculated by using the Hadlock formula. Fetuses with an estimated fetal weight (EFW) below the 10th centile at the time of the initial treatment were defined as small for gestational age and excluded from the study.

The effects of betamethasone on neonatal anthropometrics (birth weight, head circumference, body length), placental weight, ponderal index, umbilical cord blood gases (umbilical artery blood pH and umbilical vein blood pH), base excess, Apgar scores (1-, 5-, 10-minute), and neonatal mortality were analyzed separately for both sexes. Neonatal morbidity included respiratory distress syndrome or asphyxia, hypoglycemia (newborn plasma concentration <1.7 mmol/L within 24 hours of delivery), and neonatal infections requiring antibiotic treatment.

Standard curves for fetal weight in the control population were generated using LMS ChartMaker (Medical Research Council, Cambridge, UK); centiles and *Z* scores for anthropometric data were calculated with LMS Growth (Medical Research Council, Cambridge, UK). To analyze the effects of betamethasone on fetal growth, initial and follow-up EFW *Z* scores were calculated and betamethasone-associated changes were controlled for possible confounders.

Considering the periods in pregnancy clinically relevant for neonatal outcome, groups were divided by gestational age: very early preterm (group I: 25^{+0}–27^{+6} weeks; group II: 28^{+0}–30^{+6} weeks), early preterm (31^{+0}–33^{+6} weeks), late preterm (31^{+0}–36^{+6} weeks), term (37^{+0}–39^{+6} weeks), and post-term (≥40 weeks).

Effects of betamethasone treatment on neonatal body measurements, placental weight, ponderal index, umbilical cord blood gases, neonatal mortality and morbidity, and Apgar scores were analyzed using the Mann–Whitney *U* test. Sex-specific statistical analyses were performed in the whole cohort. Betamethasone effects were analyzed among three different dosages (≤16 mg, 24 mg, and >24 mg) using the Mann–Whitney *U* test. By multivariate analyses of variance, betamethasone-associated birth weight changes were controlled for possible confounders.

Data are presented as mean ± standard error. Analyses were performed by using SPSS version 20 (IBM, Armonk, NY, USA). The odds ratios (ORs) with 95% confidence intervals (CIs) for a birth weight in the 10th centile or less and Apgar scores of less than 7 were calculated by binary logistic regression using a birth weight reduction equal to or less than the 10th centile and/or an Apgar score of less than 7 as dependent variables and betamethasone dose as covariates. $P < 0.05$ was considered significant.

3. Results

The betamethasone group included 1799 newborns (979 male and 820 female) and the control group included 42 240 newborns (21 773 male and 20 467 female). The overall number of women treated with betamethasone per year was 63 (4.0%; range 42–86 [2.5%–6.0%]) among pregnancies with female fetuses and 75 (4.6%; range 45–115 [2.7%–7.6%]) among those with male fetuses. Regarding pregnancy prolongation after betamethasone exposure, 558 (68.0%) women carrying female fetuses and 734 (75.0%) women carrying male fetuses remained pregnant for longer than 7 days after treatment; 369 (45.0%) and 480 (49.0%) women, respectively, delivered after 34^{+0} weeks, and 213 (26.0%) and 274 (28.0%) women, respectively, delivered after 37^{+0} weeks. Maternal characteristics are shown in Table 1. None of the maternal variables examined accounted for anthropometric changes after treatment in multivariate analyses (Supplementary Material S1).

Standard curves for fetal weight in the control population were generated (Supplementary Material S2) and the newborns (EFW ≥10

Table 1
Maternal characteristics of the study group.[a]

Maternal characteristics	Female newborns			Male newborns		
	Control group (n = 20 467)	BMS group (n = 820)	*P* value[b]	Control group (n = 21 773)	BMS group (n = 979)	*P* value[b]
Age at delivery, y	28.8 ± 0.0	29.3 ± 0.2	0.029	28.8 ± 0.0	29.0 ± 0.2	0.322
Weight before pregnancy, kg	64.8 ± 0.1	63.8 ± 0.5	0.001	64.9 ± 0.1	63.7 ± 0.5	<0.001
Weight at delivery, kg	77.9 ± 0.1	73.7 ± 0.6	<0.001	78.4 ± 0.1	74.1 ± 0.5	<0.001
Weight gain, kg	13.2 ± 0.0	10.1 ± 0.3	<0.001	13.5 ± 0.4	10.5 ± 0.2	<0.001
Height, cm	164.1 ± 0.1	163.6 ± 0.6	0.818	163.8 ± 0.1	164.0 ± 0.4	0.167
BMI before pregnancy	23.7 ± 0.0	23.4 ± 0.2	0.001	23.8 ± 0.0	23.3 ± 0.2	<0.001
BMI at delivery	28.5 ± 0.0	27.1 ± 0.2	<0.001	28.7 ± 0.0	27.2 ± 0.2	<0.001
BMI gain	4.9 ± 0.0	3.8 ± 0.1	<0.001	4.9 ± 0.0	3.9 ± 0.1	<0.001
Disease						
Diabetes	510 (2.5)	45 (5.5)	<0.001	573 (2.6)	71 (7.2)	<0.001
Hypertensive disorders[c]	391 (1.9)	90 (11.0)	<0.001	421 (1.9)	71 (7.2)	<0.001
Country of origin						
Germany	11053 (54.0)	547 (66.7)	<0.001	11 706 (53.8)	593 (60.6)	<0.001
Turkey	4132 (20.2)	96 (11.7)	<0.001	4406 (20.2)	138 (14.1)	<0.001
Other	5282 (25.8)	177 (21.6)	0.004	5661 (26.0)	248 (25.3)	0.334

Abbreviations: BMS, betamethasone; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).
[a] Values are given as mean ± standard error or number (percentage), unless indicated otherwise.
[b] Calculated by Mann–Whitney *U* test for maternal parameters, and Fisher exact test for maternal complications and country of origin.
[c] Hypertension and pre-eclampsia.