Preterm birth, early growth and adult metabolic health

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8 Antenatal glucocorticoid treatment for preterm birth is not associated with long-term metabolic risks

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Abstract

Objectives:

A single course of maternal glucocorticoid treatment is effective in reducing neonatal mortality after preterm birth. However, in animals, maternal glucocorticoid treatment is associated with lifelong hyperglycaemia and hypertension, and impaired nephrogenesis in offspring. Findings from studies in humans on this topic are highly contradictory due to a number of methodologic flaws and renal function after glucocorticoid exposure has never been assessed. Therefore, we assessed in a well-described population of preterm subjects whether antenatal glucocorticoid treatment for preterm birth is associated with long-term metabolic risks, including renal function, in adulthood.

Methods:

There were 365 19-year-olds born <32 gestational weeks from the Project On Preterm and Small-for-gestational-age infants cohort. Outcomes, i.e. body composition, insulin resistance, the serum lipid profile, blood pressure, and estimated renal function, were related to maternal betamethasone administered twice with a 24-h interval.

Results:

Neonatal survival in the betamethasone-exposed group was 82% compared to 70% among unexposed (log rank P=0.0016). We did not find any long-term adverse effects of antenatal betamethasone, with the exception of an effect on glomerular filtration rate (GFR) in women. In 19-year-old female survivors, GFR was lower after betamethasone: -7.4 (95% CI: -13.3 to -1.5) ml/min per 1.73 m^2.

Conclusions:

The reduction in neonatal mortality associated with a single course of maternal betamethasone is not accompanied by long-term metabolic risks in survivors of preterm birth. The only adverse effect found was lower GFR in women. Although this difference was not clinically relevant at 19 years, it might predict an increased risk of chronic renal failure in prematurely born women who were exposed antenatally to betamethasone.

Introduction

Neonatal survival after preterm birth has greatly improved in the past decades (1). One of the factors responsible is the widespread application of antenatal glucocorticoid treatment. This is effective in reducing the incidence of the respiratory distress syndrome after preterm birth (2). In animals, maternal glucocorticoid administration throughout, or during part of, gestation is associated with lifelong hyperglycaemia and hypertension, and impaired nephrogenesis in offspring (3-7). Recently, in the human, preterm birth has also been associated with subsequent insulin resistance and hypertension (8;9). However, due to a number of controversial findings by studies in survivors of preterm birth, it is still not known whether antenatal glucocorticoid exposure contributes to these associations.

One study in 177 adolescents aged 14 years found a higher blood pressure after antenatal exposure to betamethasone (10). However, possible effects of early glucocorticoid exposure on the onset and tempo of puberty invalidate a correct interpretation of these data, since pubertal stage has a large impact on blood pressure (reviewed in (11)). Conversely, another study in 81 individuals found a lower systolic blood pressure 20 years after betamethasone (12), whereas a larger study in 30-year-old offspring found that betamethasone was associated with higher insulin levels 30 minutes after an oral glucose load but not with blood pressure (13). However, in the latter, two-thirds of participants had received an inappropriately low dose of betamethasone, which is also reflected by the failure to demonstrate a reduction in neonatal mortality. Obviously, for those reasons, the long-term effects on offspring metabolic health after an appropriate dose of maternal glucocorticoids remain unclear. Moreover, to date, effects on renal function after antenatal glucocorticoid treatment have never been addressed.

Therefore, we studied in a large birth cohort of prematurely born men and women who were followed until 19 years of age the effect of a single treatment course of 24 mg maternal betamethasone on body composition, insulin resistance, the serum lipid profile, blood pressure, and estimated renal function.

Methods

Population

Subjects were drawn from the Project On Preterm and Small-for-gestational-age infants (POPS) cohort. The POPS study is a multicenter prospective follow-up study, comprising 94% of all liveborn very preterm (<32 gestational weeks) and/or very-low-birth-weight (<1,500 g) infants born in The Netherlands in 1983 (14), and has documented birth, growth, and various other characteristics from birth onwards (15). The POPS cohort originally comprised of 992 non-syndromic infants born before 32 weeks' gestation. In 3 children, no data on maternal betamethasone treatment was available.

Table 1. Perinatal characteristics of original birth cohort members and participants by antenatal betamethasone exposure.

Characteristic	Original birth cohort (N=989)			Participants at 19 yrs (N=365)		
	Exposed	Unexposed	P	Exposed	Unexposed	P
N	171	818	-	73	292	-
General						
Males (%)	105 (61%)	441 (54%)	0.08	43 (59%)	130 (45%)	0.03
Whites (%)	150 (88%)	692 (85%)	0.42	64 (88%)	255 (89%)	0.84
Parental socio-economic status (1-6)	2.9±1.8	2.6±1.9	0.05[a]	3.6±1.6	3.5±1.6	0.52[a]
Obstetric						
Maternal age (yrs)	27.5±5.3	26.4±6.4	0.04	27.1±5.7	27.0±5.6	0.85
Parity >0 (%)	82 (48%)	390 (48%)	0.98	36 (49%)	137 (47%)	0.73
Part of multiple pregnancy (%)	54 (32%)	203 (24%)	0.07	15 (21%)	72 (25%)	0.46
Hypertension during pregnancy (%)	18 (11%)	119 (15%)	0.17	6 (8%)	57 (20%)	0.02
Gestational diabetes (%)	7 (4%)	40 (5%)	0.65	2 (3%)	17 (6%)	0.39
Use of drugs and/or intoxication during pregnancy (%)[b]	87 (51%)	383 (47%)	0.33	39 (53%)	147 (50%)	0.64
Prolonged rupture of membranes (%)	45 (26%)	175 (21%)	0.16	20 (27%)	63 (22%)	0.29
Neonatal						
Gestational age (weeks)	29.4±1.7	29.1±2.0	0.04	29.6±1.4	29.8±1.5	0.22
Birth weight						
- g	1,293±330	1,235±353	0.05	1,346±319	1,330±339	0.72
- SD score	-0.05±0.88	-0.11±1.01	0.47	0.03+0.91	-0.13+1.05	0.19
Low Apgar score after 5 min (%)	32 (19%)	181 (25%)	0.13	6 (9%)	35 (13%)	0.29
Respiratory distress syndrome (%)	81 (47%)	482 (59%)	0.006	32 (44%)	146 (50%)	0.35
Intracranial haemorrhage (%)	42 (25%)	259 (32%)	0.07	18 (25%)	55 (19%)	0.27
Convulsions (%)	7 (4%)	59 (7%)	0.14	1 (1%)	8 (3%)	0.69
Necrotising enterocolitis (%)	6 (4%)	46 (6%)	0.24	2 (3%)	20 (7%)	0.27
Sepsis (%)	65 (38%)	283 (35%)	0.45	31 (43%)	95 (33%)	0.12
Postnatal glucocorticoid treatment (%)	9 (5%)	60 (7%)	0.33	6 (8%)	26 (9%)	0.85

Values represent N(%) or mean±SD. Continuous variables were compared with the unpaired t test.
Dichotomous variables were compared by the χ^2 test or Fisher's exact test.
[a] Mann-Whitney U test.
[b] Smoking, drinking alcohol, or using soft drugs, hard drugs or methadone during pregnancy.

In 1983, 12 mg betamethasone, administered twice with a 24-h interval, was the only therapy used to accelerate fetal lung maturation in the Netherlands (16). In the early 1980s, fear for possible long-term deleterious effects on the unborn child refrained many Dutch obstetricians from administering betamethasone to mothers with impending preterm delivery, while others routinely prescribed this therapy (17). Thus, in the POPS study, the allocation to betamethasone could be considered as a random process, reflecting the prescribing obstetrician's own preference, rather than a clinical decision based upon the prognosis of the unborn child.

At 19 years of age, all 669 subjects alive were invited to participate in the POPS-19 study, of whom 415 gave written informed consent (62% response rate). Response in the POPS-19 study is described in detail elsewhere (18). The data of subjects with endocrine disease (N=0)

or systemic glucocorticoid therapy (N=2), as well as of pregnant women (N=1), were excluded for this specific study. The data of not-fasted subjects (N=18) were not analyzed either. Furthermore, 29 subjects failed to provide blood, resulting in a total of 365 subjects included in the statistical analyses at 19 years of age. This study was approved by the medical ethical committees of all centers participating in the POPS-19 study.

Study protocol

Subjects were seen between 8.30 and 10.00 h at one of the outpatient clinics of the 10 participating centers after an overnight fast. Assessors were blinded to the perinatal characteristics of the subjects, including betamethasone exposure.

After 30 minutes in supine position, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured 3 times consecutively with an automatic blood pressure device (Dinamap, Critikon, Germany) at the non-dominant arm. The mean values of these measurements were used in the statistical analyses. The cuff size was adjusted to fit arm length and circumference. Mean arterial blood pressure (MAP) was calculated as: (SBP + 2 x DBP) / 3. Venous blood was subsequently drawn. Thereafter, weight was measured to the nearest 0.1 kg on a balance scale, and height to the nearest 0.1 cm with a fixed stadiometer. Waist circumference was measured at 0.1-cm accuracy, with a flexible tape measure.

Laboratory analysis

Serum samples were stored at -80 ^{o}C and thawed only once immediately before analysis. Serum glucose, total cholesterol, triglyceride, and creatinin concentrations were measured in a fully automated computerized laboratory system with a Hitachi 747 (Hitachi, Tokyo, Japan) chemistry analyzer. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were measured with a turbidimetric assay on a Hitachi 911. Insulin was measured with a highly sensitive radioimmunoassay (Linco, St Charles, MO 63304, USA). The sensitivity of this assay is 0.1 mU/l, and the interassay coefficient of variation ranges from 4.7 to 12.2% at different levels.

Homeostatic model assessment for insulin resistance index (HOMA-IR) was calculated (19). Insulin level and HOMA-IR correlate strongly with Si assessed by the frequently-sampled intravenous glucose tolerance test in young persons (20;21). Estimated glomerular filtration rate (GFR) was calculated with the Cockroft-Gault equation, adjusted for body surface area (ml/min per 1.73 m^2) (22).

Statistical analysis

In the entire birth cohort as well as among the responders at age 19 years, perinatal characteristics between betamethasone exposed and unexposed groups were compared with the unpaired t test for continuous variables and by the χ^2 square test for dichotomous variables, as appropriate. When necessary, Fisher's exact test was used. Neonatal (i.e., 28-day)

mortality rates between exposed and unexposed groups were compared with the Kaplan-Meier method.

Continuous outcomes at age 19 years were compared with the unpaired t test. Multivariate linear regression was used to assess the effect of antenatal betamethasone exposure adjusted for the potential confounders race (white or non-white), parental socio-economic status (≤2 or >2), and obstetric characteristics (presence or absence for each variable separately listed in Table 1). Variables with skewed distributions (insulin, HOMA-IR, and triglycerides) were ^{10}log-transformed before statistical comparison.

Results

Perinatal data

The mothers of 171 of the 989 non-syndromic children born before 32 gestational weeks (17%) were treated with betamethasone prior to delivery (Table 1). The prescription of betamethasone was associated with a slightly older maternal age and tended to associate with socio-economic status and multiple pregnancies.

In the offspring, betamethasone was associated with a lower incidence of the respiratory distress syndrome. Sixty-nine children were treated with glucocorticoids postnatally, mostly because of difficulties to wean them from the ventilator, and 9 of them were also exposed in utero. Among participants, betamethasone exposure was negatively associated with female gender and hypertensive disease during pregnancy.

Table 2. Characteristics of participants at age 19 years by sex.

Characteristic	Men	Women	P
N	173	192	-
Height (cm)	179.4±7.8	166.4±7.2	<0.001
BMI (kg/m^2)	21.7±3.0	21.6±3.2	0.96
Waist circumference (cm)	80.1±8.7	76.7±8.6	<0.001
Glucose (mmol/l)	5.18±0.42	4.81±0.37	<0.001
Log Insulin (mU/l)	0.93±0.19	0.93±0.17	0.69
Log HOMA-IR	0.29±0.20	0.26±0.18	0.23
Total cholesterol (mmol/l)	3.92±0.81	4.45±0.84	<0.001
HDL cholesterol (mmol/l)	1.19±0.24	1.45±0.32	<0.001
LDL cholesterol (mmol/l)	2.34±0.72	2.62±0.76	<0.001
Log Triglycerides (mmol/l)	-0.11±0.21	-0.06±0.21	0.08
SBP (mmHg)	126.0±12.1	120.7±12.6	<0.001
DBP (mmHg)	63.8±7.7	68.2±8.5	<0.001
MAP (mmHg)	84.5±8.2	85.7±9.2	0.20
Creatinin (µmol/l)	87.6±8.9	77.1±8.4	<0.001
GFR (ml/min per 1.73 m^2)	110.0±13.9	103.1±15.4	<0.001

Values represent mean±SD. Variables were compared with the unpaired t test.

Table 3. Effect of antenatal betamethasone exposure on the metabolic profile at age 19 years.

3A. Men

Outcome	Antenatal betamethasone exposure		Mean difference (95% CI)	
	Exposed	Unexposed	Crude	Adjusted[a]
N	43	130	-	-
Height (cm)	179.0±7.7	179.5±7.8	-0.6 (-3.3 to 2.2)	-0.9 (-3.6 to 1.8)
BMI (kg/m^2)	21.5±2.5	21.7±3.2	-0.2 (-1.3 to 0.8)	-0.3 (-1.3 to 0.7)
Waist circumference (cm)	78.4±7.2	80.8±9.1	-2.4 (-5.4 to 0.7)	-2.8 (-5.8 to 0.1)
Glucose (mmol/l)	5.10±0.45	5.21±0.41	-0.12 (-0.26 to 0.03)	-0.10 (-0.25 to 0.04)
Log Insulin (mU/l)	0.88±0.20	0.94±0.18	-0.06 (-0.13 to 0)	-0.06 (-0.12 to 0.01)
Log HOMA-IR	0.23±0.22	0.31±0.20	-0.07 (-0.14 to 0)	-0.07 (-0.14 to 0.01)
Total cholesterol (mmol/l)	3.84±0.82	3.94±0.81	-0.09 (-0.38 to 0.18)	-0.06 (-0.34 to 0.23)
HDL cholesterol (mmol/l)	1.18±0.22	1.19±0.24	-0.01 (-0.09 to 0.07)	-0.01 (-0.09 to 0.08)
LDL cholesterol (mmol/l)	2.32±0.77	2.35±0.70	-0.02 (-0.28 to 0.23)	0.02 (-0.24 to 0.27)
Log Triglycerides (mmol/l)	-0.13±0.19	-0.09±0.21	-0.04 (-0.11 to 0.03)	-0.04 (-0.12 to 0.03)
SBP (mmHg)	123.2±12.0	126.9±12.1	-3.7 (-7.9 to 0.4)	-3.3 (-7.5 to 0.8)
DBP (mmHg)	61.3±7.8	64.6±7.5	-3.3 (-5.9 to -0.7)	-3.4 (-6.0 to -0.7)
MAP (mmHg)	81.9±8.1	85.4±8.1	-3.4 (-6.2 to -0.6)	-3.4 (-6.2 to -0.6)
Creatinin (µmol/l)	88.7±9.0	87.2±8.9	1.5 (-1.6 to 4.6)	1.4 (-1.8 to 4.5)
GFR (ml/min per 1.73 m^2)	107.7±11.8	110.8±14.5	-3.1 (-8.0 to 1.8)	-3.0 (-7.8 to 1.7)

Values represent mean±SD.

[a] Adjusted for race (white or non-white), socio-economic status (≤2 or >2), and obstetric characteristics (presence or absence).

3B. Women

Outcome	Antenatal betamethasone exposure		Mean difference (95% CI)	
	Exposed	Unexposed	Crude	Adjusted[a]
N	30	162	-	-
Height (cm)	166.7±8.1	166.4±7.1	0.3 (-2.5 to 3.2)	-0.2 (-3.1 to 2.7)
BMI (kg/m^2)	21.5±3.1	21.7±3.2	-0.1 (-1.4 to 1.2)	-0.1 (-1.4 to 1.1)
Waist circumference (cm)	75.9±9.3	76.9±8.5	-1.0 (-4.4 to 2.4)	-1.3 (-4.8 to 2.2)
Glucose (mmol/l)	4.78±0.34	4.82±0.38	-0.04 (-0.18 to 0.11)	-0.05 (-0.19 to 0.10)
Log Insulin (mU/l)	0.87±0.16	0.95±0.17	-0.08 (-0.15 to -0.01)	-0.08 (-0.15 to -0.01)
Log HOMA-IR	0.19±0.18	0.28±0.18	-0.08 (-0.15 to -0.01)	-0.08 (-0.16 to -0.01)
Total cholesterol (mmol/l)	4.38±0.74	4.46±0.86	-0.08 (-0.41 to 0.25)	-0.14 (-0.47 to 0.20)
HDL cholesterol (mmol/l)	1.43±0.24	1.45±0.33	-0.02 (-0.15 to 0.10)	-0.02 (-0.16 to 0.11)
LDL cholesterol (mmol/l)	2.52±0.73	2.64±0.76	-0.12 (-0.42 to 0.18)	-0.14 (-0.45 to 0.17)
Log Triglycerides (mmol/l)	-0.06±0.23	-0.06±0.21	0 (-0.08 to 0.08)	-0.01 (-0.09 to 0.07)
SBP (mmHg)	117.9±11.0	121.2±12.9	-3.4 (-8.3 to 1.6)	-3.3 (-8.4 to 1.8)
DBP (mmHg)	66.5±7.5	68.5±8.6	-2.1 (-5.4 to 1.2)	-1.9 (-5.3 to 1.4)
MAP (mmHg)	83.6±8.0	86.1±9.4	-2.5 (-6.1 to 1.1)	-2.4 (-6.1 to 1.3)
Creatinin (µmol/l)	80.9±8.1	76.4±8.3	4.5 (1.2 to 7.7)	4.7 (1.4 to 7.9)
GFR (ml/min per 1.73 m^2)	97.4±11.5	104.1±15.8	-6.7 (-12.8 to -0.6)	-7.4 (-13.3 to -1.5)

Values represent mean±SD.

[a] Adjusted for race (white or non-white), socio-economic status (≤2 or >2), and obstetric characteristics (presence or absence).

The betamethasone exposed and unexposed groups differed in neonatal survival, in favour of the exposed group (Figure 1; log rank P=0.0016). Cumulative survival was already significantly different at 24 hours after birth (P=0.009). This difference increased up to the age of 28 days. At that age, 82% of the betamethasone exposed children were still alive compared to 70% of the unexposed. The odds ratio for neonatal mortality after betamethasone exposure was 0.51 (95% CI: 0.33-0.77).

Data obtained at age 19 years

At 19 years of age, there were gender-specific differences between men and women. Men had a larger waist circumference and higher fasting glucose levels than women (Table 2). Moreover, SBP, creatinin levels, and GFR were higher in men. Women, in turn, had higher fasting cholesterol levels and DBP than men.

In general, there were no adverse effects in 19-year olds after antenatal betamethasone exposure, with only one exception (GFR in women, see below). Betamethasone exposed and unexposed persons did not differ for height, BMI, waist circumference, and cholesterol levels (Tables 3A and 3B). Men exposed to betamethasone had significantly lower DBP and MAP. These observations persisted after correction for race, socio-economic status, and obstetric characteristics. Exposed men had a tendency towards lower insulin levels and HOMA-IR, but these observations were not statistically significant. Exposed women had significantly lower insulin levels and HOMA-IR. Their creatinin levels were significantly higher and their GFR lower. All of these relations in women persisted after adjustment for race, socio-economic status, and obstetric characteristics. In both men and women, restriction of analyses to subjects born after non-hypertensive pregnancies did not alter the results (data not shown).

Discussion

The overall conclusion of our study is that the short-term benefits of a single treatment course of maternal betamethasone grossly outweigh the potential long-term metabolic risks in survivors of very preterm birth.

We found that women who were exposed antenatally to betamethasone had a lower GFR, although within normal limits, at 19 years of age. This finding is in line with studies in rats, showing a reduction in glomerular numbers and function after maternal glucocorticoid treatment (4;6), even after short treatment with corticosterone (23), the principal glucocorticoid in rats.

Contrary to expectation, antenatal betamethasone exposure was associated with lower fasting insulin levels and HOMA-IR, and, in men, it was also associated with lower DBP and MAP. Therefore, with the exception of lower GFR in women, we did not find any long-term adverse effects of antenatal exposure to betamethasone.

There are several potential limitations to the design of our study. First, non-randomized allocation of a treatment, such as in our study, carries the risk of selection bias. It is unknown whether the differences in characteristics known at the time of betamethasone prescription were due to random fluctuation or created by the obstetricians involved. However, statistical adjustment for these characteristics did not change our results. Moreover, it was recently explained by Vandenbroucke that the side effects of a therapy can be studied with an observational study as reliably as with a randomized trial, provided that these cannot be predicted from any clinical data at the time of prescription (24). For our study, it seems fair to assume that the lack of knowledge in 1983 about potential long-term metabolic risks of antenatal glucocorticoid treatment has precluded obstetricians from guiding their decisions by relevant prognostic data (e.g., positive family history for diabetes mellitus, chronic renal failure or cardiovascular disease).

Second, as we had incomplete follow-up data, it may be argued that the observed associations could be biased by non-response. Possible relations between betamethasone exposure and outcome variables would be concealed if either the betamethasone exposed or the unexposed subjects with an adverse metabolic profile selectively declined to participate. This seems not very likely.

Third, our results pertain to individuals born at a gestational age <32 weeks. Subjects exposed to betamethasone before 32 weeks and born later were not part of the sample.

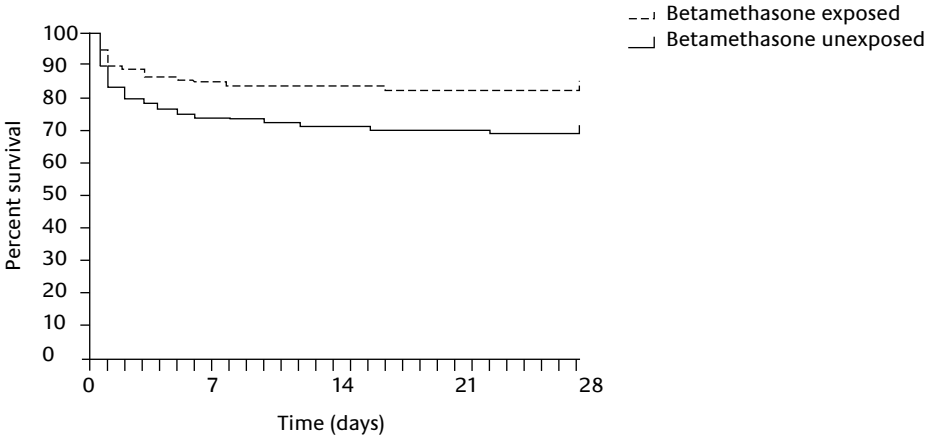
The difference in neonatal survival between the betamethasone exposed and unexposed groups was associated with a lower incidence of the respiratory distress syndrome in the exposed group, in line with the data of a meta-analysis of randomized trials (1). Betamethasone readily crosses the placenta, resulting in high cord vein glucocorticoid bioactivity that returns to the reference level within1 to 2 days after the last steroid dose (25). In preterm newborns, the effects of antenatal glucocorticoids are likely to be more pleiotropic, at least shortly after exposure, than merely reflected in a lower incidence of the respiratory distress syndrome. A recent study showed that preterm newborns who were exposed antenatally to betamethasone, had a transient elevation of insulin and C-peptide levels, and HOMA-IR in cord blood (26), which is indicative for insulin resistance. Furthermore, another study showed that treatment was associated with less need for blood pressure support during the first 48 hours after birth (27). In this regard, some comments should be made on the paradoxical influences of antenatal betamethasone exposure on adult blood pressure and markers of insulin resistance found in our study. In preterm newborns, hypotension is a strong predictor of severe intracranial haemorrhage, ischemic cerebral lesions, or death within 48 hours (28), and, in survivors, of poorer neurological outcome at term (29). There is lack of scientifically sound studies which address the prognostic value of neonatal hypoglycaemia in preterm newborns (30), with the exception of one study, showing that it is associated with adverse neurodevelopment at 18 months of age (31). Such observations stress the importance of adequate blood pressure and

glucose availability after preterm birth. Therefore, a possible explanation for the paradoxical associations in our study is that the neonatal survival of 'betamethasone depleted' newborns was more dependent on intrinsic factors associated with blood pressure regulation and glucose/insulin homeostasis, predisposing to later hypertension and insulin resistance.

Conclusions

We conclude that a single treatment course of maternal betamethasone does not adversely influence long-term metabolic health in very preterm offspring. The only adverse effect found was lower GFR in women. Although this difference was not clinically relevant at 19 years of age, it could predict an increased risk of chronic renal failure in prematurely born women who were exposed antenatally to betamethasone. Long-term follow-up of this study population is necessary to address this possibility. Persistent effects of multiple courses of maternal glucocorticoids in their children need to be explored by future studies.

Figure 1. Neonatal survival after very preterm birth in betamethasone exposed (N=171) and unexposed groups (N=818).



Dashed line represents the betamethasone exposed group. During the neonatal period, 30 events had occurred in the exposed group compared to 242 in the unexposed group. The odds ratio for neonatal mortality after betamethasone exposure was 0.51 (95% CI: 0.33 to 0.77).

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