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Impact of antenatal corticosteroids on head circumference of full-term newborns: a French multicentre cohort study

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Conflict of interest

None

ABSTRACT

Introduction: Our main objective was to evaluate whether antenatal corticosteroids increase the risk of small head circumference in children born at term. Secondary objectives were to evaluate whether they increase the risk of small birthweight and birth length among those children. **Material and methods:** A historical cohort included 275 270 live term born children between 2000 and 2013 in 175 French maternity units. The rate of head circumference below the fifth percentile among children born at term and exposed to antenatal corticosteroids was compared with that of two unexposed groups: those children born at term whose mothers had an episode of threatened preterm labour without corticosteroids and those whose mothers had neither threatened preterm labour nor corticosteroids. The association between this treatment and head circumference was evaluated by calculating adjusted risk ratios (aRRs) and their 95% confidence intervals (CIs). The main outcome measure was a head circumference below the fifth percentile at birth, adjusted for sex and gestational age according to the AUDIPOG curves. Secondary outcomes were birthweight and birth length below the fifth percentile. **Results:** The rate of head circumference below the fifth percentile was 5.8% (n=3388) among children exposed to antenatal corticosteroids and 4.3 % (n=7077) and 4.6% (n=198462) respectively for the two unexposed groups. After adjustment, the risk of having a head circumference below the fifth percentile did not differ between the exposed group and the two control groups (aRR 1.28 (95% CI: 0.97-1.69) and aRR 0.91 (95% CI: 0.74-1.13)). We did not find an association between antenatal corticosteroids and the rate of birthweight below the fifth percentile. Children exposed to antenatal corticosteroids had a higher risk of a birth length below the fifth percentile when compared to those with neither exposure to threatened preterm labour nor corticosteroids. **Conclusions:** We found no association between antenatal corticosteroids and increased risk of head circumference below the fifth percentile in children born at term.

Key words

antenatal corticosteroids, term, head circumference, birthweight, birth length.

Abbreviations

AUDIPOG Paediatric, Obstetrics, and Gynaecology Electronic Records Users Association

CI confidence interval

RR relative risk

UE Unexposed Group

Key message

Antenatal corticosteroids are not associated with an increased risk of having a head circumference below the 5th percentile in children born at term.

INTRODUCTION

Because antenatal corticosteroids reduce perinatal and neonatal deaths by reducing the rates of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis and systemic infections in preterm infants, current French guidelines recommend that women at risk of preterm delivery receive a single course of this treatment, which consists of two injections of 12 mg of intramuscular betamethasone.^{1,2} There is strong evidence that they reduce mortality and morbidity among preterm newborns, but also concern that they may restrict growth.^{1,3,4} Studies have reported that antenatal corticosteroids are associated with reduced head circumference, weight and length at birth, independently of other predictive factors.^{3,5-7} Moreover, the apparent link between the extent of growth restriction and the corticosteroid dose suggests a causal relation between them.^{8,9}

Most studies examining the possible adverse effects of antenatal steroids have focused on preterm infants, but more than half the women admitted for preterm labour who receive corticosteroids finally give birth after 37 weeks of gestation. Inadequate assessment of the risk of preterm delivery thus results in the unnecessary exposure to antenatal corticosteroids of approximately 25 000 fetuses in France each year. The effects of antenatal corticosteroids for threatened preterm labor on growth parameters among children who go on to deliver at term are not known.

The main objective of this study was to assess whether children born at term who received antenatal corticosteroids have a higher risk of a head circumference at birth below the fifth percentile. The secondary objectives were to assess whether they are at higher risk of a birthweight or a birth length below this cutoff.

MATERIAL AND METHODS

Population

This historical cohort study concerned deliveries included in the Paediatric, Obstetrics, and Gynaecology Electronic Records Users Association (AUDIPOG) sentinel network database. This network, created in 1994, comprises the public and private maternity units in every region in France that voluntarily contribute individual data on mothers and infants for pooling and analysis. Each hospital participates for a given period each year, chosen by them usually one month but sometimes the entire year. They forward all data about women giving birth and their newborns during this period at a gestational age ≥ 22 week (or a birthweight ≥ 500 g).

The objective of this network is to provide epidemiological surveillance of perinatal health indicators and medical practices. The details of the methodology for data collection have been published elsewhere.¹⁰ At the time of this study, the database included 822 061 pregnancies, from 1994 to 2013, from 252 participating hospitals. Because collection of data about antenatal corticosteroid administration only began in 2000, only 667 567 births from 175 hospitals from 2000 to 2013 were eligible for this specific study. This cohort study included all infants born at term (at or after 37 weeks of gestation). Medically indicated terminations of pregnancy, stillbirths, infants for whom fetal malformations were antenatally suspected were excluded as well as those cases for which relevant data for this study were missing.

Exposure

The studied exposure was antenatal corticosteroid administration for threatened preterm labour, between ≥ 22 weeks and < 34 weeks, regardless of the specific substance or dose administered. The 2002 French guidelines call for the administration of one course of corticosteroids (that is, two injections of 12 mg of betamethasone 24 hours apart) to women with threatened preterm labour (combination of painful, regular uterine contractions with cervical modifications between 24 and 34 weeks of gestation).¹¹

Outcomes

The main outcome was a head circumference measured immediately after birth below the fifth percentile. The secondary outcomes were a birthweight or a birth length below this cutoff. Percentiles were adjusted for sex and gestational age according to the AUDIPOG curves and calculated from the AUDIPOG database.¹²

Statistical analyses

Mothers' social, demographic, obstetric and delivery characteristics and children's anthropometric measurements were described for the overall cohort and according to antenatal corticosteroid exposure. Two unexposed groups were used for comparisons: children born at term whose mothers had had an episode of threatened preterm labour without this treatment (unexposed group 1: UE1) and those born at term of mothers who had had neither preterm labour nor steroid treatment (unexposed group 2: UE2). Categorical variables were compared by chi-square tests (or Fisher's exact test, when appropriate).

The rates of children with head circumference, weight and length at birth below the fifth percentile were compared according to antenatal exposure (chi-square or Fisher's exact

test, as appropriate). The relative risk ratios (RRs) for each outcome were calculated with their 95% confidence intervals (95% CIs). A log-binomial model was used to calculate adjusted risk ratios (aRR) to take into account known or suspected confounding factors: maternal age in years (<20; 20-34; ≥ 35), body mass index (<18.5; 18.5-24.9 and ≥ 25), smoking during pregnancy, multiple pregnancy, pregnancy-related disorders (overall disorders except preterm labour, hypertension, diabetes or amniotic fluid anomaly) and sex. The model also included clinically relevant prognostic factors such as parity, family situation (living with partner: yes/no), geographical origin (Metropolitan France, Southern Europe, North Africa, other), gestational age at birth in weeks of gestation (≥ 40 weeks versus <40 weeks), year of birth (2000-2004 vs. 2005-2009 vs 2010-2013) and maternity unit level of delivery (I, II, and III, according to level of neonatal care available).

We conducted secondary analysis to investigate whether including children with missing data for “fetal or neonatal congenital malformation” changed the association between the exposure and the outcome.

Statistical significance was set at $P < 0.05$. All statistical analyses were performed with SAS software version 9 2002-2010 (SAS Institute Inc., Cary, NC, USA).

Ethical approval

Study ethics approval was obtained on the 5th of April 2019 (CECIC Rhône-Alpes-Auvergne, Grenoble, IRB 5921, number of approval CECIC-GREN-19-02).

RESULTS

Population

The population was selected from 667 567 eligible births between 2000 and 2013. Medically indicated terminations of pregnancy (n=66) and stillbirths (n=1621) were excluded, as were infants for whom fetal malformations were antenatally suspected or diagnosed at birth (n=4 759 children) (Figure 1). Lastly, we excluded those cases for which relevant data for this study were missing (missing data for fetal or neonatal congenital malformation: n= 113 731; missing data on corticosteroids or threatened preterm labour: n=161 101 and missing data on neonatal anthropometric measures: n= 52 342)). Finally this study included 275 770 infants born at term.

Description of the overall cohort

The mean maternal age in the overall cohort was 29.5 ± 5.3 years, the mean body mass index was 23.4 ± 4.7 , and 72.1% of the women were born in France (Table 1). More than half the women (56.9%) were nulliparous, and 15.9% smoked during their pregnancy. Half the women gave birth at or after 40 weeks. Labour began spontaneously for 75.0 % of the cohort, and 72.4% had a spontaneous vaginal delivery (Table 2). For the infants, the mean head circumference, birthweight and birth length were $34.5 \text{ cm} \pm 1.5$, $3351 \text{ g} \pm 455$ and $49.8 \text{ cm} \pm 2.1$, respectively. In the overall cohort, the rates of head circumference, birthweight and birth length below the fifth percentile were 4.6, 4.8 and 5.0% respectively.

Comparison of the exposed and unexposed groups

Maternal social and demographic characteristics all differed significantly between the exposed group and the two control groups (Table 1). Women in the exposed group were younger, were more frequently multiparous, and had a higher rate of multiple pregnancy (Tables 1 and 2).

Head circumference

The rates of head circumferences below the fifth percentile were 5.8% in the exposed group and 4.3 and 4.6% respectively in the two control groups (Table 3). Children exposed to antenatal corticosteroids had a greater risk of a head circumference below the cut off than those born after threatened preterm labour but unexposed to antenatal corticosteroids as well as those who had neither threatened preterm labour nor antenatal corticosteroids: $RR_{UE1}=1.34$ (95% CI: 1.13-1.60) and $RR_{UE2}=1.25$ (95% CI: 1.09-1.43), respectively. However, these risks were not statistically significant after adjustment; $aRR_{UE1}=1.28$ (95% CI: 0.97-1.69) and $aRR_{UE2}=0.91$ (95% CI: 0.74-1.13), respectively.

Birthweight

The rates of birthweight below the fifth percentile were 8.9% in the exposed group and 5.1 and 4.7% in the two control groups (Table 3). Exposed infants had a greater risk of a birthweight below the fifth percentile than those in the control groups: $RR_{UE1}=1.72$ (95% CI, 1.51-1.96) and $RR_{UE2}=1.87$ (95% CI, 1.69-2.07), respectively. Again, however, the adjusted risks did not differ significantly ($aRR_{UE1}=1.19$ (95% CI, 0.98-1.45) and $aRR_{UE2}=1.06$ (95% CI, 0.92-1.22), respectively (Table 3).

Birth length

The rates of birth length below the fifth percentile were 8.9% in the exposed group and 6.0 and 4.9% in the two control groups (Table 3). Children exposed to antenatal corticosteroids were at higher risk of a birth length below this cutoff than those with threatened preterm labour without corticosteroids (RR_{UE1} 1.47, 95% CI, 1.27-1.70), but not after adjustment (aRR_{UE1} 1.24, 95% CI 1.00-1.54). Children exposed to antenatal corticosteroids had a higher risk of a birth length below the fifth percentile than the control group with neither exposure to threatened preterm labour nor corticosteroids (RR_{UE2} 1.81, 95% CI 1.62-2.03), even after adjustment for the confounding factors (aRR_{UE2} 1.35 (95% CI: 1.15-1.58) (Table 3).

Secondary analyses were conducted among a population which included the 113 731 children with missing data for “suspicion fetal or neonatal congenital malformation”. These analyses, performed on 389 501 children, showed no difference for the association between the exposure and the studied outcomes (data in Supporting Information Table S1).

DISCUSSION

After adjustment for the confounding factors, antenatal corticosteroids were not associated with a significantly higher percentage of newborns with head circumference or birthweight below the fifth percentile, compared with controls, although they were associated with a greater risk of a birth length below that cutoff (only when compared to children with neither exposure to threatened preterm labour nor corticosteroids). According to the AUDIPOG database, 1.5% of children born at term are exposed to antenatal corticosteroids, likely due to the absence of adequate tools for predicting preterm deliveries, which results in widespread use of corticosteroid administration. In addition to the urgency of improving prediction of premature births, it is essential to assess the potential side effects of this antenatal treatment for children finally born at term.

The main strength of our study is that it is the first, to our knowledge, to evaluate the effect of antenatal corticosteroids on so large a sample of children born at term. Previous studies have evaluated these effects on both term and preterm children and on much smaller populations of the children born at term.^{7,9} Another important strength lies in the validity of the AUDIPOG database, which has been confirmed by the consistency of its national perinatal indicators with those of national surveys commissioned by the Ministry of Health. Moreover, this database is used regularly for scientific studies; a list of all publications is available on the website (<https://www.audipog.net>). The collection of information for this

database by midwives and doctors —professionals who have been in direct contact with the patients — reduces any recall bias.

Several study limitations must nonetheless be discussed. The first is that nearly half of the cohort had to be excluded due to missing data. Specially, because the variable congenital abnormally (yes/no) at birth was underreported in the database (n= 113 731). However, secondary analysis performed including these children found similar results. The second is the observational design of the study, which cannot provide the same level of evidence as would a randomised controlled trial. Nonetheless, in view of the suspected side effects of corticosteroids shown by clinical and animal studies, a randomised trial comparing corticosteroids to a placebo for normal pregnancies would be unethical. Therefore, only observational data can answer the question about the risk of growth restriction, assessed by anthropometric measurements at birth among children born at term who received corticosteroids. The third limitation is that the number of courses of corticosteroids was not collected in the database. Some children may have been exposed to multiple courses, which would tend to bias the association toward overestimation of an association between antenatal corticosteroids and small head circumference. Nonetheless, a French national survey in 2005 reported that antenatal corticotherapy for fetal lung maturation was administered to 70.1% of women with threatened preterm delivery, and 84.5% used a single course.¹³ Side effects of antenatal corticosteroids may also vary according to the gestational age at which corticosteroids were administered, but we were not able to assess this variable in our study as this data was unavailable. Finally, although regression analyses were used to adjust for confounding factors and pertinent prognostic factors, such as year of birth, unknown additional factors may have affected fetal weight gain and perinatal outcomes.

The only association we observed that persisted after adjustment for all confounding factors was a birth length reduction for children exposed to antenatal corticosteroids. Accordingly, this treatment may affect this anthropometric parameter at birth for children born at term. We nonetheless interpret this result with reservations because of the known high inter- and intra-observer variability for birth length, due to the lack of a valid method for its measurement.¹⁴

Finally, there is an indication bias related to antenatal corticosteroid therapy, and it must be discussed: only women with threatened preterm labour receive antenatal corticosteroids. We thus had two hypotheses about this bias. The first was that premature contractions might result from an intrauterine process that affects fetal growth, and the second that preterm uterine contractions might affect fetal growth and thus be responsible for

modifying anthropometric parameters at birth.¹⁵ For that reason, we chose to use two control/unexposed groups in our study: a group of women with threatened preterm labour and no corticosteroids (UE1) and another group with neither threatened preterm labour nor antenatal corticosteroids (UE2).

One study demonstrated that antenatal corticosteroids reduce birth size among preterm children with a strong dose-response relationship in evidence,¹⁶ however the effect of this treatment on children born at term remains to be elucidated as half of treated women deliver at term. In a larger and more recent study assessing the association between antenatal corticosteroids and birth size for term new-borns, authors analysed data from the Finnish Medical Birth Register and found a significant reduction in birth size.⁷ Design differences between their study and ours may explain the different results: first, their study was not limited to term births; secondly, they integrated potential confounding factors into a propensity score matching strategy but did not adjust for them; finally, outcomes were presented as quantitative variables; results showed a 90g reduction for the birth weight of term born children who received antenatal corticosteroids. Differences of birth weight expressed in grams are difficult to interpret and even if the difference is statistically significant, it is difficult to know whether or not it is clinically relevant. In the Finnish study, differences for birth size tended to be smaller towards term and were not significant for pregnancies who reached 42 weeks. Given that half of our cohort was born after 40 weeks of gestation, the two studies do not differ so much in their results.

Even though our results show no association between antenatal corticosteroids and head circumference and birthweight below the fifth percentile, it is urgent that better tools for prediction of preterm deliveries be developed, as corticosteroids may have side effects on other outcomes, including hypertension and insulin resistance or neurodevelopmental disorders among children.¹⁷⁻²¹ Additional research is needed to explore corticosteroids exposure. These other types of adverse effects should be evaluated among a cohort of adults for whom antenatal data were collected.

Between 25 and 60% of patients receiving antenatal corticosteroid end up giving birth after 37 weeks of gestation; ultimately then their treatment was unnecessary. It is thus essential to improve our ability to determine the risk of premature birth. Combining predictive clinical and laboratory factors should be considered to increase positive predictive values.

CONCLUSION

We did not find an association between antenatal corticosteroids and the rates of head circumference or birthweight below under the fifth percentile, but did find a higher rate of birth length below this cutoff among children born at term who received antenatal corticosteroids when compared with those whose mother had neither threatened preterm labour nor corticosteroids. Clinicians should continue to give corticosteroids whenever there is a risk of preterm birth but further studies need to be conducted to elucidate the potential effects of antenatal corticosteroids on children born at term.

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Supporting Information legend:

Table S1. Anthropometric parameters of children according to antenatal corticoid exposure (including 389 501 children with missing data).

Legend

Figure 1: Flow chart of the population of newborns.

Table 1: Maternal, social and demographic characteristics of mothers according to antenatal corticosteroid exposure

	Overall cohort N=273 275 (n) %	Exposed group N=3758 (n) %	UE1 group N=9829 (n) %	P value ‡	UE2 group N=259 688 (n)%	P value §
Maternal age	(n=272 302)	(n=3750)	(n=9790)		(n=258 762)	
< 20 years	2.7	6.9	4.1	< 10 ⁻⁴	2.6	< 10 ⁻⁴
20-34 years	79.2	82.0	82.7		79.1	
≥ 35 years	18.1	11.2	13.2		18.3	
Family situation	(n=221 633)	(n=2746)	(n=8101)		(n=210 786)	
single	7.3	8.9	7.2	0.003	7.2	0.0007
lives with partner	92.7	91.1	92.8		92.8	
Geographic origin	(n=213 684)	(n=2766)	(n=7849)		(n=203 069)	
France*	72.1	68.8	78.5	< 10 ⁻⁴	71.9	< 10 ⁻⁴
Southern Europe	2.2	2.0	1.9		2.2	
North Africa	10.5	9.3	8.0		10.6	
Other	15.2	19.8	11.6		15.3	
Body mass index †	(n=250 196)	(n=3129)	(n=9000)		(n=238 067)	
< 18.5	8.0	15.1	14.0	0.22	7.7	< 10 ⁻⁴
18.5-24.9	64.9	68.7	69.2		64.7	
≥ 25	27.0	16.1	16.8		27.6	

UE, unexposed

* Continental (metropolitan) France.

† Pre-pregnancy Body mass index

‡ Comparison of the exposed group and controls UE1.

§ Comparison of the exposed group and controls UE2

Table 2: Obstetric, pregnancy and delivery characteristics of mothers according to antenatal corticosteroid exposure

	Overall cohort N=273 275 n (%)	Exposed group N=3758 n (%)	UE1 N=9829 n (%)	P value	UE2 N=259 688 n (%)	P value
Parity	(n=250 969)	(n=3356)	(n=8830)		(n=238 783)	
Nulliparous	56.9	51.1	56.2	< 10 ⁻⁴	57.0	< 10 ⁻⁴
Previous cesarean section	(n=241 335)	(n=3235)	(n=8490)		(n=229 610)	
	9.1	5.4	5.5	0.85	9.3	< 10 ⁻⁴
History of stillbirth or neonatal death	(n=239 525)	(n=3197)	(n=8419)		(n=227 909)	
	1.3	2.7	1.6	0.0002	1.3	< 10 ⁻⁴
Smoking during pregnancy	(n=248 260)	(n=3295)	(n=9319)		(n=235 646)	
	15.9	17.8	18.3	0.49	15.8	0.001
Multiple pregnancy	(n=273 275)	(n=3758)	(n=9829)		(n=259 688)	
	0.9	7.9	2.1	< 10 ⁻⁴	0.8	< 10 ⁻⁴
Any pregnancy-related disorder*	(n=273 267)	(n=3758)	(n=9829)		(n=259 680)	
Overall except preterm labour	25.8	39.6	32.0	< 10 ⁻⁴	25.4	< 10 ⁻⁴
Diabetes	4.6	5.1	4.3	0.06	4.6	0.18
Hypertension	2.2	2.6	2.5	0.62	2.2	0.08
Amniotic fluid anomaly	(n=27 234)	(n=3290)	(n=8904)		(n=259 040)	
Oligoamnios	0.5	1.9	1.0	< 10 ⁻⁴	0.5	< 10 ⁻⁴
Polyhydramnios	0.6	0.9	0.5		0.6	

Gestational age at delivery	(n=273 275)	(n=3758)	(n=9829)		(n=259 688)	
≥ 40 weeks	50.6	24.3	36.3	< 10 ⁻⁴	51.5	< 10 ⁻⁴
Year of delivery	(n=273 275)	(n=3758)	(n=9829)		(n=259 688)	
2000-2004	18.5	20.4	24.0	< 10 ⁻⁴	18.3	< 10 ⁻⁴
2005-2009	42.9	38.1	45.9		42.9	
2010-2013	38.6	41.5	30.2		38.8	
Level of maternity ward	(n=273 275)	(n=3758)	(n=9829)		(n=259 688)	
	20.7	13.5	33.1	< 10 ⁻⁴	20.4	< 10 ⁻⁴
I	39.5	38.1	33.7		39.8	
III	39.7	48.4	33.2		39.9	
II						
Onset of labour	(n=271 857)	(n=3742)	(n=9797)		(n=258 318)	
Spontaneous	74.8	76.1	79.2	0.0006	74.6	< 10 ⁻⁴
Induction	18.5	19.1	16.7		18.6	
Caesarean	6.7	4.8	4.2		6.8	
Mode of delivery	(n=273 160)	(n=3757)	(n=9823)		(n=259 580)	
Spontaneous vaginal delivery	72.4	71.9	77.9	< 10 ⁻⁴	72.2	< 10 ⁻⁴
Caesarean	15.4	12.5	10.3		15.7	
Operative vaginal delivery	12.2	15.6	11.8		12.1	
Instrumental deliveries	92.1	81.6	90.7	< 10 ⁻⁴	92.4	< 10 ⁻⁴
Other manoeuvres**	7.9	18.4	9.3		7.6	
Sex: female	(n=275 566)	(n=4049)	(n=10 022)		(n=261 495)	
	49.5	46.9	47.9	0.38	49.6	0.003

*Any preexisting disease or pregnancy related pathology (except preterm labor) which may interfere with the studied pregnancy

** Other manoeuvres = maneuver for shoulders dystocia, internal cephalic version, total breech extraction

UE, unexposed

Table 3. Anthropometric parameters of children according to antenatal corticoid exposure

	Exposed group (N = 4055)	UE 1 group (N = 9256)	Crude RR_{UE1} (95% CI)	aRR_{UE1}[*] (95% CI)	UE 2 group (N=242 386)	Crude RR_{UE2} (95%CI)	aRR_{UE2}[*] (95%CI)
HC at birth	(n=3388)	(n=7077)			(n=198 462)		
< 5th p	5.8%	4.3%	1.34 (1.13-1.60)	1.28 (0.97-1.69)	4.6%	1.25 (1.09-1.43)	0.91 (0.74-1.13)
Birthweight	(n=4043)	(n=10 008)			(n=261 006)		
< 5th p	8.9%	5.1%	1.72 (1.51-1.96)	1.19 (0.98-1.45)	4.7%	1.87 (1.69-2.07)	1.06 (0.92-1.22)
Birth length	(n=3276)	(n=6848)			(n=193 319)		
< 5th p	8.9%	6.0%	1.47 (1.27-1.70)	1.24 (1.00-1.54)	4.9%	1.81 (1.62-2.03)	1.35 (1.15-1.58)

* RR adjusted for the following confounding factors [maternal age (20-34 years vs. <20 vs. ≥ 35), body mass index (18.5-24.9 vs. <18.5 vs. ≥ 25), smoking during pregnancy (yes vs. no), singleton (yes vs. no), pregnancy related disorder (yes vs. no), and baby sex (girl vs. boy)], and for the following clinical prognostic factors parity, family situation (living with partner: yes/no), geographic origin (France vs. South of Europe vs. North Africa, vs. others countries), parity (nulliparous vs. multiparous), gestational age at birth (≥40 weeks vs. < 40 weeks), year of birth (2000-2004 vs. 2005-2009 vs 2010-2013), and level of maternity ward (III vs. I vs. II)]. No interaction has been found. UE, unexposed; HC, head circumference.

Figure 1: Flow chart of the population of newborns