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Effects of antenatal dexamethasone for maternal antepartum haemorrhage on term babies

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Objective: This study aims to compare the outcomes of term babies with or without in utero exposure to dexamethasone as a result of maternal antepartum haemorrhage (APH).
Methods: Medical records of women with antepartum haemorrhage who had a singleton livebirth delivered at ≥37 weeks of gestation in the Queen Elizabeth Hospital, Hong Kong, between 1 January 2019 and 31 December 2021 were retrospectively reviewed. Primary outcomes were the small-for-gestational-age (SGA) rate, the neonatal intensive care unit (NICU) admission rate, and low Apgar score at 5 minutes. Secondary outcomes were the Caesarean section rate and the operative vaginal delivery rate.
Results: A total of 898 women were included; 50 (5.6%) of them had completed a course of antenatal dexamethasone. Compared with women without antenatal dexamethasone, women with antenatal dexamethasone were associated with higher rates of gestational diabetes mellitus (22% vs 7.2%, p<0.001), operative vaginal delivery (16% vs 9.8%, p=0.005), earlier gestational week at delivery (38.2 vs 39.2 weeks, p<0.001), and lower neonatal birthweight (3001.4 vs 3149.6 g, p=0.004). In logistic regression analysis, antenatal exposure to dexamethasone was associated with an increased risk of having an operative vaginal delivery (adjusted odds ratio=2.98, p=0.016) and a reduced risk of having an SGA baby for every 1-week increase in pregnancy (adjusted odds ratio=0.69, p=0.002).
Conclusion: Antenatal dexamethasone for women with antepartum haemorrhage was not associated with SGA infants, NICU admission, or low Apgar score but was associated with earlier delivery, lower neonatal birthweight, and a higher rate of operative vaginal delivery. The latter remained significant in logistic regression analysis. More studies are needed to identify any potential effects on term babies exposed to antenatal corticosteroids.

Keywords: Apgar score; Dexamethasone; Infant, small for gestational age; Intensive care units, neonatal

Introduction

Antenatal corticosteroids given to pregnant women within 7 days of preterm delivery can reduce the risks of fetal prematurity including respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, and even neonatal death[1,2]. Antepartum haemorrhage (APH) is associated with preterm delivery; unexplained APH carries a threefold higher risk of preterm delivery[3], notwithstanding placenta abruptio or heavy bleeding associated with placenta praevia. APH may also be an early sign of preterm labour. Patients with spotting, even if the most likely cause is lower genital tract bleeding, may consider taking antenatal corticosteroids[4], but the optimal regimen and the effects of corticosteroids on term infants are unclear[5]. In utero exposure to betamethasone is associated with a higher risk of having a small-for-gestational-age (SGA) infant and neonatal intensive care unit (NICU) admission[6]. This study aimed to compare the outcomes of term babies with or without in utero exposure to dexamethasone as a result of maternal APH.

Materials and methods

Medical records of women with APH who had a singleton livebirth delivered at ≥37 weeks of gestation in the Queen Elizabeth Hospital, Hong Kong, between 1 January 2019 and 31 December 2021 were retrieved from the Clinical Data Analysis and Reporting System and retrospectively reviewed. Those who did not receive a complete course of dexamethasone or had preterm premature rupture of membranes were excluded.

The diagnosis and management of APH were based on history taking, physical examination, ultrasonography, and speculum examination, with reference to guidelines from the Royal College of Obstetricians and Gynaecologists[4]. Cardiotocography was used to assess fetuses at ≥26 weeks of gestation. Delivery was considered in patients with severe vaginal bleeding, evidence of fetal compromise, or pregnancy at term. Antenatal corticosteroids were given to women with major vaginal bleeding between a gestational age of 24+0 and 33+6 weeks. The dexamethasone regimen was decided by the attending obstetrician: either three intramuscular doses of dexamethasone 8 mg every 8 hours

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or two intramuscular doses of dexamethasone 12 mg every 12 hours. A repeated course of dexamethasone was only given by specialist obstetricians for women who had a recurring threat of preterm birth within 7 days of 33 weeks' gestation with an interval of >14 days after completing the first course.

Maternal variables collected included age at delivery, race, mode of delivery, antenatal complications (ie, APH, gestational diabetes mellitus [GDM], hypertensive disorder), estimated date of confinement, and date of dexamethasone administration. Neonatal variables collected included gestational age at birth, birth weight, sex, date of birth, Apgar score at 5 minutes, and NICU admission within 24 hours of delivery.

Primary outcomes were the SGA rate, the NICU admission rate, and low Apgar score (<7) at 5 minutes. Birthweights were compared against the World Health Organization estimated fetal weight chart based on the Hadlock formula, using a cut-off of the <10th percentile at the corresponding gestational age at birth[7]. Secondary outcomes were the Caesarean section rate and the operative vaginal delivery rate (ie, ventouse or forceps delivery).

Assuming one-third of patients with APH were prescribed with antenatal corticosteroids[8,9], the proportion of SGA infants was expected to increase from 5% to 10% after exposure to in utero dexamethasone. To achieve alpha of 0.05 and 80% power, the sample size required was 1085. In our hospital, about 300 to 400 patients delivering at term each year have a history of APH, and thus 3 years of records were retrieved. Statistical analysis was performed using SPSS (Windows version 28.0; IBM Corp, Armonk [NY], USA). The dexamethasone and control groups were compared using Chi-squared and *t* tests. Continuous variables were compared using two-sample independent *t* tests. Binary logistic regression analysis was used to determine associations of in utero exposure to dexamethasone with the SGA rate, the NICU admission rate, the Caesarean section rate, and the operative vaginal delivery rate.

Results

A total of 898 women were included in analysis; 50 (5.6%) of them had completed a course of antenatal dexamethasone (Table 1). The mean gestation age at the time of exposure to dexamethasone was 30.95±2.27 weeks, and the mean interval from completion of dexamethasone to delivery was 7.2±2.47 weeks. No patient had a repeated course of corticosteroids.

Compared with women without antenatal dexamethasone (n=848), women with antenatal dexamethasone (n=50) were associated with higher rates of gestational diabetes mellitus (22% vs 7.2%, p<0.001), operative vaginal delivery (16% vs 9.8%, p=0.005), earlier gestational week at delivery (38.2 vs 39.2 weeks, p<0.001), and lower neonatal birthweight (3001.4 vs 3149.6 g, p=0.004) but was not associated with SGA infants, NICU admission, or low Apgar score (Table 1).

In logistic regression analysis, antenatal exposure to dexamethasone was associated with an increased risk of having an operative vaginal delivery (adjusted odds ratio [aOR]=2.98, p=0.016) and a reduced risk of having an SGA baby for every 1-week increase in gestational age at delivery (aOR=0.69, p=0.002) [Table 2]. Every 1-week increase in gestational age at delivery was associated with a reduced odds of having a Caesarean section (aOR=0.59, p<0.001) and an increased odds in having an operative vaginal delivery (aOR=1.47, p=0.003). Women with GDM were two times more likely to have a Caesarean section (aOR=2.09, p=0.005).

Discussion

Antenatal corticosteroids for APH did not increase the risks of having an SGA infant, NICU admission, or low Apgar score. This is in contrast to the findings of a study that reported an increase in the rates of NICU admission and SGA among babies delivered at term after antenatal exposure to betamethasone[6]. This may be due to differences in case selection criteria, as in the present study only patients with a clinically significant episode of APH were given antenatal dexamethasone. Nonetheless, another study reported no difference in neonatal morbidities after in utero exposure to corticosteroids[10].

Exposure to antenatal corticosteroids has been reported to be associated with lower neonatal birthweight[11], which was related to earlier delivery in the present study, although the clinical significance may be limited to a 1-week difference at term. Besides, the odds of operative vaginal delivery increased in women with antenatal dexamethasone. Further studies are needed to establish the underlying cause.

The inverse associations of gestational age with SGA infants and with Caesarean section rates may provide support for expectant management at term for patients with a history of APH, unless there is evidence of fetal compromise such as sonographic features of fetal growth restriction or abnormal cardiotocography.

Table 1. Maternal and fetal characteristics and outcomes in women with or without antenatal dexamethasone

	Antenatal dexamethasone		
	Yes (n=50)*	No (n=848)*	p Value
Maternal age, y	32.8±4.2	32.4±4.2	0.475
Advanced maternal age (>35 y)	15 (30)	242 (28.5)	0.824
Race			0.159
Chinese	44 (88)	790 (93.2)	
Non-Chinese Asian	6 (12)	43 (5.1)	
Caucasian	0	2 (0.2)	
Others/unknown	0	13 (1.5)	
Gestational diabetes mellitus	11 (22)	61 (7.2)	<0.001
Hypertensive disorder in pregnancy	0	1 (0.1)	0.808
Maternal asthma	2 (4)	15 (1.8)	0.261
Mode of delivery			0.005
Normal vaginal delivery	25 (50)	540 (63.7)	
Operative vaginal delivery	8 (16)	83 (9.8)	
Caesarean section	17 (34)	225 (26.5)	
Cause of antepartum haemorrhage			0.472
Unknown origin	44 (88)	745 (87.9)	
Placenta praevia	6 (12)	82 (9.7)	
Other	0	21 (2.5)	
Fetal characteristics			
Gestational week at delivery	38.2±0.97	39.2±1.1	<0.001
Birthweight, g	3001.4±353.2	3149.6±351.9	0.004
Apgar score at 5 min	8.34±0.59	8.23±0.57	0.179
Sex of baby			0.722
Male	26 (52)	419 (49.4)	
Female	24 (48)	429 (50.6)	
Small for gestational age	3 (6)	66 (7.8)	0.453
Neonatal intensive care unit admission	5 (10)	89 (10.5)	0.911
Low Apgar score (<7) at 5 min	1 (2)	5 (0.6)	0.292
Caesarean section	17 (34)	225 (26.5)	0.248
Indication for Caesarean section			0.057
Placenta praevia	5 (29.4)	71 (31.7)	
Previous uterine scar	5 (29.4)	14 (6.3)	
Failed induction	4 (23.5)	87 (38.7)	
Malpresentation	0	10 (4.4)	
Cephalopelvic disproportion	2 (11.8)	16 (7.1)	
Abnormal cardiotocograph	0	16 (7.1)	
Other	1 (5.9)	10 (4.4)	
Operative vaginal delivery	8 (16)	83 (9.8)	0.077
Indication for operative vaginal delivery			0.297
Abnormal cardiotocograph	3 (37.5)	40 (48.2)	
Prolonged second stage	4 (50)	41 (49.4)	
Other	1 (12.5)	2 (2.4)	

* Data are presented as mean ± standard deviation or No. (%) of participants

Table 2. Logistic regression analysis of outcomes adjusted for covariates

	Small-for-gestational-age baby*	p Value	Neonatal intensive care unit admission*	p Value	Caesarean section*	p Value	Operative vaginal delivery*	p Value
Dexamethasone (exposed vs non-exposed)	0.54 (0.16-1.82)	0.318	1.00 (0.38-2.66)	0.997	0.74 (0.39-1.43)	0.37	2.98 (1.23-7.26)	0.016
Maternal age (1-year increase)	0.97 (0.92-1.03)	0.313	1.02 (0.97-1.07)	0.537	1.03 (0.99-1.07)	0.104	0.99 (0.94-1.05)	0.78
Gestational age at delivery (1-week increase)	0.69 (0.55-0.87)	0.002	1.00 (0.82-1.22)	1.00	0.59 (0.51-0.69)	<0.001	1.47 (1.14-1.90)	0.003
Gestational diabetes mellitus (yes vs no)	0.96 (0.39-2.38)	0.925	0.59 (0.22-1.53)	0.276	2.09 (1.25-3.52)	0.005	2.04 (0.82-5.12)	0.127
Maternal asthma (yes vs no)	0.67 (0.09-5.22)	0.705	1.17 (0.26-5.21)	0.84	0.95 (0.31-2.87)	0.95	-	-

* Data are presented as adjusted odds ratio (95% confidence interval)

The presence of GDM has been reported to be associated with a higher Caesarean section rate[12]. Although the present study found that GDM was associated with dexamethasone use, 64% (n=7) of patients were diagnosed to have GDM before they were given dexamethasone. In the remaining 36% (n=4) of patients, the mean gestational age at the time of exposure to dexamethasone was 27.32±0.94 weeks and the time from dexamethasone completion to diagnosis of GDM was 12 to 46 days. Thus, the effect of dexamethasone on GDM was minimal, as the interval from dexamethasone completion to diagnosis of GDM was >72 hours[13]. As an oral glucose tolerance test was not routinely performed after dexamethasone administration, the actual prevalence of GDM in both groups may be underestimated.

The use of antenatal corticosteroids has well-established benefits for preterm babies, whereas the evidence for adverse effects in term babies is inconsistent. Antenatal corticosteroids should be given if there is a high chance of preterm delivery. The fibronectin test[14], transvaginal ultrasound measurement of cervical length[15], and uterine contractions[16] are useful predictors of preterm labour. The timing of the single course of antenatal corticosteroid should be carefully planned[17]. Repeated courses of corticosteroids should be avoided, as the long-term benefits and harms are not well understood.

Our study population consisted of mainly Chinese women, so the findings can be used as a reference for clinical practice in Hong Kong and China. However, the present study was prone to bias because of its retrospective nature. The small proportion of patients exposed to dexamethasone (5.6%) could be an indicator of reliable clinical experience among obstetricians in predicting preterm birth in those presenting with APH. Even so, the power of the study is limited by the small sample size in the exposed group. Furthermore, the severity of APH was not studied. The clinical judgement of significant APH or risk of preterm delivery may be subject to interobserver differences. In addition, the underlying cause of earlier deliveries was not investigated. Our findings might be attributed to different severities of APH or underlying pathologies, rather than the effects of dexamethasone. Hence, further observational studies are warranted to determine whether in utero exposure to dexamethasone is associated with earlier spontaneous onset of labour and a higher proportion of iatrogenic deliveries. There were no data on respiratory distress or long-term outcomes such as neurological deficits in the newborn. Maternal smoking was not assessed, but the effect was expected to be insignificant given active smoking in pregnancy is rare in Hong Kong[18]. Further studies are warranted to identify the underlying cause of the association between dexamethasone use and operative vaginal delivery.

Conclusions

Antenatal dexamethasone for APH was not associated with SGA infants, NICU admission, or low Apgar score but was associated with earlier delivery, lower neonatal birthweight, and a higher rate of operative vaginal delivery. The latter remained significant in logistic regression analysis. More studies are needed to identify any potential effects on term babies exposed to antenatal corticosteroids.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, KYL was not involved in the peer review process of this article. All other authors have disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee (reference: KC/KE-22-0092/ER-2). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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