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Antenatal corticosteroid administration before elective caesarean section at term to prevent neonatal respiratory morbidity: a randomized controlled trial

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ABSTRACT

Objective: To assess the effect of prophylactic corticosteroid administration before elective caesarean section at term (between 38 and 38^{+6} weeks) in reducing neonatal respiratory morbidity and admission to a neonatal intensive care unit (NICU) with respiratory complications.
Methods: Women in this study ($n = 1290$) were randomized into two groups: the dexamethasone group ($n = 645$) and the control group ($n = 645$). Women in the dexamethasone group received three doses of intramuscular dexamethasone 8 mg, 12 h apart, 48 h before caesarean section. Women in the control group received intramuscular saline as a placebo in the same dosage as the dexamethasone group.
Primary outcome: Comparison of NICU admission rates and the occurrence of neonatal respiratory morbidity between the two groups.
Results: The NICU admission rate for respiratory morbidity was significantly lower in the dexamethasone group compared with the control group [10/616 (1.6%) vs 24 (3.9%), respectively; $p = 0.014$]. Antenatal administration of dexamethasone was significantly associated with almost 2.5-fold reduction in the risk of NICU admission for respiratory morbidity (relative risk 0.41, 95% confidence interval 0.2–0.86; number needed to treat ≅43).
Conclusion: Antenatal corticosteroids reduce the incidence of NICU admission with respiratory morbidity after elective caesarean section at term.

Introduction

Infants born preterm are at high risk of neonatal lung disease and associated complications [1]. Respiratory distress syndrome, a consequence of immature lung development, is the primary cause of early neonatal mortality [2] and long-term morbidity in survivors [3].

Maternal steroid treatment before preterm delivery is one of the best documented and most cost-effective life-saving treatments in prenatal medicine [4,5].

In comparison with intended vaginal delivery, elective caesarean section has a two- to four-fold higher risk of overall neonatal respiratory morbidity, and even higher relative risks (RR) of serious respiratory morbidity in term newborns. Hansen et al. suggested that a significant reduction in neonatal respiratory morbidity may be obtained if elective caesarean section is postponed to 39 weeks of gestation [6].

The risk of respiratory complications, mainly respiratory distress syndrome and transient tachypnoea, decreases from 37 weeks to 39 weeks of gestation. Maternal corticosteroid injections have been shown to reduce the risk of breathing problems in babies born before 34 weeks of gestation [7].

Randomized trials regarding maternal administration of steroids before elective caesarean section at term are sought to evaluate whether giving the recommended dose of corticosteroids before delivery may lead to a reduction in respiratory morbidity in babies [7].

As such, a large randomized clinical trial was undertaken to study the effectiveness of corticosteroids on the prevention of

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neonatal respiratory complications in babies born at term by elective caesarean section.

Materials and methods

This randomized prospective placebo control trial was conducted at Ain Shams University Maternity Hospital between November 2011 and December 2014 to assess the role of prophylactic antenatal dexamethasone administration before elective caesarean section at term (between 38 and 38^{+6} weeks).

Protocol approval

Before commencement of the study and in accordance with local regulations, the protocol and all corresponding documents received ethical and research approval from the Council of the Obstetrics and Gynaecology Department, Ain Shams University on 1 November 2011.

Patient selection

The study population was divided into two groups: the dexamethasone group and the control group. The dexamethasone group consisted of 645 women who received intramuscular prophylactic dexamethasone 8 mg every 12 h for 2 days, 48 h before elective caesarean section. The control group consisted of 645 women who received intramuscular saline as a placebo before elective caesarean section. All patients attended the Maternity Hospital of Ain Shams University for routine antenatal care prior to delivery.

All cases underwent elective caesarean section 48 h after completion of the antenatal steroid course (or placebo). Neonatal outcomes were examined for respiratory or non-respiratory morbidities, and the results were analyzed using Statistical Package for the Social Sciences Version 16 (IBM Corp., Armonk, NY, USA).

Inclusion criteria included women with singleton pregnancies, pregnant women between 38 and 38^{+6} weeks of pregnancy (as calculated from the first day of the last menstrual period), age between 20 and 40 years, absence of any medical problem that could affect fetal well-being, absence of uterine contractions, and tenderness (which can be a sign of intrauterine infection).

Each woman underwent an ultrasound examination to ensure the date, and the absence of multifetal pregnancy, intrauterine growth restriction, oligohydramnios, hydramnios or fetal congenital malformations. Women who developed spontaneous labor were excluded from this study.

Consent process

Patients were recruited during routine antenatal visits and counseled about the study at 36 weeks of gestation.

The population sample under study was instructed about the research protocol, and verbal informed consent was received from each participant before randomization. Patients were randomized using computer-based tables, and allocation was performed using the closed envelope technique.

Elective caesarean sections were performed by senior residents, and the neonates were managed by a senior neonatologist. Neonates were assessed by recording: the incidence of NICU admission with respiratory distress; the incidence of transient tachypnoea of the newborn; the incidence of respiratory distress syndrome; the need for mechanical ventilation; and Apgar scores at 1 and 5 min.

Outcome measures

Primary outcome

The primary outcome was NICU admission with respiratory distress.

Secondary outcomes

Secondary outcomes were: respiratory distress syndrome; transient tachypnoea of the neonate; development of neonatal respiratory complications (pneumonia, air leak syndrome); perinatal death (within first 24 h); and need for mechanical ventilation.

Sample size justification

The sample size was calculated using EpiInfo Version 6.0, with type 1 (α) error of 0.05 and power (1-β) of 0.8. Data from previous studies showed that administration of corticosteroids decreased the incidence of NICU admission with respiratory distress following elective caesarean section at term from 22/464 (4.9%) to 7/373 (1.9%). Calculations according to these values indicated a minimal sample size of 611 women in each group. Assuming a drop-out rate of 5%, the total sample size was 1290 women.

Statistical methods

Descriptive statistics for measured variables were expressed as range, mean and standard deviation (SD) for metric data; range, median and interquartile range for discrete data; and number and proportions for categorical data. Demographic data, and primary and secondary outcomes of both groups were compared using Student's *t*-test for quantitative parametric measures, Mann–Whitney's *U*-test for quantitative non-parametric measures, and Chi-squared and Fischer's exact tests for categorical measures. Associations between variables were assessed using Pearson's correlation coefficient for metric variables, and Spearman's correlation coefficient for rank variables. RR of respiratory distress was calculated for both groups, with the corresponding 95% confidence interval (CI). Excel Version 2007 (Microsoft Corp., Redmond, WA, USA) and Statistical Package for the Social Sciences Version 16.0 (IBM Corp.) were used for data presentation and statistical analysis.

Results

This study recruited 1290 women planned for elective caesarean section at gestations between 38 and 38^{+6} weeks.

The mean age of study participants was 28.87 (SD 4.92) years (range 20–40 years). Median parity was 1 (range 0–5, interquartile range 1–3). The mean gestational age was 38^{+4} weeks (SD 3 days) (range 38–38^{+6} weeks).

No significant differences in age, parity and gestational age were found between the women in the two groups (Table 1).

Indications for elective caesarean section in the recruited women included previous caesarean section [$n = 1180$ (91.5%)], malpresentation [$n = 67$ (5.2%)], and infertility or advanced maternal age [$n = 43$ (3.3%)] (Table 1).

No significant differences in indications for caesarean section and type of anesthesia were found between the women in the two groups (Table 1). In addition, no significant differences in neonatal sex, birth weight, and 1- and 5-min Apgar scores were found between the two groups (Table 2).

The NICU admission rate was significantly lower in the dexamethasone group compared with the control group [19/616 (3.1%) vs 41 (6.7%), respectively; $p = 0.003$]. Antenatal administration of dexamethasone was significantly associated with almost

Table 1
Difference between study groups regarding demographic data, indications for caesarean section (CS) and type of anesthesia.

	Dexamethasone group ($n=645$)	Control group ($n=645$)	*P*-value
Age (years)			
Range	20–40	20–40	0.405
Mean (SD)	28.75 (4.89)	28.98 (4.97)	NS
Parity			
Range	0–5	0–5	0.698
Median (IQR)	2 (1–3)	2 (1–3)	NS
Gestational age (weeks)			
Range	$38–38^{+6}$	$38–38^{+6}$	0.517
Mean (SD)	38^{+4} (2 days)	38^{+4} (2 days)	NS
Indications for CS			
Previous CS	583 (90.4%)	597 (92.5%)	0.061
Malpresentation	43 (6.6%)	24 (3.7%)	0.061
Infertility/advanced	19 (2.9%)	24 (3.7%)	NS
Type of anesthesia			
General	475 (73.3%)	455 (70.5%)	0.190
Spinal	170 (26.7%)	190 (29.5%)	NS

SD, standard deviation; IQR, interquartile range [central 50% of ascendingly-ordered set of data]; NS, non-significant.

two-fold reduction in the risk of neonatal NICU admission [RR 0.46, 95% CI 0.27–0.78; number needed to treat (NNT) ≅ 28] (Table 2).

The rate of transient tachypnoea of the newborn was significantly lower in the dexamethasone group compared with the control group [8/616 (1.3%) vs 21 (3.4%), respectively; $p = 0.014$]. Antenatal administration of dexamethasone was significantly associated with almost 2.5-fold reduction in the risk of transient tachypnoea of the newborn (RR 0.38, 95% CI 0.17–0.85; NNT ≅ 47) (Table 2).

The rate of neonatal respiratory distress syndrome was slightly lower in the dexamethasone group compared with the control group [4/616 (0.6%) vs 10 (1.6%), respectively]; however, this difference was not significant ($p = 0.993$). Antenatal administration of dexamethasone was associated with almost 1.5-fold reduction in the risk of neonatal respiratory distress syndrome, but this association was not significant (RR 0.66, 95% CI 0.11–3.94; NNT ≅ 601) (Table 2).

The NICU admission rate for respiratory morbidity was significantly lower in the dexamethasone group compared with the control group [10/616 (1.6%) vs 24 (3.9%), respectively; $p = 0.014$]. Antenatal administration of dexamethasone was significantly associated with almost 2.5-fold reduction in the risk of NICU admission for respiratory morbidity (RR 0.41, 95% CI 0.2–0.86; NNT ≅ 43) (Table 2).

The rate of need for mechanical ventilation was slightly lower in the dexamethasone group compared with the control group [5/616 (0.8%) vs 11 (1.8%), respectively]; however, this difference was not

Table 2
Differences between groups in terms of adverse neonatal outcomes and complications.

	Dexamethasone group ($n=616$)	Control group ($n=611$)	*p*-Value	RR (95% CI)	NNT
Neonatal sex					
Male	262 (42.5%)	236 (38.6%)	0.163		
Female	354 (57.5%)	375 (61.4%)	NS		
Birth weight (g)					
Range	1800–4500	1900–4400	0.134		
Mean (SD)	3072.89 (483.98)	3113.67 (468.55)	NS		
1-min Apgar score					
Range	2–9	2–9	0.122		
Median (IQR)	7 (7–7)	7 (7–7)	NS		
1-min Apgar score <7	87 (14.1%)	69 (11.3%)	0.137 NS		
5-min Apgar score					
Range	6–9	6–9	0.638		
Median (IQR)	9 (9–9)	9 (9–9)	NS		
5-min Apgar score <7	18 (2.9%)	31 (5.1%)	0.054 NS		
Admission to PCBU	19 (3.1%)	41 (6.7%)	0.003 S	0.46 (0.27–0.78)	28
TTN	8 (1.3%)	21 (3.4%)	0.014 S	0.38 (0.17–0.85)	47
Neonatal RDS	4 (0.6%)	10 (1.6%)	0.103 NS	0.4 (0.13–1.26)	101
Admission to NICU for respiratory morbidity	10 (1.6%)	24 (3.9%)	0.014 S	0.41 (0.20–0.86)	43
Need for mechanical ventilation	5 (0.8%)	11 (1.8%)	0.127 NS	0.45 (0.16–1.29)	101
Perinatal mortality	1 (0.2%)	2 (0.3%)	0.994 NS	0.5 (0.05–5.46)	606

RR, relative risk; CI, confidence interval; S, significant; NS, non-significant; NNT, number needed to treat; PBUC, primary baby care unit; TTN, transient tachypnoea of the newborn; RDS, respiratory distress syndrome; NICU, neonatal intensive care unit.
Data presented as *n* (%).

significant ($p = 0.127$). Antenatal administration of dexamethasone was associated with almost two-fold reduction in the risk of need for mechanical ventilation, but this association was not significant (RR 0.45, 95% CI 0.16–1.29; NNT ≅ 101) (Table 2).

There were three cases of perinatal mortality in total; one (0.2%) in the dexamethasone group and two (0.3%) in the control group. The difference between the groups was not significant (Table 2).

Comments

As a result of the rapid increase in the caesarean section rate over the past few years, there is an urgent need to study the complications of this procedure, particularly those related to respiratory morbidity.

When infants are delivered near to or at term and before 39 weeks, especially by elective caesarean delivery before the onset of spontaneous vaginal delivery, they are usually deprived of necessary hormonal changes. This can result in the development of respiratory complications, particularly neonatal distress syndrome.

This study showed that the administration of corticosteroids before an elective caesarean section at term led to a significant improvement in fetal respiratory function and reduced fetal respiratory complications.

Stutchfield et al. [8] undertook a study in 998 women due to deliver by elective caesarean section; 503 women were randomized to the treatment group and received corticosteroids prior to elective caesarean section, and 495 women were assigned to the control group and received placebo. In agreement with the present study, Stutchfield et al. concluded that antenatal betamethasone before elective caesarean section at term reduces NICU admissions due to respiratory distress. They also stated that the risk of respiratory distress and the likely benefits of antenatal corticosteroids should be considered when planning an elective caesarean section [8].

Morrison et al. found that betamethasone given immediately before elective caesarean section at term reduced respiratory distress and admission to a special care baby unit. They also found that the benefits of antenatal steroids persisted until 39 weeks [9], which was slightly different from the present study which evaluated corticosteroid administration 48 h before the caesarean section.

James et al. [10] and Bhuta et al. [11] reported that surfactant deficiency and/or dysfunction are major determinants of respiratory distress in term infants diagnosed with transient tachypnoea of the newborn, and that enhanced surfactant production by betamethasone may explain its reduced incidence, independent of other effects. Low levels of phosphatidylglycerol in lung fluid and amniotic fluid were reported in patients with transient tachypnoea of the newborn in more than two studies [10]. Reduced bubble clicking in tracheal and gastric aspirates of these infants was also reported [11], which supports the use of corticosteroids as prophylaxis against transient tachypnoea of the newborn.

The results of the present study were in agreement with those of Sotridais et al. [7], who undertook research on the babies of 942 women born at term by elective caesarean section in order to compare prophylactic administration of betamethasone ($n = 467$) with usual treatment without steroids ($n = 475$). Women randomized to the treatment group received two intramuscular doses of betamethasone in the 48 h before caesarean section, whereas the control group received treatment as usual. Prophylactic betamethasone significantly decreased the risk of NICU admission for respiratory morbidity (main outcome). In agreement with the present study, no significant reduction in the incidence of neonatal respiratory distress syndrome, need for mechanical ventilation and length of NICU stay was found. However, in contrast to the present study, prophylactic betamethasone did not significantly reduce the overall NICU admission rate for any indication (i.e. respiratory and non-respiratory indications), and did not significantly decrease the rate of transient tachypnoea of the newborn [7].

The results of the present study also contrast with those of Hutchon [12], who found that corticosteroids had no role in elective caesarean section at term. Hutchon assumed that if a larger study was designed and adequately powered to show an overall difference in admissions, he could be confident that a reduction would be seen as a direct result of fewer babies admitted with respiratory distress [12].

Pollak and Birnbacher stated that premature female infants have a significantly greater chance of surviving than male infants at similar birth weights and gestational ages, and have an advantage over males in terms of better outcomes with less morbidity. They reported that the exact mechanisms responsible for the sex difference remain to be determined [13]. However, the present study did not study sex as a risk factor.

This study aimed to provide more data regarding the administration of dexamethasone 48 h before elective caesarean section in order to minimize respiratory morbidity, using a sample of 1290 cases, allocated at random. This study found that antenatal administration of corticosteroids before elective caesarean section at term may be beneficial in reducing neonatal respiratory morbidity.

Conflict of interest

None declared.

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References

[1] Abeywardana S. Report of the Australian and New Zealand Neonatal Network 2003. Sydney: ANZNN; 2005.
[2] Laws PJ, Abeywardana S, Walker J. Australia's mothers and babies 2005. Perinatal Statistics Series No. 20. Per 40. Sydney: Australian Institute of Health and Welfare, National Perinatal Statistics Unit; 2007.
[3] Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008;371:261–5.
[4] Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006;3:CD004454.
[5] Marciniak B, Patro-Malysza J, Poniedzialek-Czajkowska E, et al. Glucocorticoids in pregnancy. Curr Pharm Biotechnol 2011;12:750–7.
[6] Hansen AK, Wisborg K, Uldbjerg N, Henriksen TB. Elective caesarean section and respiratory morbidity in the term and near-term neonate. Acta Obstet Gynecol Scand 2007;86:389–94.
[7] Sotiriadis A, Makrydimas G, Papatheodoru S, Ioannidis JPA. Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. Cochrane Database Syst Rev 2009;4:CD006614.
[8] Stutchfield PR, Whittaker R, Russell I. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section; pragmatic randomised trial. BMJ 2005;331:662–4.
[9] Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. Obstet Gynaecol 1995;102:101–6.
[10] James DK, Chiswick ML, Harces A. Non-specificity of surfactant deficiency in neonatal respiratory disorders. BMJ 1984;288:1635–8.
[11] Bhuta T, Kent-Biggs J, Jeffery HE. Prediction of surfactant dysfunction in term infants by the click test. Pediatr Pulmonol 1997;23:287–91.
[12] Hutchon DJR. A clearer explanation of no benefit for steroids. BMJ 2005 [e-Letter 08.12.05].
[13] Pollak A, Birnbacher R. Preterm male infants need more initial respiratory support than female infants. Acta Paediatr 2004;93:447–8.