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Does antenatal steroids treatment prior to elective cesarean section at 34–37 weeks of gestation reduce neonatal morbidity? Evidence from a case control study

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Abstract

Objective To determine whether antenatal corticosteroids administration prior to an elective cesarean section (ECS) at 34–37 weeks gestation is associated with improved neonatal outcome.

Materials and methods A case control study of women with singleton pregnancies who underwent ECS between 34 and 37 weeks of gestation including two groups: (1) study group in which patients were treated with betamethasone prior to ECS ($n = 58$) and (2) control group matched for gestational age at delivery in which patients did not receive betamethasone ($n = 107$). Neonatal measures including respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), oxygen requirement, admission to the special care unit, hypoglycemia, hyperbilirubinemia and length of hospitalization were determined in both groups. Composite respiratory morbidity was defined as the presence of either RDS, TTN, mechanical ventilation or oxygen requirement.

Results There was no significant difference in the rate of composite respiratory morbidity nor its components between patients with and without betamethasone treatment (25.9 vs. 25.2%, respectively, $p = 0.9$).

Conclusion Antenatal treatment with corticosteroids prior to ECS at 34–37 weeks of gestation did not result in significant reduction in neonatal respiratory morbidity in our cohort of patients.

Keywords Antenatal corticosteroids · Elective cesarean section · Neonatal morbidity · Late prematurity

Introduction

Late preterm births account for 75% of all preterm births. The proportion of late preterm infants has dramatically increased during the last two decades, mostly due to increase in obstetric interventions following maternal or fetal complications [1]. Infants born at 34–37 weeks of gestation are at higher risk for neonatal morbidity, particularly respiratory morbidity, as well as greater risk of being admitted to intensive care, compared with term infants. The rate of respiratory complication including respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), oxygen requirement and ventilator support is approximately 10%, with an obvious higher risk among the earlier gestational age of this range [2–5]. In order to improve the neonatal outcome of late preterm infants, antenatal treatment with corticosteroids to excel fetal lung maturation has been suggested. The beneficial effects of corticosteroids before 34 weeks of pregnancy have been well established [6, 7]. However, the results regarding the efficacy of corticosteroids beyond 34 weeks of gestation have been conflicting [8, 9]. Moreover, the American College of Obstetricians and Gynecologists has recommended that corticosteroids should be administered to pregnant women who are at risk for preterm delivery only before 34 weeks of gestation [10].

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Recently, a large randomized trial has found that antenatal administration of corticosteroids to women at risk for late preterm delivery decreased the need for respiratory support after birth. Sub-group analysis has suggested that neonates born by elective cesarean section will benefit most from antenatal corticosteroids treatment [11].

Indeed, the route of delivery has been shown to be associated with the prevalence of neonatal respiratory complications independent of gestational age [12]. Elective cesarean section (ECS) is associated with a twofold to fourfold increase in the risk of overall neonatal respiratory morbidity compared to intended vaginal delivery [13, 14]. The antenatal steroids for term elective cesarean section (ASTECS) study demonstrated a significant reduction in the rate of admission to neonatal intensive care units for respiratory complications in patient who received corticosteroids prior to ECS at term [15]. However, the possible side effects of antenatal steroids treatment, especially when given in multiple doses, must be considered before deciding on such treatment; a single course of antenatal steroids might increase the risk of neonatal hypoglycemia [11] and multiple courses are associated with decreased weight, length, and head circumference at birth [16]. Furthermore, antenatal exposure to steroids might result in later development of insulin resistance during adulthood [17].

The aim of our study was to evaluate the efficacy of corticosteroids treatment prior to an elective cesarean section at 34 + 0–37 + 0 weeks of gestation.

Materials and methods

This is a case control study of pregnant women delivered by elective cesarean section at 34 + 0–37 + 0 weeks of gestation. All women received prenatal care and delivered at a single tertiary medical center between January 2011 and December 2013. The study was approved by the ethics committee of Sheba Medical Center. Due to its retrospective nature, a consent for participation was not necessary. The study group included patients who received two intramuscular doses of 12 mg betamethasone 24 h apart 2–7 days prior to delivery. The control group consisted patients who underwent ECS between 34 and 37 weeks of gestation without receiving corticosteroids prior to delivery. The decision whether to treat or not to treat with antenatal steroids prior to ECS was at the discretion of the attending physician. Gestational age was calculated by the last menstrual period date and validated by first trimester ultrasound examination. Multiple gestations were excluded as well as pregnancies that were complicated by congenital anomalies, chromosomal abnormalities or chorioamnionitis. The charts of all women and their infants were reviewed for the variables of interest. Maternal characteristics and their pregnancy outcomes

were abstracted from the obstetric electronic charts. Neonatal outcome measures were collected, recorded and compared between the two groups including respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), oxygen requirement, admission to the special care unit, hypoglycemia (defined as glucose level ≤ 45 mg/dL), hyperbilirubinemia that required phototherapy and length of hospitalization. The primary outcome measure was a composite respiratory morbidity outcome defined as the presence of either RDS, TTN, mechanical ventilation or oxygen requirement. RDS was defined as early respiratory distress that comprised cyanosis, grunting, retraction and tachypnea combined with ground glass appearance and air bronchogram on chest X-ray. TTN was defined as respiratory distress with prominent perihilar streaking and fluid in the interlobar fissure on chest X-ray. Respiratory support was given when neonates had a PaO_2 level of < 50 mm Hg in room air, central cyanosis or saturation < 90% in room air. Oxygen requirement included supplemental oxygen with a fraction of inspired oxygen above 0.21 for any period of time after delivery. Special care unit is where neonates are admitted when they require continuous medical monitoring but no invasive treatment.

Statistical analyses were conducted with the SPSS version 21.0 (SPSS Inc., Chicago, IL). Normality of the data was tested using Shapiro–Wilk or Kolmogorov–Smirnov tests. Data are presented as median and range or as mean ± SD. Comparison of continuous variables between the two groups was conducted using Mann–Whitney U test or Student's t test as appropriate. Chi-square or Fisher exact test were used for comparison of categorical variables. Logistic regression analysis was conducted to determine which factors were significantly and independently associated with the composite respiratory morbidity outcome. Significance was accepted at a probability value of < 0.05.

Results

The study group included 58 patients who received corticosteroids prior to the ECS and were matched according to gestational age at delivery to 107 patients who did not receive corticosteroids prior to their ECS and served as controls. Demographic and clinical characteristics of the two groups are shown in Table 1. No significant differences were found between the groups with respect to maternal age, parity and the rate of pregnancy complications including intra-uterine growth restriction and gestational diabetes mellitus. The rate of hypertensive complications was higher among the group that was not treated with antenatal corticosteroids; this difference did not reach statistical significance. Gestational age at delivery, birth weight and neonatal male:female ratio were also similar between the two groups. The indications for

Table 1 Demographic and clinical characteristics

Variable	Corticosteroids (n = 58)	No corticosteroids (n = 107)	P value
Maternal age, years (median, range)	38 (26–45)	36 (22–53)	0.65
Parity (median, range)	2 (0–9)	2 (0–9)	0.35
Hypertensive disease of pregnancy, n (%)	5 (8.6)	21 (19.6)	0.06
IUGR, n (%)	4 (6.8)	9 (8.4)	0.73
GDM, n (%)	12 (20.7)	17 (15.9)	0.44
Gestational age at delivery weeks, median (range)	36 (34–37)	35.5 (34–37)	0.60
Birth weight (g) (mean ± SD)	2540 ± 370	2630 ± 425	0.18
Male/female ratio	25/33	49/58	0.74

IUGR Intra-uterine growth restriction, *GDM* gestational diabetes mellitus

Table 2 Indication for delivery

Indication for early delivery	Corticosteroids (n = 58)	No corticosteroids (n = 107)	P value
Uterine scar	23 (39.6)	27 (25.2)	0.08
Placenta/vasa previa	18 (31)	34 (31.7)	0.90
Hypertensive disease	3 (5.2)	15 (14)	0.14
IUGR	4 (6.8)	9 (8.4)	0.96
PPROM	1 (1.7)	2 (1.8)	1.0
Maternal disease	0	4 (3.7)	0.3
Non-reassuring fetal status	3 (5.2)	7 (6.5)	1.0
BOH	3 (5.2)	5 (4.6)	1.0
Oligohydramnion	2 (3.4)	2 (1.8)	0.60
IHCP	1 (1.7)	1 (0.9)	1.0
Chronic abruption	0	1 (0.9)	1.0

Values are presented as *N* (%)

IUGR intra-uterine growth restriction; *PPROM* preterm premature rupture of membranes; maternal disease includes chronic renal failure, chronic heart failure, orthopedic complication and transient ischemic attack; *BOH* bad obstetric history; *IHCP* intra-hepatic cholestasis of pregnancy

ECS are summarized in Table 2. The major indications for cesarean section were previous complication of uterine scar, placenta previa or vasa previa and were distributed equally between the two groups. Neonatal outcomes are detailed in Table 3. There was no difference in the rate of composite respiratory morbidity between patients with and without betamethasone treatment (24.1 vs 24.3%, respectively, $p = 0.9$). Similarly, no difference was found between the groups regarding the rates of RDS (5.2 vs 7.5%, $p = 0.57$), TTN (10.3 vs 11.2%, $p = 0.86$), any oxygen requirement (22.4 vs 23.4%, $p = 0.88$) and oxygen requirement for at least 4 h (17.2 vs 19.9%, $p = 0.9$). In addition, the rates of intra-ventricular hemorrhage, necrotizing enterocolitis and sepsis as well as hypoglycemia, hyperbilirubinemia and NICU admission were also similar between both groups. However, significantly more newborns of mothers in the betamethasone group required admission to the special care unit (56.9 vs 40.2%, $p = 0.04$). Sub-analysis of the rate of composite respiratory morbidity according to gestational age at delivery showed similar results with no difference between the two groups (Table 4). Logistic regression analysis was employed to examine the association between composite respiratory morbidity, corticosteroids treatment and other confounding factors including birth weight, gestational diabetes mellitus, indication for cesarean section, gestational age at delivery and neonatal gender (Table 5). The final regression model revealed that corticosteroids treatment was not associated with the rate of composite respiratory morbidity, whereas gestational age at delivery ($p = 0.01$) and neonatal gender ($p = 0.009$) were significantly associated with adverse respiratory morbidity outcome with relative protective effect for females.

In order to determine whether corticosteroids treatment was significantly and independently associated with admission to the special care unit, logistic regression analysis was used adjusting for other factors that can potentially affect this outcome. Birth weight ($p < 0.001$) but not corticosteroids use was found to be significantly associated with special care unit admission (Table 5).

Discussion

The results of the present study indicate that antenatal treatment with corticosteroids prior to an elective cesarean section at 34 + 0–37 + 0 weeks of gestation does not decrease the incidence of neonatal respiratory morbidity. Furthermore, corticosteroids administration was associated with an increased rate of admission to the special care unit. Of note, this association did not remain statistically significant after adjustment for confounding factors.

This study confirms previous findings indicating high rate of respiratory complications among late preterm infants [18–20]. Indeed, 5–10% of infants were complicated by RDS, approximately 10% had TTN and more than

Table 3 Neonatal complications

Variable	Corticosteroids (n = 58)	No corticosteroids (n = 107)	P value
Apgar 5 min ≤ 7	2 (3.4)	0	0.12
Composite respiratory morbidity[a]	14 (24.1)	26 (24.3)	0.98
RDS	3 (5.2)	8 (7.5)	0.57
TTN	6 (10.3)	12 (11.2)	0.86
Oxygen requirement	13 (22.4)	25 (23.4)	0.88
Length of oxygen requirement in hours (median, range)	11 (1–192)	8 (1–144)	0.48
CPAP or mechanical ventilation	4 (6.9)	7 (6.5)	0.93
Hypoglycemia	26 (44.8)	35 (32.7)	0.12
Jaundice requiring phototherapy	7 (12.1)	15 (14)	0.70
NICU admission	4 (6.9)	13 (12.1)	0.30
Special care unit admission	33 (56.9)	43 (40.2)	0.04
IVH	0	1 (0.9)	1.0
NEC	0	1 (0.9)	1.0
Sepsis	0	0	1.0

Values are presented as *N* (%)

RDS respiratory distress syndrome; *TTN* transient tachypnea of the newborn; *CPAP* continuous positive airway pressure; *IVH* intra-ventricular hemorrhage; *NEC* necrotizing enterocolitis

[a]The presence of either RDS, TTN, mechanical ventilation or oxygen requirement

Table 4 The rate of composite respiratory outcome stratified by gestational age

	Composite outcome Steroids	Composite outcome Non-steroids	P value
34–35 weeks (n = 12)	1/4	3/8	0.66
35–36 weeks (n = 39)	7/16	5/23	0.14
36–37 weeks (n = 114)	6/38	18/76	0.33

20% of newborns required oxygen. Given the large proportion of late preterm infants affected by clinically important morbidity, decreasing the rate neonatal morbidity in this population by antenatal treatment with corticosteroids would have great public health impact. Unfortunately, antenatal corticosteroids did not reduce neonatal complications in our cohort of patients. In accordance with our results, a previous randomized controlled trial, which included 320 women, showed that antenatal treatment with corticosteroids at 34–36 weeks of gestation did not reduce the incidence of respiratory disorders in newborn infants [9]. There was no reduction in the risk of respiratory morbidity even after adjustment for subgroups according to gestational age. Moreover, antenatal treatment with corticosteroids was ineffective in reducing the rate of other complications of late prematurity with the exception of jaundice [9]. Unlike our study, the aforementioned study included women in labor, and almost 70% of women in this study underwent vaginal delivery. We chose to focus on patients who undergo ECS, as cesarean section per se is a known to be a risk factor for neonatal respiratory complications in both term and preterm newborns [13, 21]. The risk is attributed to the inactivity of the sodium channels, which promotes alveolar fluid reabsorption, in fetuses not exposed to the stress of normal labor [22, 23]. Due to the well-established association between cesarean section and

Table 5 Regression analysis

Variable	Composite respiratory morbidity			Special care unit admission		
	Odds ratio	CI 95%	P value	Odds ratio	CI 95%	P value
Steroids	0.85	0.83–1.07	0.4	1.7	0.19–1.17	0.1
Birth weight	1	0.99–1	0.5	0.99	0.99–1	< 0.001
GDM	0.88	0.34–2.27	0.8	0.42	0.19–1.17	0.1
Indication for delivery	0.94	0.83–1.07	0.4	0.9	0.88–1.1	0.8
GA at delivery	0.52	0.32–0.86	0.01	0.85	0.54–1.35	0.5
Gender	2.7	1.28–5.74	0.009	0.72	0.36–1.54	0.3

GDM gestational diabetes mellitus, *GA* gestational age

respiratory morbidity, the ASTECS study was carried out in order to evaluate the effectiveness of antenatal corticosteroids in 998 women who were candidates for full-term ECS. In contrast to our findings, the authors reported a significant reduction of 54% in admissions to special care baby unit for respiratory distress [15]. Importantly, they found no reduction in the objective measures of respiratory morbidity. In addition, a systematic review examining the efficacy of antenatal corticosteroids prior to elective cesarean section at term in reduction of neonatal respiratory morbidity, concluded that there are insufficient data to recommend the use of corticosteroids under these clinical circumstances [24]. Avoiding unnecessary cesarean sections and delaying ECS until after 39 weeks of gestation when possible, seem to be safer and more effective in preventing neonatal respiratory morbidity [25]. Recently, a large multicenter randomized trial found that antenatal administration of corticosteroids to women at risk for late preterm delivery decreased the need for substantial respiratory support during the first 72 h after birth [11]. Consistent with our findings, Gyamfi-Bannerman et al. reported on a similar rate of RDS in the betamethasone and placebo groups. However, the rates of TTN and bronchopulmonary dysplasia were significantly lower in the betamethasone group. Furthermore, neonatal hypoglycemia was significantly more common in the betamethasone group [11]. Likewise, the infants in our cohort, who were exposed to antenatal corticosteroids, were also more likely to be complicated by hypoglycemia, although this difference did not reach statistical significance. The inconsistency in the results between the above-mentioned study and the results presented herein could be attributed to our relatively small sample size, but can also be explained by the different cohort of patients included in these studies. We have included only patients prior to an elective CS, most of them due to previous complications of uterine scar or placenta or vasa previa, whereas the above-mentioned study included a large proportion of patients with preterm birth and placental mediated complications such as hypertensive diseases (25% of patients) and fetal growth restriction. The relationship between maternal hypertensive disorders and neonatal respiratory complications is controversial. Langelvend et al. demonstrated that the incidence of RDS was reduced in late preterm infants born to mothers with preeclampsia [26]. On the other hand, Ting-An et al. did not demonstrate this protective effect in late preterm neonates [27] and even more, two other studies found an increase in BPD rate in pregnancies with placental mediated complications [28, 29]. Of note, the inherent disadvantages of a retrospective cohort study design limited our ability to control for potential confounding factors. The decision whether to treat or not to treat with antenatal steroids was at the discretion of the attending physician, which could lead to a selection bias, resulting in more complicated cases in the study group. However, the indications for early delivery were included in the logistic regression analysis and did not significantly affect the neonatal morbidity rate. The strength of the current study is being a single-center study in which all women and newborns were uniformly managed using a standardized protocol regarding maternal follow-up, indication for early delivery and neonatal care, as well as the well-defined cohort of women undergoing an elective late preterm CS.

We have previously shown that antenatal steroid administration after 34 weeks of gestation was associated with improved neonatal outcome in the presence fetal lung immaturity documented by amniocentesis [8]. Recently, a novel non-invasive method to predict fetal lung maturity was developed based on quantitative analysis of ultrasound images of the fetal lung and has been shown to accurately predict neonatal respiratory morbidity [30, 31]. Giving the potential long-term impact of antenatal exposure to steroids, including insulin resistance and attention problems [17, 32] and due to the conflicting findings regarding the beneficial effect of antenatal corticosteroids after 34 weeks of gestation, the decision on whether or not to treat a patient at risk for late preterm delivery with corticosteroids should probably be tailored for each patient according to her risk for fetal lung immaturity. Hopefully, a non-invasive and accurate estimation of this risk will be possible in the near future.

In conclusion, our study suggests that antenatal treatment with corticosteroids prior to ECS at 34–37 weeks of gestation does not result in significant reduction in neonatal respiratory morbidity. However, in view of the recent results of the multicenter randomized trial showing beneficial effect for antenatal corticosteroids treatment in women at risk for late preterm delivery [11], justification of routine use of corticosteroids prior to late preterm delivery is still questionable. We believe that clinicians should decide whether to administer steroids in women over 34 weeks of gestation according to the estimated risk of fetal lung immaturity based on either amniocentesis or non-invasive analysis of fetal lung texture.

Authors contributions MK: study design and planning, data analysis and manuscript writing. SMT: data analysis, manuscript writing. UA: data analysis. RM, ES, ES: study design and planning. YY: study design and planning, data analysis and manuscript writing.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Human and animal rights statement This article does not contain any studies with human participants performed by any of the authors.

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