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Original Research Article

## The neonatal outcomes of Dexamethasone administration before scheduled cesarean delivery at term: a randomized clinical trial

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### ABSTRACT

**Background:** Caesarean delivery (CD) rates in developing countries are rising beyond the recommended rates of World health organization. Objective of this study was to evaluate whether Dexamethasone injections reduce neonatal incubation admissions when given before scheduled caesarean delivery (CD) at term or not.

**Methods:** A double blinded, two armed, randomized clinical trial was conducted at Tanta University hospitals in the period from October 2017 to March 2019. Four hundred pregnant women admitted for scheduled CD with gestational age  $\geq 37$  weeks were included. Patients were randomized into study group and control group. The study group was given 3 dexamethasone doses, 8 mg each while control group was given saline injections simultaneously as a placebo drug. The primary outcome was the neonatal incubatory admissions.

**Results:** Demographic data in both groups were comparable. Transient tachypnea of newborn (TTN) was 15.47% in study group versus 20.33% in control group with  $p=0.227$ . The respiratory distress (RDS) in study group was 6.63% versus 9.89% in control group with  $p=0.260$ . The incubation admissions were nasal oxygen 12.71% versus 15.38%, continuous positive airway pressure ventilation (CPAP) 5.52% versus 8.24% and mechanical ventilation was 3.87% versus 6.59% in the study and control groups respectively.

**Conclusions:** Although Dexamethasone administration before scheduled CD at term reduced both respiratory morbidity and incubation admissions, the differences between study and control groups were not significant.

**Keywords:** Cesarean delivery, Dexamethasone, Respiratory distress syndrome, Steroids, Transient tachypnea of newborn

### INTRODUCTION

Caesarean delivery (CD) rates in developing countries are rising beyond the recommended rates of World health organization.<sup>1</sup> This rise in CD rates may be explained by improved surgical techniques and facilities for control of anticipated postoperative pain and complications like hemorrhage, infection, and thromboembolism. These improvements increased the safety and acceptability of the procedure by both obstetricians and pregnant women.<sup>2</sup>

Although maternal risks have been improved, CD still had effects on the new-borns like respiratory composite morbidity including transient tachypnoea of new-born (TTN), respiratory distress syndrome (RDS) and even respiratory failure. These complications increase neonatal admissions to incubations and neonatal intensive care units (NICU). Many studies had strengthened on this correlation between scheduled caesarean delivery at term and respiratory morbidity where 50% of new-borns with respiratory distress were delivered by CD. The most

common respiratory problems were TTN followed by RDS.<sup>3,4</sup>

Respiratory complications are inversely correlated to gestational age at the time of delivery. As the gestational age increases, the respiratory complications decrease and vice versa. These complications could be reduced by giving antenatal steroids for inducing lung maturity especially when preterm delivery is anticipated.<sup>5,6</sup>

The benefits of steroids before scheduled CD at term are still controversial where some studies reported benefits and reduction in respiratory morbidity; other studies not recommend its use at term or even linked its use to some complications.<sup>7-12</sup> This study was conducted to evaluate whether dexamethasone injections at term is beneficial in reducing neonatal incubation admissions or not.

## METHODS

This study is a double blinded, randomized controlled clinical trial conducted at the Department of obstetrics and gynecology, Tanta University, Tanta, Egypt during period from October, 1, 2017 to March, 31, 2019. All patients were informed about the study aims and drugs given, and they signed a written consent.

This study was approved by local ethical committee of Tanat University and registered at UMIN clinical trial registry. ([https://upload.umin.ac.jp/cgi-bin/ctr\\_e/ctr\\_view\\_reg.cgi?recptno=R000033247](https://upload.umin.ac.jp/cgi-bin/ctr_e/ctr_view_reg.cgi?recptno=R000033247)) and has the following ID: UMIN000029070.

### Patients

Initial recruitment enrolled 417 patients admitted for parturition. Patients were included in the study according to inclusion and exclusion criteria.

### Inclusion criteria

- Age 20-40 years
- Singleton pregnancy
- Gestational age  $\geq 37$  weeks
- Scheduled cesarean section.

### Exclusion criteria

- Multiple gestation
- Obstetric complications such as pre-eclampsia, diabetes mellitus, antepartum hemorrhage, PROM and preterm delivery
- Malformed baby
- Patients in labour
- Patients with contraindication to spinal anesthesia
- Refusal to participate in the study.

Assuming that dexamethasone is beneficial if given prior to scheduled CD at term (H0) in reducing neonatal incubation

admission. A 95% confidence level, confidence interval of 5 and 50% percentage were settled. The sample size was calculated with internet-based Epi info program version 7.2. The estimated sample size was 388.

### Randomization, blinding and allocation

Patients were randomly allocated into 2 groups (study and control groups) using a computer assisted program (Excel, 2010). Each patient was given a concealed envelope containing the allocated group. This study was double blinded where both patients and researchers were not informed by the given drugs. Dexamethasone or saline were prefilled in 2 ml syringes and both have the same external appearance.

### Interventions

#### Study group

They received dexamethasone sodium phosphate (EPIDRON®, EPICO Company, Egypt) 6mg IM every 12 hours for 4 doses with the last dose at least 24 hours before scheduled CD. This regimen was recommended by WHO.<sup>13</sup>

#### Control group

They received 2 ml normal saline 0.9% IM every 12 hours for 4 doses with the last dose at least 24 hours before scheduled CD. All patients were given spinal anesthesia and 1 gm Cephadrine IV after delivery of the baby. All cases were operated by the first 6 authors. Routine postoperative care was given to all patients including IV fluids, antibiotics, vital signs assessment, and pre-discharge hemoglobin. Babies were assessed by a pediatrician specialized in neonatology.

### Study outcomes

Primary outcome was neonatal incubation admission due to respiratory morbidity. The secondary outcomes were neonatal mortality.

### Study variables

The study variables registered were demographic characteristics, gestational age, duration of surgery, neonatal weight, Apgar scores (mean of values at 0 and 5 minutes), respiratory morbidities and other adverse neonatal outcomes. The need for incubation admissions and duration of admissions were also recorded.

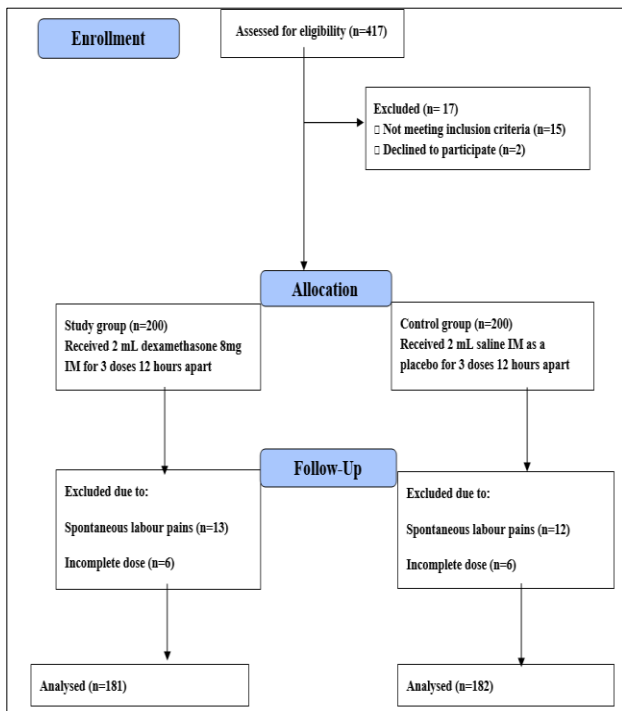
### Statistical analysis

Data were collected, tabulated, statistically analyzed by computer using SPSS version 21 (SPSS Inc., Chicago, IL), two types of statistics were done: Quantitative data were expressed as the mean, and standard deviation (SD). Qualitative data were expressed as frequencies and

percentage. Chi-square ( $\chi^2$ ) and independent t-test were used to compare both groups. p value <0.05 was considered statistically significant.

**RESULTS**

The recruited patients (n=417) were assessed for eligibility where 17 cases were excluded either not meeting inclusion criteria or declined to participate in this study. The flow of patients during the study is shown in Figure 1.



**Figure 1: Enrolled patients during the study.**

Characteristics of enrolled patients in were demonstrated in Table 1. Patients were average in weight with the mean BMI of 24.3±2.23. Most patients were repeat CD 258(71.07%). The mean haemoglobin concentration before surgery was 11.32±1.06 gm/dL. The most common indications for caesarean section were repeat CD (71.07%), CD on maternal request (9.64%) and cephalopelvic disproportion (6.34%). Other indications were reported in Table 1.

**Table 1: Characteristics of all enrolled patients and indications of caesarean section (n = 363).**

Age (years)	31.45±4.58	
Parity	2.81±1.24	
BMI (kg/m <sup>2</sup> )	24.3±2.23	
Cesarean section type	Number	%
Primary	105	28.93
Repeat	258	71.07
Gestational age (weeks)	38.13±1.10	
Preoperative Hb (gm/dL)	11.32±1.06	
Indications of cesarean section	Number	%
Previous cesarean delivery	258	71.07
Breech presentations	11	3.03
Cesarean delivery on maternal request	35	9.64
Cephalopelvic disproportion	23	6.34
Placenta previa	14	3.86
Genital warts	3	0.83
Prior myomectomy	3	0.83
Prior classical repair	4	1.10
Precious baby	7	1.92
History of difficult vaginal delivery	5	1.38

SD: Standard deviation, BMI: Body mass index, Hb: hemoglobin

**Table 2: Outcomes of the study in both groups.**

	Study group "Dexa group" (n=181)	Control group "placebo group" (n=182)	p value
Operative time (minutes) (mean±SD)	64.52±7.82	64.87±5.78	0.627
Neonatal birth weight (mean±SD gm)	3026.70±211.54	3002.76±212.91	0.283
Apgar score < 7	23 (12.71%)	31 (17.03%)	0.248
Respiratory morbidity (n, %)			
TTN	28 (15.47%)	37 (20.33%)	0.227
RDS	12 (6.63%)	18 (9.89%)	0.260
Total respiratory morbidity	40 (22.10%)	55 (30.22%)	0.078
Incubation admission (n, %)			
Nasal oxygen	23 (12.71%)	28 (15.38%)	0.464
CPAP	10 (5.52%)	15 (8.24%)	0.306
Mechanical ventilation	7 (3.87%)	12 (6.59%)	0.245
Total incubation admissions	40 (22.10%)	55 (30.22%)	0.078
Neonatal mortality (n, %)	3 (1.66%)	3 (1.65%)	0.994
Neonatal discharge (days) (mean±SD)	7.33±1.27	7.17±1.88	0.342

TTN: Transient tachypnea of new-born, RDS: Respiratory distress syndrome, CPAP: Continuous positive airway pressure ventilation

Study outcomes were shown in Table 2. Operative time was not prolonged in study and control groups ( $64.52 \pm 7.82$  and  $64.87 \pm 5.78$  minutes respectively,  $p=0.627$ ). Neonatal birth weight was not significantly different in both groups ( $p=0.283$ ). Apgar scores in both groups were comparable. There was a non-significant difference between both groups regarding the incidence of Transient tachypnoea of new-born (TTN) or Respiratory distress syndrome (RDS) although the

notable increase in the occurrence of TTN and RDS in the control group. New-borns who required incubation admissions were 40(22.10%) versus 55(30.22%) in the study and control groups respectively ( $p=0.078$ ). Most of cases required incubation with nasal oxygen with more cases in control group than in study group. Neonates were discharged after  $7.33 \pm 1.27$  days in the study group and after  $7.17 \pm 1.88$  days in the control group ( $p=0.342$ ). Neonatal mortality was comparable in both groups.

**Table 3: Correlation of respiratory morbidity and incubation admissions to gestational age in both groups.**

Respiratory morbidity	Gestational age	Study group "Dexa group" (n=181)	Control group "Placebo group" (n=182)	p value
TTN	37-37+6	12 (6.62%)	15 (8.24%)	0.556
	38-38+6	10 (5.52%)	12 (6.59%)	0.669
	$\geq 39$	6 (3.31%)	10 (5.49%)	0.312
RDS	37-37+6	6 (3.31%)	11 (6.04%)	0.218
	38-38+6	4 (2.21%)	5 (2.75%)	0.741
	$\geq 39$	2 (1.10%)	2 (1.10%)	1.000
Nasal oxygen	37-37+6	14 (7.73%)	18 (9.89%)	0.468
	38-38+6	6 (3.31%)	7 (3.85%)	0.782
	$\geq 39$	3 (1.66%)	3 (1.65%)	0.994
CPAP	37-37+6	6 (3.31%)	9 (4.95%)	0.433
	38-38+6	2 (1.10%)	4 (2.20%)	0.411
	$\geq 39$	2 (1.10%)	2 (1.10%)	1.000
Mechanical ventilation	37-37+6	4 (2.21%)	7 (3.85%)	0.362
	38-38+6	2 (1.10%)	3 (1.65%)	0.653
	$\geq 39$	1 (0.55%)	2 (1.10%)	0.563

TTN: Transient tachypnea of new-born, RDS: Respiratory distress syndrome, CPAP: Continuous positive airway pressure ventilation

Correlation of respiratory morbidity to gestational age was displayed in Table 3 where greater incidence of TTN and RDS was found in earlier gestations below 39 weeks. Moreover, the type of incubation admissions was found to be linked to gestational age. More need for nasal oxygen, CPAP and mechanical ventilation in earlier gestations less than 39 weeks.

## DISCUSSION

Safety of scheduled CD on the newborn is still a matter of debate. Neonatal respiratory morbidities were linked to scheduled CD and as the rates of CD increase the need for new preventative strategies to reduce respiratory morbidities are required.<sup>4</sup> Tita et al, conducted a large study including 24077 scheduled CD at term and found that that scheduled CD before 39 weeks was linked to respiratory complications, neonatal hypoglycemia, and admission to the NICU.<sup>14</sup>

Preventive strategies were recommended to minimize CD related respiratory morbidities. These strategies included the administration of steroids before scheduled CD being an important inducer for surfactant and consequently increasing lung maturity. The second preventive strategy

is planning scheduled CD at or beyond 39 weeks as recommended by American Council of Obstetricians and Gynaecologists (ACOG), Royal College of Obstetricians and Gynaecologists (RCOG) and NICE guidelines.<sup>15-17</sup>

In the current study, we found no significant difference in the incidence of TTN or RDS in study and control groups. Our findings are in agreement with Nabhan et al, who conducted a randomized clinical trial on 130 patients with dexamethasone injection prior to scheduled CD in late preterm gestations (34-37 weeks). They reported no benefits from steroids administration prior to scheduled CD.<sup>12</sup> Similarly, Kirshenbaum et al, conducted a case-controlled study in late preterm babies (34-37 weeks) with no significant difference in the rate of neither respiratory morbidity nor its types between study and control groups.<sup>18</sup> On the other side many studies proved that steroids given at term prior surgical delivery were effective in reducing respiratory morbidity, neonatal sepsis and special care units admissions.<sup>8,9,19</sup> A large trial (ASTEC trial) found that the incidence of respiratory distress at term are reduced to the half and 6-fold decrease in the rate of NICU admission in patient given antenatal steroids.<sup>20</sup> Recently, many researchers requested to revisit steroids before scheduled CD based on the facts

that steroids are similar to all drugs having both benefits and risks either short term or long-term risks. The short-term risks included reduction in fetal heart rate variability, decreased fetal gross movements and breathing activity.<sup>21,22</sup>

Moreover, steroids were found to be linked to meconium stained amniotic fluid as stated by Dawood et al.<sup>10</sup> The long-term risks include effects on neuro-endocrine system, psychological and cognitive functions. These long-term risks are still under investigation and evidence didn't reach to a conclusion till now.<sup>23,24</sup>

In the current study, we found more incubation admissions when CD was performed at earlier gestations prior to 39 weeks. The admissions to special care units were correlated also to gestational age where more needs for nasal oxygen, CPAP and mechanical ventilations at gestations less than 39 weeks. The duration of admissions was not significantly different in both groups. These results were similar to ACOG, RCOG, and NICE guidelines who recommended planning CD at or beyond 39 weeks.<sup>15-17</sup>

Lastly Srinivasjois et al, conducted a systematic review and meta-analysis including three randomized controlled trials (N = 2740 patients). They concluded that although steroid administration before scheduled CD reduces the neonatal morbidities; however, routine administration of steroids prior scheduled CD should be cautiously because of long-term risks related to steroids.<sup>25</sup>

The strength points in the current study are blinding of both participants and obstetricians and the use of saline as a placebo was increasing the power of the study. Moreover, the primary outcome, the need for incubation admission was not dependent on maternal characteristics. The study limitations include the small sample size in both groups, and inability to maintain the total recruited sample till the end of study due to escape of some cases from hospital.

## CONCLUSION

Administration of steroids prior to scheduled CD was not beneficial in reducing neither respiratory morbidities nor admissions to special care units. Although notable increased incidence of respiratory morbidity and incubation admissions in control group, non-significant difference between both groups was found.

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