

Impact of antenatal oxytocin infusion on neonatal respiratory morbidity associated with elective cesarean section

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Abstract

Introduction: This study was designed to estimate respiratory morbidity associated with elective cesarean section (ECS) and to determine the effect of antenatal oxytocin exposure on this morbidity.

Material and methods: Nine hundred and sixty-five neonates ≥ 37 weeks' gestation delivered by cesarean section during 1 year were included in this retrospective study and classified into two groups according to oxytocin exposure before cesarean deliveries. Respiratory morbidity for each group was recorded and statistically analyzed.

Results: Transient tachypnea of newborn (TTN) was significantly more frequent in group II (ECS group) than in group I (cesarean section after oxytocin exposure) (8.19% vs. 2.92%; respectively, $p = 0.0006$). Mechanical ventilation, continuous positive airway pressure (CPAP) and oxygen therapy were significantly more frequent in group II than in group I (1.78%, 2.14% and 4.28% versus 0.44%, 0.58% and 1.46%, respectively; $p = 0.039$, and $p = 0.033$ and $p = 0.009$, respectively). The number of newborns admitted to the neonatal unit and neonatal intensive care unit (NICU) was significantly higher in group II than in group I (6.41% and 2.14% vs. 2.05% and 0.58%, respectively; $p = 0.001$ and $p = 0.033$, respectively). Surfactant, fluid therapies and parenteral nutrition were significantly more frequent in group II than in group I (2.14%, 4.28% and 2.49% vs. 0.15%, 1.46% and 0.73%, respectively; $p = 0.001$, $p = 0.009$ and $p = 0.02$, respectively).

Conclusions: Neonatal respiratory morbidity associated with ECS significantly decreased after antenatal oxytocin exposure. A significant reduction of neonatal respiratory morbidity would be achieved if ECS were performed after 39 weeks' gestation.

Key words: oxytocin, neonatal, respiratory, morbidity, elective cesarean sections.

Introduction

The percentage of newborns delivered by cesarean section has risen in recent years, reaching 29.6% in Kuwait, more than 30% in the United States and United Kingdom (UK), 19.31% in Italy and as high as 48% in Brazil. Cesarean section rates have increased rapidly even among low risk women with a full-term singleton infant in vertex presentation [1–7].

Previous studies documented high incidence of respiratory distress and neonatal intensive care unit (NICU) admissions for infants delivered

by cesarean section before the onset of spontaneous labor [8–21].

A significant number of term infants are delivered by elective cesarean section (ECS) admitted to the NICU each year in the United States with transient tachypnea of newborn (TTN), respiratory distress syndrome (RDS) and severe persistent pulmonary hypertension of newborn (PPHN) [22–28].

Infants delivered by ECS are at higher risk of TTN (RDS type II, wet lung syndrome), RDS and PPHN [28].

The timing of an ECS is critical; many authors have concluded that respiratory morbidity following ECS is inversely related to gestational age at ECS and a significant reduction of neonatal respiratory morbidity would be achieved if ECS were performed after 39 weeks' gestation [22, 24, 28].

Physiologic events in the last few weeks of pregnancy and the onset of spontaneous labor are usually associated with changes in maternal and fetal hormonal milieu and clearance of fetal lung fluid. Clearance of fetal lung fluid is crucial for gas exchange and neonatal transition, and mediated in large part by trans-epithelial sodium reabsorption through amiloride-sensitive sodium channels in the alveolar epithelial cells [29–31].

Failure of lung clearance is associated with neonatal respiratory difficulty, NICU admission, mechanical ventilation and surfactant therapy. Preventive and therapeutic strategies should be developed to reduce respiratory morbidity and to improve neonatal outcomes after ECS. Antenatal oxytocin exposure could be an effective preventive measure to reduce respiratory morbidity in term infants delivered by ECS. This study was designed to estimate respiratory morbidity associated with ECS and to determine the effect of antenatal oxytocin exposure on this morbidity.

Material and methods

This retrospective observational study was conducted over one year from May 2013 to May 2014 in Sabah Maternity Hospital (the biggest maternity hospital) and Ahmadi Hospital, Kuwait Oil Company (KOC), Kuwait. Women ≥ 37 weeks' gestation delivered by cesarean section and their neonates were included in this study, and their medical records were evaluated after receiving approval of the study from the ethical committee of both hospitals and after informed consent from participants to estimate respiratory morbidity associated with ECS and to determine the effect of antenatal oxytocin exposure on this morbidity. The gestational age was calculated from the first day of the last menstrual period (LMP) and confirmed by early ultrasound scan (done before 20 weeks' gestation).

Women < 37 weeks' gestation or women with medical or obstetrical disorders affecting the

neonatal outcome such as congenital fetal malformations, prolonged premature rupture of fetal membranes (PROM), intrauterine growth restriction (IUGR), intra-partum fetal distress, diabetes mellitus, preeclampsia, or genetic or metabolic disorders were excluded from this study.

Studied women and their neonates (965) were classified into two groups according to antenatal oxytocin exposure before delivery: group I – newborns exposed antenatally to oxytocin infusion ≥ 8 h and delivered by cesarean section; and group II – newborns not exposed to oxytocin infusion and delivered by ECS.

Maternal data collected include timing of cesarean section, whether cesarean section was done electively as scheduled or after trial of labor, relevant complications during pregnancy and reason for cesarean section. Neonatal data collected include gestational age at birth, birth weight, gender, small or large for gestational age, immediate resuscitation after delivery and Apgar scores. The following data were also collected: admission to neonatal unit and/or NICU, length of hospital stay, mortalities, respiratory disorders (hyaline membrane disease, TTN, meconium aspiration syndrome and pneumothorax), required respiratory support (continuous positive airway pressure (CPAP) or mechanical ventilation) and use of surfactants.

Neonatal morbidity data collected include birth trauma, asphyxia, hypoxic ischemic encephalopathy, intracranial hemorrhage, meconium aspiration and air leaks (pneumothorax). Also, hypoglycemia, polycythemia, sepsis (confirmed by clinical examination and cultures) [32, 33] jaundice, need for fluid therapy and parenteral nutrition were collected as neonatal morbidity data. The primary outcome in this study measures neonatal respiratory morbidity.

The typical respiratory morbidity in term newborns is TTN. The TTN was diagnosed in term babies (≥ 37 weeks) if signs of respiratory distress (tachypnea, retractions, grunting, nasal flaring or mild cyanosis) started within hours after delivery with signs of wet lungs (congestion and perihilar streaking in chest X rays). The TTN is usually improved after oxygen supplementation; also, symptoms and radiographic findings of TTN are transient, self-limited within the first week of life (3–4 days). Based on the clinical course and radiographic findings, TTN was confirmed when other pathologies such as pneumonia or respiratory distress syndrome were excluded.

Sample size

Sample size was calculated using Epilnfo version 6.0, setting power at 80%, significance level at 0.05 and using data from the previous study,

which concluded that there is increased risk of neonatal respiratory morbidity after ECS [24].

Statistical analysis

Data were collected and statistically analyzed using Statistical Package for the Social Sciences (SPSS) computer software version 18 (Chicago, IL, USA). Numerical variables were presented as mean and standard deviation (\pm SD), while categorical variables were presented as number (n) and percentage (%). Statistical analysis was performed using Student's t and chi-square (χ^2) tests. A difference with a p -value < 0.05 was considered statistically significant.

Results

Nine hundred and sixty-five (965) alive newborns were delivered by cesarean section during this study; 684 of them were delivered by emergency cesarean section after trial of labor and oxytocin infusion ≥ 8 h (group I) and 281 were delivered by elective cesarean section (group II) (267 (95%) were born after 39 weeks' gestation and 14 (5%) were born at 38–39 weeks' gestation). There was no significant difference between the two studied groups regarding maternal age, parity, pre-labor weight, body mass index (BMI) or gestational age at time of cesarean section (Table I).

The most common indication for ECS was 2 or more previous cesarean sections (78%), one previous cesarean section with refused trial of labor (19%) and previous myomectomy (3%). On the other hand, the most common indication for emergency cesarean section is failure to progress, and emergency cesarean section conducted due to fetal distress was excluded from this study. Failure to progress is due to cephalo-pelvic disproportion (58.12%), malposition (37.64%) and macrosomia (4.24%).

There was no significant difference between the two studied groups regarding time of cesarean section, which was 38.15 ± 1.03 weeks' gestation in group I (CS after trial of labor and oxytocin infusion) and was 39.24 ± 0.54 weeks' in group II (ECS group) (Table I).

Cesarean section complications were recorded in 1.88% of the studied population in the form of: 0.86% wound infection, 0.27% uterine lacerations and extension of cesarean section incisions, 0.15% urinary bladder injury, 0.03% intestinal injury, 0.43% intra-partum hemorrhage requiring blood transfusion, 0.11% deep venous thrombosis and 0.03% pulmonary embolism.

There was no significant difference between the two studied groups regarding birth weight, number of small for gestational age babies, large for gestational age babies, babies with Apgar score < 5 at 1 min, babies with Apgar score < 5 at 5 min and babies with cord PH < 7.2 (4 (0.58%) vs. 3 (1.068%), respectively) (Table II).

The frequency of TTN was significantly higher in group II than in group I (23 (8.19%) vs. 20 (2.92%); respectively). The frequency of mechanical ventilation, CPAP and oxygen therapy was significantly higher in group II than in group I (5 (1.78%), 6 (2.14%) and 12 (4.28%) vs. 3 (0.44%), 4 (0.58%) and 10 (1.46%), respectively) (Table III).

The number of newborns admitted to the neonatal unit and NICU unit was significantly higher in group II than in group I (18 (6.41%) and 6 (2.14%) vs. 14 (2.05%) and 4 (0.58%), respectively). Surfactants, fluid therapies and parenteral nutrition were used significantly more often in group II than in group I (6 (2.14%), 12 (4.28%) and 7 (2.49%) vs. 1 (0.15%), 10 (1.46%) and 5 (0.73%), respectively) (Table III).

There were no cases of neonatal mortality, birth trauma, meconium aspiration, pneumothorax, neonatal sepsis, intracranial hemorrhage, perinatal asphyxia or hypoxic ischemic encephalopathy

Table I. Descriptive characteristics of two studied groups

Variables	Group I: cesarean section after trial of labor and oxytocin exposure (N = 684)	Group II: elective cesarean section (N = 281)	P-value, significance (95% confidence interval) Test used (t test)
Maternal age [years] Mean \pm SD	31.5 \pm 6.3	33.7 \pm 7.2	$p = 0.99$ (> 0.05), NS (95% CI: -3.2; -2.2; -1.2)
Parity Mean \pm SD	3.1 \pm 1.4	4.2 \pm 2.1	$p = 1$ (> 0.05), NS (95% CI: -1.3; -1.1; -0.8)
Pre-labor weight [kg] Mean \pm SD	89.6 \pm 5.2	92.1 \pm 6.5	$p = 1$ (> 0.05), NS (95% CI: -3.3; -2.5; -1.6)
Pre-labor BMI [kg/m ²] Mean \pm SD	30.4 \pm 4.3	32.3 \pm 5.1	$p = 0.99$ (> 0.05), NS (95% CI: -2.6; -1.9; -1.2)
Gestational age at time of cesarean section [weeks] Mean \pm SD	38.15 \pm 1.03	39.24 \pm 0.54	$p = 0$ (> 0.05), NS (95% CI: -1.2; -1.09; -0.9)

NS – non-significant.

Table II. Neonatal outcomes in two studied groups

Variables	Group I: cesarean section after trial of labor and oxytocin exposure (N = 684)	Group II: elective cesarean section (N = 281)	P-value, significance, test used (95% confidence interval)
Gestational age at birth [weeks] Mean \pm SD	38.15 \pm 1.03	39.24 \pm 0.54	$p = 0$ (> 0.05), NS, t test (95% CI: -1.2; -1.09; -0.9)
Birth weight [kg] Mean \pm SD	3.62 \pm 1.27	3.79 \pm 1.22	$p = 0.2$ (> 0.05), NS, t test (95% CI: -0.3; -0.2; 0.001)
Number (%) of small for gestational age babies	8 (1.17)	6 (2.14)	$p = 0.2$ (> 0.05), NS, χ^2 test
Number (%) of large for gestational age babies	18 (2.63)	12 (4.27)	$p = 0.1$ (> 0.05), NS, χ^2 test
Number (%) of babies with Apgar score less than 5 at 1 min	18 (2.63)	10 (3.55)	$p = 0.09$ (> 0.05), NS, χ^2 test (95% CI: -0.3; -0.2; 0.001)
Number (%) of babies with Apgar score less than 5 at 5 min	12 (1.75)	6 (2.14)	$p = 0.6$ (> 0.05), NS, χ^2 test
Number (%) of babies with cord PH less than 7.2	4 (0.58)	3 (1.068)	$p = 0.4$ (> 0.05), NS, χ^2 test

NS – non-significant, χ^2 – chi-square test.

Table III. Respiratory neonatal outcome in two studied groups

Variables	Group I: cesarean section after trial of labor and oxytocin exposure (N = 684)	Group II: elective cesarean section (N = 281)	P-value, significance, test used
Transient tachypnea of newborn (TTN), n (%)	20 (2.92)	23 (8.19)	$p = 0.0006$ (< 0.05), S, χ^2 test
Conventional mechanical ventilation, n (%)	3 (0.44)	5 (1.78)	$p = 0.039$ (< 0.05), S, χ^2 test
Continuous positive airway pressure, n (%)	4 (0.58)	6 (2.14)	$p = 0.033$ (< 0.05), S, χ^2 test
Oxygen therapy, n (%)	10 (1.46)	12 (4.28)	$p = 0.009$ (< 0.05), S, χ^2 test
Neonatal unit admission, n (%)	14 (2.05)	18 (6.41)	$p = 0.001$ (< 0.05), S, χ^2 test
Neonatal intensive care unit admission, n (%)	4 (0.58)	6 (2.14)	$p = 0.033$ (< 0.05), S, χ^2 test
Surfactant therapy, n (%)	1 (0.15)	6 (2.14)	$p = 0.001$ (< 0.05), S, χ^2 test
Fluid therapy, n (%)	10 (1.46)	12 (4.28)	$p = 0.009$ (< 0.05), S, χ^2 test
Parenteral nutrition, n (%)	5 (0.73)	7 (2.49)	$p = 0.02$ (< 0.05), S, χ^2 test

S – significant; χ^2 – chi-square test.

recorded in either studied group. One baby in group I born at 37.4 weeks with a birth weight of 2200 g (small for gestational age) developed necrotizing enterocolitis.

Discussion

Higher rates of mechanical ventilation, oxygen therapy, extracorporeal membrane oxygenation (ECMO) and death were reported after TTN delivered by ECS, and Roth-Kleiner *et al.* reported that me-

chanical ventilation was dramatically high in infants who developed respiratory distress after ECS [34].

Performing ECS after 39 weeks' gestation seems to be associated with significant reduction of neonatal respiratory morbidity.

The American College of Obstetricians and Gynecologists (ACOG) Guidelines recommended scheduling ECS at 39 weeks or at spontaneous labor pains to reduce the occurrence of iatrogenic prematurity associated with ECS [22, 24, 28].

Other authors suggested increased risk of uterine rupture and perinatal death in mothers with previous cesarean section who went into spontaneous labor after 39 weeks [35, 36].

In this study, rates of TTN, mechanical ventilation, CPAP, oxygen therapy and NICU were significantly higher in group II (ECS group) than in group I (delivered by cesarean section after oxytocin exposure). In addition, surfactant, fluid therapies and parenteral nutrition were significantly more frequent in group II than in group I.

Recent obtained data from the Cesarean Section Registry maintained by the Maternal Fetal Medicine Units Network (MFMU) support previously published data showing higher incidence of respiratory distress in infants delivered by elective repeat cesarean section (ERCS) compared to those delivered vaginally after previous cesarean section (VBAC). The MFMU reported that 6.2% of infants delivered by ERCS \geq 37 weeks' gestation developed respiratory distress and 11.1% required NICU admission compared to 3.3% respiratory distress and 7.5% NICU admission in VBAC [30].

Physiologic event in the last few weeks of pregnancy coupled with the onset of spontaneous labor is associated with clearance of fetal lung fluid. Clearance of fetal lung fluid is crucial for gas exchange and for increase in pulmonary blood flow to match ventilation with perfusion [29–31].

Failure of these events can jeopardize neonatal transition and cause neonatal respiratory distress. Traditional explanations, which relied on “starling forces” and “vaginal squeeze”, can only account for a fraction of the fluid absorption. Amiloride-sensitive sodium transport by lung epithelia through epithelial sodium channels (ENaC) has emerged as a key event in the trans-epithelial movement of alveolar fluid [37].

This study was based on the hypothesis that oxytocin had an effect on epithelial sodium channels, and in this study, oxytocin administration for \geq 8 h in group I was associated with a significant reduction in respiratory morbidity compared to group II delivered by ECS.

The results of this study also explain the ACOG guidelines which recommend delaying ECS at spontaneous labor pains to take advantage of oxytocin release and its effect on ENaC, which in turn will clear fluids from the lung and prepare it for gas exchange with subsequent reduction in neonatal respiratory morbidity. Also, the results of this study explain and support previously published data of higher incidence of respiratory distress in infants delivered by ERCS compared to those delivered vaginally after previous cesarean section reported by MFMU.

There is an urgent need for a preventive strategy that can optimize the outcome of vulnerable

newborns delivered by ECS. Delaying ECS until 39 weeks' gestation seems to be the first logical steps in reducing iatrogenic prematurity and risks of respiratory morbidity, and antenatal steroids have an established role in reducing life-threatening respiratory morbidity of ECS [30].

This study was the first to explain the benefits of delaying ECS at spontaneous labor pains based on clearance of fetal lung fluid through epithelial sodium channels mediated by oxytocin. Retrospective nature was the only limitation of this study.

In conclusion, neonatal respiratory morbidities associated with ECS significantly decreased after antenatal oxytocin exposure. A significant reduction of neonatal respiratory morbidity would be achieved if ECS were performed after 39 weeks' gestation.

Conflict of interest

The authors declare no conflict of interest.

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