Risk factors for development of transient tachypnea of newborns

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ABSTRACT

Background: Transient tachypnea of the newborn (TTN) is a frequently encountered form of neonatal respiratory distress. The underlying mechanism involves residual lung fluid that is delayed in clearance. TTN primarily occurs soon after birth and can last from 24 to 72 hours. Risk factors for TTN include elective cesarean section, male sex, late prematurity, low birth weight, macrosomia, polycythemia, maternal asthma and maternal diabetes. Treatment is often supportive with observation and potential oxygen supplementation.

Objective: To identify the risk factors associated with development of transient tachypnea of newborns who were delivered either normally or through cesarean section, at 36 weeks or beyond and to compare the results with those of others.

Patients and methods: This is a case control study of 200 newborns suffering from respiratory distress during a period from the 1st of September 2011 to the 1st of September 2013 in the neonatal intensive care unit at AL-Kansaa Teaching hospital in Mosul. The perinatal history of newborns was analyzed. TTN was diagnosed on clinical basis and by exclusion of other diseases affecting the respiratory system including sepsis. The study included 200 healthy newborns as control.

Results: Multivariate analysis identified that the development of TTN was significantly associated with elective cesarean section 56% (p-value=0.001), male sex 66.5% (p-value=0.001), late prematurity 21% (p-value=0.009), maternal diabetes 8% (P-value=0.014), maternal asthma 10.5% (p-value=0.01), birth asphyxia (low APGAR score) 9.5% (p-value=0.005), low birth weight 16.5% (p-value=0.003), prolonged labor or using (forceps or vacuum) 22% (p-value=0.037) and in vitro fertilization 2.5% (p-value=0.024).

Conclusion: Transient tachypnea of newborns is strongly related to elective cesarean section, male sex, late prematurity, maternal diabetes, maternal asthma, birth asphyxia, low birth weight (1500-2500g), prolonged labor or using forceps or vacuum and in vitro fertilization.

Keywords: Transient tachypnea of newborn, elective cesarean section, low gestational weight, in vitro fertilization.
INTRODUCTION

Transient tachypnea of the newborn (TTN), first described by Avery in 1966, represents the most common cause of respiratory distress, and occurs in approximately 6/1000 births.\(^1\)\(^,\)\(^2\)

The incidence of neonatal respiratory distress in the newborn is approximately 7%\(^1\). In utero, fluid is produced by the fetal lung. Some of this fluid is swallowed by the neonate and excreted by the kidneys resulting in amniotic fluid. The fetal larynx periodically opens and closes, so most of the fluid is swallowed but some fluid enters the lungs to keep them expanded.\(^3\)

Lung fluid production drops as epinephrine levels increase, which also accelerates fluid transport via sodium channels. Recent studies have demonstrated that certain genetic abnormalities in catecholamine receptors can predispose a newborn to TTN.\(^4\)

Malignant TTN has been reported in infants born by elective cesarean section who initially present with signs and symptoms of TTN that may last more than 72 hours. These infants demonstrate refractory hypoxia due to pulmonary hypertension and may require extracorporeal membrane oxygenation (ECMO).\(^5\)

Transient tachypnea of the newborn represents the most frequent cause of neonatal respiratory distress among all newborns, constituting over 40% of cases.\(^6\)

Newborns with TTN usually present with tachypnea intercostal or subcostal retractions, grunting, nasal flaring and poor feeding. Cyanosis is not common but could be present in severe cases. Symptoms can last from few hours to over 2 or 3 days. Although hypoxemia is not typical, it can be present.\(^7\)

Chest x-ray (CXR) can show hyperaeration, parenchymal infiltrates, and intralobar fluid accumulation. CXR findings, however, are often shared by other causes of respiratory distress and rarely fit classical description. TTN diagnosis is usually based on the clinical assessment.\(^7\) Copetti and Cattarossi demonstrated that differences in ultrasonographic findings between the upper and lower lung fields could potentially be diagnostic of TTN and can differentiate it from other causes of respiratory distress. Although tested in a small study using a high-resolution linear probe, the authors achieved a sensitivity and specificity rate of 100%. These findings suggest the need for larger, blinded, prospective studies.\(^7\)
Risk factors for the development of TTN\textsuperscript{7-9} include: elective cesarean section delivery without preceding labor (especially with gestational age < 38 weeks), maternal diabetes, maternal asthma, male sex, multiple gestations, macrosomia (birth weight > 4 Kg) and precipitous delivery. Less common risk factors for TTN\textsuperscript{10,11} include: delayed clamping of umbilical cord (optimal time 45 seconds) which leads to increased placental transfusion and this causes left ventricular dysfunction, fluid overload of the mother, especially with oxytocin infusion, negative amniotic fluid phosphatidylglycerol, birth asphyxia, excessive maternal sedation and analgesia, exposure to B-mimetic agents, prolonged labor and polycythemia.

Aims of the study

1. To identify the risk factors associated with development of transient tachypnea of newborns.
2. To compare the results with others.

PATIENTS AND METHODS

This is a case-control study, it was conducted over two years period, from the 1\textsuperscript{st} of Sep. 2011 to the 1\textsuperscript{st} of Sep. 2013 in the neonatal intensive care unit at AL-Kansaa Teaching hospital in Mosul.

The perinatal history of two hundred newborns were reviewed regarding risk factors of TTN. They were delivered either by cesarean section or normally at 36 ≥ weeks of gestation, all of them were suffering from respiratory distress that lasted > 6 hours after delivery. Cases with suspicion of TTN were validated through the absence of other morbidities affecting respiration, particularly perinatal infection, persistent pulmonary hypertension and meconium aspiration syndrome. Complete perinatal and post natal history was taken to rule out other causes of respiratory distress. They were investigated by complete blood count, sepsis screen and chest x-ray. All sepsis screen results including (blood culture, c-reactive protein and complete blood count) were negative.

The diagnosis of TTN was based on exclusion and observation of clinical features based on clinical features of tachypnea, chest retractions, expiratory grunting and occasionally cyanosis that is relieved by minimal oxygen supplementation (<40%). The chest examination revealed generally clear vesicular breath sound without rales or rhonchi and the chest radiograph showed prominent pulmonary vascular markings, fluid in the intralobar fissures, overaeration, flat diaphragms and rarely small pleural effusions.

The study also included two hundred healthy newborns as a control group, who were delivered either by cesarean section or normally. The perinatal and postnatal history of these newborns were also reviewed for the presence of risk factors of TTN.

The studied risk factors for development of TTN were: elective cesarean section, male sex, gestational age 36 ≥ weeks, maternal diabetes, maternal asthma, birth asphyxia (low APGAR score), prolonged labor or by using forceps or vacuum, history of in vitro fertilization, macrosomia, fluid overload of the mother, especially with oxytocin infusion, breech delivery, exposure to B-mimetic agent, precipitous delivery and multiple gestations.

Statistics were calculated by mean of chi-square test for categorical variables. Odd ratios and 95% confidence intervals (CIs) were also calculated. Statistical analysis was performed and P-value of < 0.05 was considered as a significant.

RESULTS

Table 1 showed that the risk factors; male sex, late prematurity, maternal diabetes, maternal asthma, birth asphyxia (low APGAR score < 7 at 1 minute), low birth weight (1500-2500 g), prolonged labor or by using forceps or vacuum and in vitro fertilization, were significant causes of TTN (P-values were 0.001, 0.009, 0.014, 0.01, 0.005, 0.003, 0.037, 0.024 respectively). While macrosomia, precipitated delivery, multiple gestations, exposure to B-mimetic drugs, maternal PET, maternal thyrotoxicosis, birth weight and fluid overload with oxytocin infusion failed to reach a significant level.

Table 2 showed the mode of delivery among the 2 groups. The number of patients who developed TTN was higher in those who were delivered by Cesarean section than normally with significant association (P=0.001). Among those patients who were delivered by cesarean section, a higher number of patients with TTN were seen in those delivered by elective cesarean section compared to emergency cesarean section.
Table 1. Distribution of risk factors among patients with TTN and control group.

| Risk factors | TTN (n=200) | Control (n=200) | OR | 95%CI | p-value |
|--------------|-------------|----------------|----|-------|---------|
| Sex          | Male        | 133 66.5%      | 67 33.5% | 2.578 | 1.720-3.865 | 0.001(s) |
|              | Female      | 96 48%         | 104 52% |       |         |         |
| Gestational age | < 36 wks | 42 21%         | 22 11%  | 0.986 | 0.772-1.226 | 0.009(s) |
|              | ≥ 36 wks    | 158 79%        | 178 94% | 0.465 | 0.267-0.809 | 1.000  |
| Maternal diabetic | < 36 wks | 16 8%          | 5 2.5%  | 3.391 | 1.262-9.089 | 0.014(s) |
|              | ≥ 36 wks    | 8 4%           | 7 3.5%  | 1.149 | 0.424-3.110 | 0.001  |
| Maternal asthma | < 36 wks | 21 10.5%       | 8 9%   | 2.816 | 1.240-6.384 | 0.01(s) |
|              | ≥ 36 wks    | 158 79%        | 178 94% | 0.465 | 0.267-0.809 | 1.000  |
| Macrosomia >4kg | < 36 wks | 8 4%           | 7 3.5%  | 1.149 | 0.424-3.110 | 0.001  |
|              | ≥ 36 wks    | 4 2%           | 2 1%    | 2.02  | 0.427-9.533 | 0.411  |
| Precipitous delivery | < 36 wks | 0 0%           | 17 8.5% | 0.109 | 0.028-0.430 | 0.001  |
|              | ≥ 36 wks    | 0 0%           | 17 8.5% | 0.109 | 0.028-0.430 | 0.001  |
| Multiple gestation | < 36 wks | 19 9.5%        | 5 2.5%  | 4.094 | 1.549-10.790 | 0.005(s) |
|              | ≥ 36 wks    | 167 83.5%      | 186 93% | 2.625 | 1.369-5.028 | 0.003  |
| Birth asphyxia. (APGAR score <7 at 1 minute) | < 36 wks | 44 22%         | 28 16.5% | 1.682 | 1.001-2.828 | 0.037  |
|              | ≥ 36 wks    | 167 83.5%      | 186 93% | 2.625 | 1.369-5.028 | 0.003  |
| Prolonged labor or by using (forceps or vacuum) | < 36 wks | 44 22%         | 28 16.5% | 1.682 | 1.001-2.828 | 0.037  |
|              | ≥ 36 wks    | 167 83.5%      | 186 93% | 2.625 | 1.369-5.028 | 0.003  |
| Breech delivery | < 36 wks | 4 2%           | 2 2%    | 4.125 | 0.496-22.22 | 0.055  |
|              | ≥ 36 wks    | 0 0%           | 17 8.5% | 0.109 | 0.028-0.430 | 0.001  |
| Exposure to B-mimetic agent | < 36 wks | 2 1%           | 0 0%    | Inf   | 0.521-inf | 0.499  |
|              | ≥ 36 wks    | 0 0%           | 17 8.5% | 0.109 | 0.028-0.430 | 0.001  |
| Maternal PET | < 36 wks | 1 0.5%         | 0 0%    | Inf   | 0.260-inf | 1.00   |
|              | ≥ 36 wks    | 0 0%           | 17 8.5% | 0.109 | 0.028-0.430 | 0.001  |
| Maternal thyrotoxicosis | < 36 wks | 1 0.5%         | 0 0%    | Inf   | 0.260-inf | 1.00   |
|              | ≥ 36 wks    | 0 0%           | 17 8.5% | 0.109 | 0.028-0.430 | 0.001  |
| Fluid overload+oxytocin infusion | < 36 wks | 2 1%           | 0 0%    | Inf   | 1.322-inf | 0.124  |
|              | ≥ 36 wks    | 0 0%           | 17 8.5% | 0.109 | 0.028-0.430 | 0.001  |
| In vitro fertilization | < 36 wks | 5 2.5%         | 0 0%    | Inf   | 1.322-inf | 0.024(s) |
|              | ≥ 36 wks    | 0 0%           | 17 8.5% | 0.109 | 0.028-0.430 | 0.001  |

Table 2. Mode of delivery among the patients with TTN and control group.

| Mode of delivery | Patients with TTN (n=200) | Control group (n=200) | OR | 95%CI | P value |
|-----------------|---------------------------|-----------------------|----|-------|---------|
| Cesarean section | Elective emergency        | 112 56%               | 58 29% |       |         |
|                 |                           | 37 18.5%              | 29 14.5% | 6.817 | 4.399-10.563 | 0.001(s) |
| Normal vaginal delivery |                     | 51 25.5%              | 113 56.5% |       |         |
| Total           |                          | 200 100%              | 200 100% |       |         |

DISCUSSION

The present study showed that TTN was more common in males (66.5%) than females (38.5%), which was comparable with Kasap B et al (2008) and Asenjo M (2007). Also, found by Liem JJ (2007), and Erol Tutdibi et al (2009). The TTN was more common in those newborns with gestational age of ≥ 36 weeks (late premature, 21%), which was comparable with Kasap B et al (2008) and Erol Tutdibi et al (2009) who found a significant association between TTN and late prematurity.

There was a significant association between low birth weight (1500-2500) and TTN (P=0.003), as also found by Liem JJ (2007) and Tutdibi Erol (2010). Both found a significant relationship between TTN and low birth weight.

No significant association was found between the most frequently encountered birth weight (2500-3000 grams) and TTN, and this may be due to small sample in this study.

A significant association was found between elective cesarean section delivery and TTN. This was similar to those found by Levine EM (2001) and AL-jurjari Z (2012). Liem JJ (2007), and Erol Tutdibi et al (2009) who found an increase of TTN by 2-3 folds in the neonates delivered by elective cesarean section than those delivered normally (P=0.001). Infants delivered through elective cesarean section often are deprived of the labor-related physiological stress response pattern at birth and consequently experience failure of postnatal respiratory transition.
A significant association between TTN and diabetic mothers was found, this was similar to that found by Dani C (1999), AL-jurjari Z (2012), and Nazarzaki (2008). Also a significant association was found between TTN and asthmatic mothers, which is the same in AL-jurjari Z (2012), Liem, JJ (2007), and Subramanian KNS et al (2006), studies.

Birth asphyxia (low APGAR score<7 at 1 minute) was also found to be significantly associated with TTN, which is similar to Michael S (1991), results.

Prolonged labor or by using forceps or vacuum also had a significant correlation with TTN, in which it may cause dysfunctional catecholamine regulation, mild pulmonary capillary leak and myocardial dysfunction, which was similar to Erol Tutdibi et al (2009) findings.

A significant correlation was found between TTN and in vitro fertilization, which is comparable to Takayata et al (2008) findings.

CONCLUSION
Transient tachypnea of newborns is significantly correlated with elective cesarean section, late prematurity, male sex, maternal asthma, maternal diabetes, birth asphyxia prolonged labor and in vitro fertilization.

RECOMMENDATIONS
1. Good antenatal care is crucial in detecting early problems during pregnancy that may have relation to increase incidence of TTN.
2. Good obstetric care during delivery has an important role in prevention of perinatal asphyxia which by itself may lead to increase incidence of TTN.

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