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Respiratory distress syndrome in near-term babies after caesarean section

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Summary

Objective: Severe respiratory distress syndrome (RDS) caused by surfactant deficiency is described not only in preterm infants but also in (near-) term babies after caesarean section (CS), especially when carried out before the onset of labour. The aim of the present study was to document the severity of this theoretically avoidable entity in order to improve obstetric and perinatal care.

Patients: All neonates admitted to the paediatric intensive care unit of the University Hospital of Bern between 1988 and 2000 with RDS on the basis of hyaline membrane disease (HMD) needing mechanical ventilation (MV) after CS and with a birthweight ≥2500 g were analysed. HMD was diagnosed when respiratory distress and the typical radiological signs were present. Patients were grouped into elective CS before onset of labour and before rupture of membranes (group 1, n = 34) and patients delivered by emergency CS or CS after onset of labour or rupture of membranes (group 2, n = 22). Analysed indices for severity of illness were duration of stay in intensive care unit and MV, ventilation mode, worst oxygenation index (OI), presence of pulmonary air leak, and systemic hypotension.

Results: Mean gestational age (GA) was 37 2/7 weeks in group 1 and 36 2/7 weeks in group 2; no patient had a GA of ≥39 0/7 weeks. Duration of MV was 4.4 days in group 1 and 3.9 days in group 2. Thirteen patients (38%) of group 1 and 7 (32%) of group 2 had to be managed by rescue high-frequency ventilation. A total of 7 patients had an OI >40. Eight patients (24%) in group 1 and 4 (18%) in group 2 developed a pulmonary air leak. Fourteen neonates (41%) in group 1 had to be supported by catecholamines versus 5 (22%) in group 2. There was one death in group 1.

Conclusion: Severe RDS on the basis of HMD can also occur in near-term babies after CS; even a fatal outcome can not be excluded. The severity of illness in elective CS without labour may be quite high and is comparable to newborns delivered by CS (after onset of labour and/or rupture of the membranes) who were 1 week younger. No case of HMD was found in our population when CS was carried out after completion of 39 postmenstrual weeks of gestation.

Key words: respiratory distress syndrome; term and near-term newborns; Caesarean section; hyaline membrane disease

Introduction

Acute respiratory disease is, beside prematurity, the leading cause for hospitalisation in neonatal intensive care units [1]. Respiratory distress syndrome (RDS) is defined as the presence of at least two of the following clinical signs: tachypnoea (>60/min), dyspnoea with inspiratory subcostal or intercostal retractions, nasal flaring, expiratory grunting and cyanosis in room air. The most fre-

Abbreviations

CS:	caesarean section	MV:	mechanical ventilation
GA:	gestational age (in postmenstrual weeks)	OI:	oxygenation-index
HFV:	high-frequency ventilation	PICU:	paediatric intensive care unit
HMD:	hyaline membrane disease	RDS:	respiratory distress syndrome
L/S-ratio:	lecithin/sphingomyelin-ratio	SP-A:	surfactant protein A

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quent underlying diagnosis of RDS during the first 48 hours are transient tachypnoea of the newborn, infections, meconium aspiration syndrome, hyaline membrane disease (HMD) and perinatal asphyxia [2]. Besides the forementioned clinical signs, HMD is characterized by stiff, non-compliant lungs and is due to surfactant deficiency [3]. Chest radiography shows diffuse reticulogranular opacities, air bronchograms and small lung volumes. In fatal cases, hyaline membranes lining the terminal airways and alveoli are present. The main factors predisposing to HMD include prematurity, male sex and maternal diabetes. Since the publications of Usher in 1964 and 1971 [4, 5], several studies showed that also caesarean section (CS), especially when carried out before the beginning of labour, even in term or near-term babies, is associated with an increased risk for respiratory problems leading to the term of "iatrogenic RDS" [6–10].

The aim of the present study was to document the frequency and severity of HMD in babies delivered by CS in order to improve obstetric and perinatal management.

Patients and methods

Epidemiologic data

The paediatric intensive care unit (PICU) of the University Children's Hospital of Bern is a third level reference unit draining a population of approximately 1.3 million people [11]. The number of livebirths in the cantons of Bern, Solothurn, Jura, and the German speaking parts of Freiburg and Valais is about 13 000/year. Deducting the approximately 1000 inborns per year at the University Women's Hospital, drained by the Division of Neonatology, the catchment area of the PICU covers around 12 000 livebirths/year. All newborn patients admitted are outborn and transported by ambulance or helicopter by a specialised neonatal transport team. During the period under review, (January 1st, 1988 to December 31st, 2000) 2740 newborn babies were admitted, 1569 were on MV (not including nasal continuous positive airway pressure), and 334 died (mortality rate 12%).

Inclusion criteria

To focus on patients at or near term with immaturity of their surfactant system, the diagnostic criteria of HMD had to be fulfilled [3], and the birth weight had to be ≥2500 g. Patients with RDS caused by infection, meconium aspiration or perinatal asphyxia were not included, nor were patients with congenital malformations affecting respiration. Only patients with severe respiratory distress requiring MV in the form of continuous positive pressure ventilation or high-frequency ventilation (HFV) through an endotracheal tube were included. Reasons for intubation were the need of FiO_2 >0.6 for sufficient oxygenation, apnoea or severe clinical signs of respiratory distress, especially when facing a neonatal transport. CS either elective or on an emergency basis had to be the mode of delivery. The search for these patients was facilitated by a large computerized database, where the search criteria of HMD, birth weight ≥2500 g and MV were entered. The criterion of gestational age was introduced into the electronic database only in 1995, whereas the birth weight and the criteria for diagnosis and treatment parameters have remained unchanged over the whole observation period. All patient datasheets for the 13 years under consideration have been filled out by the same three attending paediatric intensivists (WBP, BD, PJ).

Clinical data

Further data were collected by reviewing individual clinical charts and chest radiographs. The radiological signs of HMD had to be present and confirmed by a paediatric radiologist. Postmenstrual age was calculated by the term given by the caring obstetrician derived from the first day of last menstruation, possibly corrected by early ultrasound. Further analysis included the indication for CS, presence of labour, duration of MV (from endotracheal intubation to extubation), modes of MV (conventional or as rescue treatment, HFV), incidence of pulmonary air leaks (pneumothorax, pulmonary interstitial emphysema), highest oxygenation index (OI) [12] and lowest arterial/alveolar PO_2 ratio [13], use of exogenous surfactant, presence of cardiovascular dysfunction treated by volume expansion and use of catecholamines, duration of stay in PICU, abnormal findings in cranial ultrasound and outcome when leaving PICU (dead or alive). Data about antenatal steroids were unreliable, and therefore this item was not analysed.

Patients were then grouped into 2 categories: group 1: elective CS before onset of labour and without rupture of membranes; and group 2: CS after beginning of labour or rupture of membranes either on an elective (for history of caesarean delivery or for abnormal presentation) or emergency basis (life threatening event for mother and/or baby).

Statistics

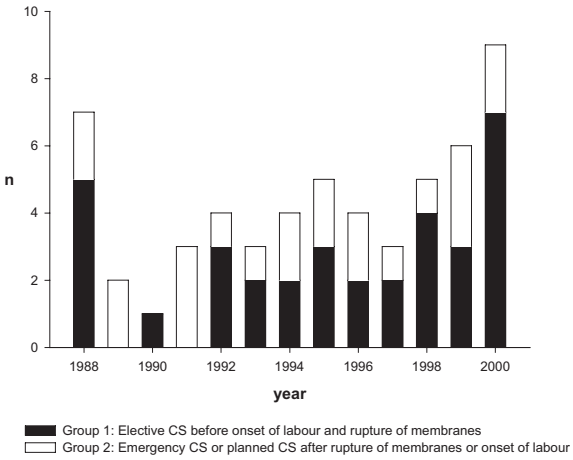
Statistical analysis was done using the Mann-Whitney-rank sum test and Fisher's exact test. P-values <0.05 were considered to be significant.

Results

During the 13 years under review, 56 newborns met the inclusion criteria. Their distribution over the study period is presented in Figure 1. Fifty-five patients were intubated before the age of 60 hours, whereas for one patient MV started only during the fourth day of life. In 34 cases CS was carried out as a planned caesarean delivery before onset of labour (group 1). Reasons for CS were one or more of the following: foregoing CS in 24 cases, abnormal foetal presentation or small pelvis in 8, maternal indications in 7, (e.g. hypertension, diabetes mellitus, acute pain, foregoing maternal in-

Figure 1

Distribution of the cases of RDS over observation period.



tracranial haemorrhage, maternal viral infection, uterus myomatosus) and/or twin pregnancy in 1 case. The indications for CS in group 2, which comprised 22 patients, were as follows: in 13 instances CS was done as an emergency delivery because of a life-threatening maternal and/or foetal situation, and in another 8 cases either planned CS was realized earlier because of the onset of labour (6 cases) or in response to rupture of the membranes (2 cases). In one case there was a change of planned vaginal delivery to CS for nonprogression of delivery. In regards to maternal risk factors like insulin dependant diabetes mellitus (1 case in each group), gestational diabetes (1 case in each group) and thyroid disease (1 case of hyperthyreosis in group 1) the two groups were comparable.

The main clinical data of the 2 groups are shown in Table 1. The only statistically significant difference of the two groups was gestational age and birth weight. Nine of the patients in group 1 (26%) and 2 patients in group 2 (9%) had a birth weight >90th percentile, but the difference didn't reach statistical significance. None of the patients was small for GA. The overall mean duration of MV was 4.2 days; mean of highest OI was 22.9, and the mean of nadir of arterial/alveolar PO_2 ratio was 0.15. Seven (13%) of the newborns had an OI >40. Fifteen (27%) of the patients were treated with surfactant, 12 (21%) suffered from pulmonary air leak, and 19 (34%) needed treatment with catecholamines. One patient in group 1 died. (In this case, severe respiratory problems needing HFV were complicated by recurrent pneumothoraces. On day 5, severe sepsis with multiresistent Achromobacter developed, and the patient died on day 7 because of refractory hypoxaemia. Additional to hyaline membranes findings at autopsy were thrombus formation in the vena cava superior and sinus sagittalis superior.) All other patients survived.

Table 1

Main clinical data.

	Group 1 Elective CS before onset of labour and rupture of membranes n = 34	**Group 2** Emergency CS or planned CS after rupture of membranes or onset of labour n = 22	p-value
Gender (m/f)	22 / 12	16 / 6	ns
Gestational age* (postmenstrual weeks)	37 2/7 (36 0/7–38 6/7)	36 2/7 (34 0/7–38 0/7)	p <0.001
Birthweight* (g)	3277 (2570–4470)	2874 (2510–3320)	p <0.001
Duration of mechanical ventilation* (days)	4.4 (2.0–8.9)	3.9 (1.6–8.9)	ns
High-frequency ventilation (n)	13	6	ns
Surfactant (n)	8	7	ns
Highest oxygenation-index*	22.7 (5.3–91.9)	23.1 (6.5–44.2)	ns
Oxygenation index >40 (n)	5	2	ns
Nadir arterial/alveolar-PaO_2-ratio*	0.17 (0.03–0.67)	0.13 (0.05–0.24)	ns
Pulmonary air leak (n)	8	4	ns
Catecholamines [dopamine, dobutamine, adrenaline] (n)	14	5	ns
Duration of PICU-hospitalisation* (days)	7.0 (3.8–12.9)	8.2 (3.8–14.8)	ns
Unilateral subependymal haemorrhage (n)	3	1	ns
Survived to discharge from PICU (n)	33	22	ns

* Data are shown as mean and range (in brackets)

Discussion

Main findings

HMD in term/near-term babies after elective CS without medical reasons still exists despite warnings in a variety of publications over the last decades [6–10; 14–16]. In our catchment area of about 1.3 million inhabitants with approximately 12 000 livebirths/year, 34 babies (group 1) developed HMD and needed mechanical ventilation following an elective CS prior to onset of labour. The HMD incidence of 0.22:1000 livebirths is slightly higher than an incidence of 0.10‰ recently described in an English population, but in the latter study there was a restriction to babies ≥37 weeks of gestation [7]. Respiratory distress of these neonates may be severe with need for respiratory support by MV for several days. The suffering babies are at high risk of developing further complications like pulmonary airleak and cardiovascular instability, even fatal outcome cannot be excluded, as shown in our series. Morrison et al. reported an incidence for RDS with at least oxygen requirement after CS of 0.83% for term babies (≥37 weeks of gestation), which rises to 1.3% when carried out before onset of labour with an odds ratio of 6.8 compared to the risk of RDS after vaginal delivery at term [8]. These authors could demonstrate an increasing incidence of RDS with decreasing GA from 41 to 37 weeks, with a special increase of risk when carried out before completion of 39 weeks of gestation. These results have been confirmed by an Australian study, elaborating gestational age of 37–38 weeks as well as CS before labour as principle risk factors in term infants for RDS needing MV [16]. There was no patient with GA ≥39 0/7 weeks in our population, a fact that has also been found in earlier reported series [7, 9, 15].

Pathophysiology

Iatrogenic RDS is the result of the coincidence of three major components: [1] early delivery, [2] CS as mode of delivery and [3] birth prior to the onset of labour. What is the evidence that HMD, which was the clinical, radiological and in 1 case also the histological diagnosis of our patients, might be responsible at least partly for the severe forms of iatrogenic RDS?

1) As discussed above, a decrease in the incidence of respiratory distress from 36 to 40 weeks of gestation is well established [7, 8]. During this period of late gestation the surfactant system undergoes an important maturation in terms of increased production and secretion and of changed composition. With increasing ratio of lecithin to sphingomyelin concentration (L/S-ratio) in amniotic fluid, which has long been used as a marker of lung maturation, the risk for developing RDS decreases [17]. Furthermore, the concentration of surfactant protein A (SP-A), another component of pulmonary surfactant, rises in amniotic fluid and cord blood during late gestation [18]. These same authors were able to show that a lower level of SP-A in cord blood goes along with a higher risk for developing HMD [19].

Endogenous glucocorticoids are an important stimulus for foetal lung maturation. Amniotic fluid concentrations of corticosteroid conjugates, which are primarily derived from the foetus, increase approximately five-fold during the third trimester in parallel with the L/S-ratio [20]. It is suggested that this rise in endogenous corticoids is one important factor in lung maturation, especially for surfactant production in late gestation.

2) The fact of being delivered by CS enhances the risk for developing respiratory distress [8, 9, 15, 16, 21]. During vaginal delivery, about one third of foetal lung fluid is removed by squeezing the baby's chest. This removal is missing during delivery by CS and may be one more explanation as to why babies born by CS have a larger residual volume of lung fluid, secrete less surfactant to the alveolar surface and are therefore at higher risk to develop HMD [22].

3) The absence of labour has been shown to be a risk factor for RDS by many authors [8, 9, 15, 16, 21]. Labour is beneficial for maturation of the surfactant system. Babies born by CS before onset of labour had significantly lower L/S-ratios than babies born after the beginning of labour, either vaginally or by CS [23, 24]. Furthermore, SP-A concentration in cord blood is significantly lower in babies close to term delivered by elective CS than in those delivered after onset of labour [18]. However, not only maturation but also secretion of surfactant is enhanced by labour and triggered by β-adrenergic agents and prostaglandins [25–27].

As outlined above, the focus of the present study was on patients with iatrogenic RDS diagnosed as HMD. However, the pathophysiological concept of HMD has undergone some changes. In recent years, more evidence arose that beside immaturity/insufficiency of the surfactant itself, an insufficient clearance of lung fluid may play an important role in the pathogenetic mechanisms of HMD [28]. In very premature infants Na^+-absorption across nasal epithelium is impaired in patients with HMD [29]. Furthermore, the discussed risk factors [1]: lower GA, [2] CS and [3] delivery before labour have also been shown to be important in the removal of lung liquid [30–32].

Severity of RDS

As shown in Table 1, patients in both groups were severely ill. This is documented mainly by high OI and important use of rescue HFV and catecholamines. Seven newborns even fulfilled criteria for extracorporeal membrane oxygenation (ECMO) as requested by the UK Collaborative ECMO Trial Group [33]. However, by the use of a high-volume strategy during HFV, all our pa-

tients showed a rapid and sustained response in oxygenation [34]. In some very sick patients additional pulmonary oedema was initially associated in the course of RDS. Permeability pulmonary oedema has been documented in newborns with HMD [35].

Reserves

The present study was done retrospectively over a rather long period, during which some therapeutic modalities have changed (introduction of exogenous surfactant, change from high-frequency jet ventilation to high-frequency oscillation, and introduction of patient triggered ventilation with tidal volume limitation).

Moreover, some changes within the catchment area over the years might have occurred. There is no central register for epidemiological data in this area, so the overall CS rate is not available. However, with 12 000 livebirths/year and an annual mean of 2.6 term babies with HMD after elective CS in the catchment area of the PICU in Berne (34 patients in group 1 over 13 years), a Swiss nationwide number of 15–20 cases/year can be estimated, which is too high for a principally preventable disease. Furthermore, there might be additional cases of severe iatrogenic RDS which do not fulfill the criteria of HMD but do fulfill the criteria of transitory tachypnoea of the newborn.

Conclusions

As shown by our series, iatrogenic RDS caused by too early elective CS before onset of labour is still a reality. Some of these patients are extremely ill and need invasive high-tech medical measures to save their lives. Even then, a fatal outcome cannot be excluded. Overall, iatrogenic RDS is a rare cause of RDS in neonates, but as a potentially preventable disease all possible efforts have to be undertaken to avoid it. As documented by our series and recent works by other authors, no case of severe HMD has been observed after completion of 39 weeks of GA.

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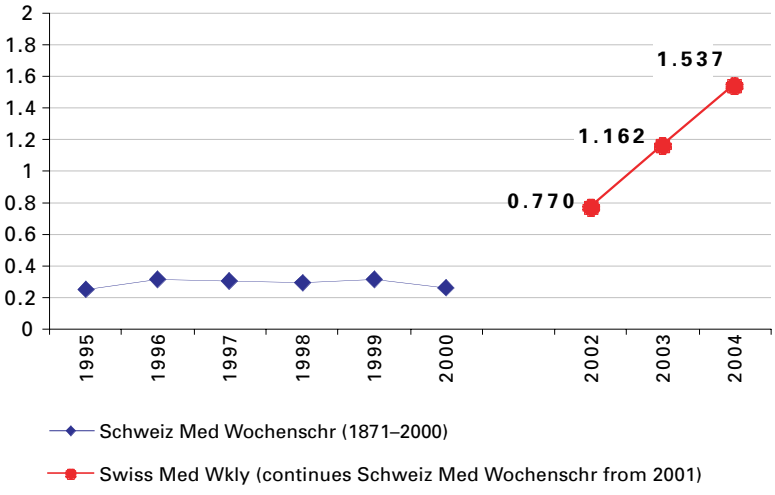

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