Chapter 6  Neonatal outcome after spontaneous onset of labour and birth before 34 weeks

Part I: Perinatal risk factors for cranial ultrasound abnormalities

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SUBMITTED
ABSTRACT

Objective: The aim of this study was to identify risk factors for ultrasound abnormalities in neonates born after spontaneous preterm labour with or without premature rupture of the membranes (PROM).

Methods: Retrospectively, a group of neonates born between 24 and 34 weeks in a tertiary referral hospital after spontaneous onset of labour with or without prolonged rupture of the membranes was studied. Medical records of mother and child were analysed for antenatal and postnatal variables and cranial ultrasound was performed in the neonatal period. Abnormal results were classified as severe intraventricular haemorrhage and cystic periventricular leucomalacia. A stepwise forward logistic regression was performed to analyse the influence of antenatal and postnatal variables.

Results: During the study period, there were 8958 deliveries and 229 of these fulfilled the entry criteria including 43 twin gestations. After a review of the cases 205 neonates were suitable for analysis and ultrasound abnormalities were identified in 27 infants. Gestational age at birth (Odds ratio for increase per day 0.96, 95% confidence interval 0.93-0.99, p=0.03) and a full course of antenatal steroids (OR 0.33, 95% CI 0.13-0.85, p=0.02) reduced the risk for cranial ultrasound abnormalities. An early onset infection (OR 3.09, 95% CI 1.24-7.70, p=0.01) increased the risk for cranial ultrasound abnormalities.

Conclusion: Gestational age at birth, an absence of a full course of antenatal steroid administration and an early onset infection are independent variables significantly associated with cranial ultrasound abnormalities in the very preterm neonate born after spontaneous labour with or without PROM.
INTRODUCTION

Recent studies have shown that neonates born after spontaneous preterm labour or prolonged rupture of the membranes in the preterm period (PROM) are at increased risk for intraventricular haemorrhage and cystic periventricular leucomalacia when compared to premature neonates born after an elective delivery due to fetal growth restriction (FGR) or maternal complications. \(^1\) Large intraventricular haemorrhages with or without parenchymal involvement and cystic periventricular leucomalacia can be detected using cranial ultrasound examination in the early neonatal period. \(^3, 4, 10, 11\) Preterm birth after spontaneous onset of labour with or without PROM is often associated with inflammation and infection of the uterus, membranes or placenta by bacterial vaginosis related micro-organisms. \(^12\) Leucotriens, cytokines and prostaglandins play an important role in the onset of preterm birth. Some of these substances are believed to be responsible for the increased vulnerability of the neonatal brain after spontaneous preterm delivery. \(^13\) The aim of this study was to investigate the relationship of antenatal and postnatal variables with the development of large intraventricular haemorrhage and cystic periventricular leucomalacia in a group of neonates born after spontaneous onset of labour with or without PROM between 24 and 34 weeks of gestation.
MATERIALS AND METHODS

All medical records of women who delivered in the period from 1 January 1990 to 31 December 1995 at the University Hospital Utrecht, a tertiary obstetrical referral hospital in the centre of the Netherlands, were reviewed for preterm birth after spontaneous onset of labour with or without PROM between 24 and 34 weeks of gestation. Gestational age was calculated from the first day of the last menstrual cycle and if necessary, adjusted by early ultrasound estimates of gestational age. Only neonates from either singleton or twin pregnancies who were born in the University Hospital Utrecht and were admitted to the neonatal intensive care unit (NICU) of the associated Wilhelmina’s Children’s Hospital, were included in the analysis. Those excluded from the study were: neonates who died during delivery or before admission to the NICU; neonates from higher order gestation; neonates electively delivered because of fetal growth restriction (FGR), maternal pregnancy induced hypertension or preeclampsia, abruptio placentae or placenta previa; or neonates with severe congenital anomalies.

From those who were selected for the study the following variables were recorded from maternal and neonatal medical records:

- twin pregnancy
- use of tocolytics (intravenously administered ritrodine)
- use of antenatal corticosteroids (betamethasone) in either an incomplete or a full course of antenatal corticosteroids (two doses given with an interval of 24 hours at least 48 hours before birth)
- use of antibiotics (amoxicilline with or without clavulanic acid) before and during delivery
- duration of rupture of membranes
- presence of an intra-amniotic infection as defined by intrapartum fever (> 37.8°C) in combination with either fetal tachycardia, foul smelling discharge, uterine tenderness or
maternal leucocytosis (> 15,000 leucocytes / µl) 18

- mode of delivery (vaginal or caesarean section)
- gestational age at birth and birth weight
- five minute Apgar score of less than 7
- use of antibiotics immediately after birth
- early onset infection defined by sepsis (positive blood culture in an infected infant), clinical sepsis (clinical suspicion of infection in a symptomatic infant) and congenital pneumonia (characteristic infiltrates noted on a chest x-ray) all diagnosed during the first 48 hours of life 18
- assisted ventilation and duration of ventilation
- results of cranial ultrasonography (normal or abnormal).

Cranial ultrasound using a UM-4 mechanical sector scanner with a rotating scan head (5-7.5-10 MHz transducer) was performed daily on all neonates during the first week of life and twice a week until discharge from the NICU. Ultrasound findings were considered abnormal when a large intraventricular haemorrhage with or without unilateral parenchymal involvement (grade III or IV according to Papile 11) or cystic periventricular leucomalacia (grade II or III according to de Vries 10) was diagnosed upon admission to the NICU.

Data were analysed using the SPSS statistical software (SPSS Inc., Chicago, Illinois, USA) and differences between categories were tested for significance using the Chi-square test and if applicable Wilcoxon’s test. The influence of the perinatal variables on the development of abnormal ultrasound findings was analysed by a stepwise forward logistic regression to investigate the interaction between these variables. Significance and odds ratio (OR) with 95% confidence interval (CI) were calculated. This logistic regression was performed for the total group as well as for the group of neonates that survived and a p-value <0.05 was considered significant.
RESULTS

There were 8958 deliveries in the University Hospital Utrecht from 1 January 1990 until 31 December 1995. Of these women 229 fulfilled the entry criteria (2.5%) including 43 twin pregnancies. In total 272 neonates were born between 24 and 34 weeks after spontaneous onset of labour with or without PROM. For various reasons 67 neonates were excluded; 60 admitted to another NICU than the Wilhelmina’s Children Hospital; 5 stillbirths and 2 congenital anomalies (Table I).

Table I

Study population

<table>
<thead>
<tr>
<th>Study population</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>total number of deliveries</td>
<td>8958</td>
</tr>
<tr>
<td>mothers with preterm birth between 24 and 34 weeks</td>
<td></td>
</tr>
<tr>
<td>after spontaneous labour or prelabour rupture of membranes</td>
<td>229</td>
</tr>
<tr>
<td>twin pregnancies</td>
<td>43</td>
</tr>
<tr>
<td>total number neonates</td>
<td>272</td>
</tr>
</tbody>
</table>

excluded because of :

- stillbirth                                           | 5     |
- severe congenital anomaly                            | 2     |
- not admitted to Wilhelmina’s Children Hospital’s NICU | 60    |

neonates suitable for analysis                         | 205   |
Of 205 neonates including the non-survivors born between 24 and 34 weeks after spontaneous onset of labour with or without PROM, all perinatal variables were available for analysis. In Table II some maternal and neonatal characteristics are shown. Nulliparae were significantly younger than multiparae. Sixteen neonates in all died during the neonatal period, fourteen due to untreatable respiratory problems, one due to a sepsis and one due to severe cerebral damage. Neonates who died had a significantly lower gestational age and birth weight.

**Table II**

**Maternal and neonatal characteristics**

mothers: n=164

- age mean in years (sd) 29 (5)
- age nulliparae in years (sd) 28 (5)*
- age multiparae in years (sd) 30 (5)*
- twin pregnancies 43

neonates: n=205

<table>
<thead>
<tr>
<th></th>
<th>number</th>
<th>gestational age in days (sd)</th>
<th>birth weight in grams (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>all neonates</td>
<td>205</td>
<td>202 (12)</td>
<td>1297 (318)</td>
</tr>
<tr>
<td>survivors</td>
<td>189</td>
<td>202 (12)**</td>
<td>1291 (318)*</td>
</tr>
<tr>
<td>non survivors</td>
<td>16</td>
<td>191 (10)**</td>
<td>1073 (249)*</td>
</tr>
</tbody>
</table>

* p < 0.01    ** p < 0.005
The severe cranial ultrasound abnormalities consisted of intraventricular haemorrhage with venous infarction found in 13 neonates (in non-survivors 4), intraventricular haemorrhage with ventricle dilatation in 4 neonates and cystic periventricular leucomalacia in 10 neonates (in non-survivors 2).

In an univariate analysis the influence of all perinatal variables on cranial ultrasound abnormalities was investigated (Table III). In neonates with an abnormal ultrasound, the following significant differences were seen when compared to those without cranial ultrasound abnormalities:

- duration of tocolysis was shorter (p<0.01)
- any form of steroids was less frequently given (p<0.01)
- a full course of antenatal steroids was less frequently given (p< 0.005)
- antibiotics during labour were less frequently administered (p<0.05)
- the incidence of caesarean sections was lower (p<0.05)
- gestational age at birth was lower (p<0.05)
- more early onset infections were seen (p<0.005)
- assisted ventilation was longer (p<0.05).
### Table III

Perinatal variables and the results of ultrasound

<table>
<thead>
<tr>
<th>Number</th>
<th>normal ultrasound</th>
<th>abnormal ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>all</td>
<td>survivors</td>
</tr>
<tr>
<td>Variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tocolysis (%)</td>
<td>87.6</td>
<td>87.4</td>
</tr>
<tr>
<td>length of tocolysis (sd)</td>
<td>3.7 (4.5)**</td>
<td>3.9 (4.1)**</td>
</tr>
<tr>
<td>antibiotics before birth (%)</td>
<td>21.3</td>
<td>22.2</td>
</tr>
<tr>
<td>any form of steroids (%)</td>
<td>87.1**</td>
<td>87.5**</td>
</tr>
<tr>
<td>full course of antenatal steroids (%)</td>
<td>57.9***</td>
<td>60.1***</td>
</tr>
<tr>
<td>antibiotics during labour (%)</td>
<td>48.3</td>
<td>48.5*</td>
</tr>
<tr>
<td>intra-amniotic infection (%)</td>
<td>39.3</td>
<td>39.3</td>
</tr>
<tr>
<td>length of ruptured membranes in hours (sd)</td>
<td>127 (243)</td>
<td>120 (230)</td>
</tr>
<tr>
<td>caesarean section (%)</td>
<td>32.6*</td>
<td>33.9*</td>
</tr>
<tr>
<td>gestational age in days (sd)</td>
<td>203 (12)*</td>
<td>203 (12)*</td>
</tr>
<tr>
<td>birth weight in grams (sd)</td>
<td>1294 (320)</td>
<td>1304 (315)</td>
</tr>
<tr>
<td>girls (%)</td>
<td>40.4</td>
<td>41.0</td>
</tr>
<tr>
<td>boys (%)</td>
<td>59.6</td>
<td>59.0</td>
</tr>
<tr>
<td>low five minute apgar score (%)</td>
<td>12.9</td>
<td>11.9</td>
</tr>
<tr>
<td>early onset infectious disease (%)</td>
<td>42.1***</td>
<td>39.2***</td>
</tr>
<tr>
<td>antibiotics postnatally (%)</td>
<td>94.4</td>
<td>94.0</td>
</tr>
<tr>
<td>assisted ventilation (%)</td>
<td>78.3*</td>
<td>77.4*</td>
</tr>
<tr>
<td>length of assisted ventilation in days (sd)</td>
<td>10.4 (13.6)*</td>
<td>10.6 (13.9)*</td>
</tr>
<tr>
<td>twin pregnancies</td>
<td>40.4</td>
<td>40.7</td>
</tr>
</tbody>
</table>

* *p < 0.05
** p < 0.01
*** p < 0.005

significance of those with normal ultrasound compared to those with abnormal ultrasound
A stepwise forward logistic regression analysis was performed to assess the independent influence of the perinatal variables on the development of cranial ultrasound abnormalities for the total group of neonates as well as for the survivors (Table IV). The risk for developing abnormal cranial ultrasound appeared to be reduced in neonates with increasing gestational age at birth (OR for increase per day 0.96, 95% CI 0.92-0.99, p=0.03) and after a full course of antenatal steroid administration (OR 0.33, 95% CI 0.13-0.85, p=0.02). An early onset infection increased the risk (OR 3.09, 95% CI 1.24-7.70, p=0.01). All other variables did not contribute significantly to the model and showed a p>0.1.

In the group that survived, the risk for abnormal cranial ultrasound decreased after a full course of antenatal steroids (OR 0.16, 95% CI 0.05-0.51, p=0.005) and increased in neonates that developed an early onset infection (OR 3.51, 95% CI 1.26-9.76, p=0.01). All other variables did not contribute significantly to the model; although, some variables (antibiotics during labour, gestational age, caesarean section, and the duration of ventilation) almost reached significance.

*Table IV*

**Logistic regression with ultrasound as dependent variable in the total group and the survivors**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total group n = 205</th>
<th>Significance</th>
<th>Odds Ratio</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>gestational age at birth</td>
<td>p=.0272</td>
<td>0.96</td>
<td></td>
<td>(0.92-0.99)</td>
</tr>
<tr>
<td>full course of antenatal steroids</td>
<td>p=.0162</td>
<td>0.33</td>
<td></td>
<td>(0.13-0.85)</td>
</tr>
<tr>
<td>early onset infection</td>
<td>p=.0115</td>
<td>3.09</td>
<td></td>
<td>(1.24-7.70)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Significance</td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------</td>
<td>------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>Survivors n = 189</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full course of antenatal steroids</td>
<td>p = .005</td>
<td>0.16</td>
<td>(0.05-0.51)</td>
<td></td>
</tr>
<tr>
<td>Early onset infection</td>
<td>p = .01</td>
<td>3.51</td>
<td>(1.26-9.76)</td>
<td></td>
</tr>
<tr>
<td>Antibiotics during labour</td>
<td>p = .053</td>
<td>0.34</td>
<td>(0.09-1.25)</td>
<td></td>
</tr>
<tr>
<td>Caesarean section</td>
<td>p = .057</td>
<td>0.53</td>
<td>(0.24-1.17)</td>
<td></td>
</tr>
<tr>
<td>Gestational age at birth</td>
<td>p = .052</td>
<td>0.97</td>
<td>(0.91-1.02)</td>
<td></td>
</tr>
<tr>
<td>Length of assisted ventilation</td>
<td>p = .056</td>
<td>1.01</td>
<td>(0.97-1.05)</td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

The analysis in a stepwise forward logistic regression model of the influence of perinatal factors on the development of abnormal cranial ultrasound in neonates born between 24 and 34 weeks after spontaneous onset of labour with or without PROM revealed that increasing gestational age and a full course of antenatal steroids significantly protected the neonate against the risk of development of abnormal cranial ultrasound and that an early onset infection significantly increased the risk. When applying this model to the surviving neonates, the significance of gestational age disappeared (p=0.06). Antibiotics during delivery, mode of delivery and length of assisted ventilation almost reached significance (p<0.1) (Table IV). The incidence of severe abnormalities on cranial ultrasound in this group is 13% and coincides with other studies.\(^7,8\)

The protective effects of increasing gestational age and of antenatal steroid therapy have been reported in earlier studies.\(^3,18,19,20\) Although there were fewer neonates with cranial ultrasound abnormalities when any form of antenatal steroid therapy was given, only a full course of antenatal steroid therapy - i.e. two doses with an interval of 24 hours given at least 48 hours before birth - emerged as a significant factor in the regression analysis. This also accords with other observations. The protective mechanism of corticosteroids may result from an increase in neonatal blood pressure which prevents blood pressure fluctuations or may result from an enhanced maturation of the cardiovascular system of the neonate, in addition to the effects on the pulmonary system resulting in a decrease of the incidence in IRDS.\(^19,20,21,22\)

An early onset infection (i.e. an infection that most likely already started in utero) was significantly associated with the development of abnormal cranial ultrasound. This occurrence has been shown in studies by Grether\(^23\) and Spinillo.\(^7\) They found associations between early onset infection and large intraventricular haemorrhages, periventricular leukomalacia.\(^23\) and
neurological impairment. The observation that antibiotic prophylaxis in cases of preterm PROM protects against the development of intraventricular haemorrhage also points to a relation between infection and cerebral damage. The mechanism is not yet elucidated. Leucotriens, cytokines and prostaglandins associated with the onset of preterm labour may be involved in the development of these types of cerebral damage. These substances are often found in high concentration in membranes, amniotic fluid, placenta and umbilical cord blood in preterm labour with spontaneous onset and play an important role in the onset of preterm birth. These substances gain access to the fetal circulation through villi, chorion and amniotic fluid and may alter the endothelium of the germinal matrix and damage the fetal blood-brain barrier. This renders the neonatal brain postpartum more vulnerable to fluctuations of the blood pressure leading to intraventricular haemorrhage and periventricular leucomalacia.

Clinical chorioamnionitis (an intra-amniotic infection) showed no significant relation to the development of abnormal cranial ultrasound, although an intra-amniotic infection was associated with early onset infection (47% versus 32%, p<0.05 chi-square). Antibiotics were antenatally administered in 85% of the cases having an intra-amniotic infection and this may have had a protective effect on the development of cranial ultrasound abnormalities. In the regression analysis, antibiotics used during labour showed a trend towards protection against the development of intraventricular haemorrhage and periventricular leucomalacia in the survivors (Table IV) while antibiotic administration immediately postpartum did not have an influence on the development of ultrasound abnormalities. This may be explained by the fact that the damaging effects of cytokines on the fetal brain already start in utero rather than after birth.

The duration of assisted ventilation showed a trend towards the development of abnormal cranial ultrasound in the survivors. This may reflect the severity of the illness in the neonate but assisted ventilation is also associated with fluctuations of blood pressure in the neonatal brain.
The trend that a caesarean section might protect against the development of intraventricular haemorrhage and periventricular leucomalacia accords with observations by Baud et al \textsuperscript{27}. They found, in cases with chorioamnionitis, a lower incidence of cerebral damage in preterm neonates born after a caesarean section compared to preterm neonates born after a vaginal delivery. The protective mechanism of a caesarean section remains speculative, but warrants further research.

It may be concluded from our study that three perinatal factors were found to be significantly associated with abnormal cranial ultrasound in neonates born between 24 and 34 weeks of gestation after spontaneous onset of labour with or without PROM; gestation age at birth, a full course of antenatal steroid administration and early onset infection. An increasing gestational age and a full course of antenatal steroids protected against the development of large intraventricular haemorrhage and cystic periventricular leucomalacia; however the occurrence of an early onset infection increased this risk.

Along with attempts to prolong gestation and the administration of steroids in cases of spontaneous preterm birth a more liberal use of antibiotics to prevent early onset infection might be a next step in preventing early neonatal neurological damage.
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