Placental lesions and outcome in preterm born children

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Chapter 7

In preterm infants ascending intrauterine infection is associated with lower cerebral tissue oxygen saturation and higher oxygen extraction

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Abstract

Background Placental lesions are associated with neurological morbidity but the mechanism leading to morbidity is unclear. To provide insight into such a possible mechanism we determined whether placental lesions were associated with regional cerebral tissue oxygen saturation (r_cSO_2) and fractional tissue oxygen extraction (FTOE) in preterm infants during their first five days after birth. We hypothesized that as a result of cerebral hypoperfusion, regional cerebral tissue oxygen saturation would be lower and fractional tissue oxygen extraction would be higher.

Method A prospective, observational study of 42 preterm infants (GA <32wk). The infants' placentas were examined for histopathology. We measured r_cSO_2 and transcutaneous arterial oxygen saturation on days one to five. FTOE was calculated as FTOE = (transcutaneous arterial oxygen saturation – r_cSO_2)/transcutaneous arterial oxygen saturation.

Results Only three placentas showed no pathology. Ascending intrauterine infection was associated with lower r_cSO_2 and higher FTOE values on days two, three, and four ($P \leq .05$). Other placental lesions were not associated with r_cSO_2 and FTOE.

Conclusion Ascending intrauterine infection is associated with lower r_cSO_2, and higher FTOE shortly after birth. The effect it has on cerebral oxygenation might be the mechanism leading to neurodevelopmental problems.

Introduction

The placenta is the link between mother and fetus during pregnancy and as such it is an essential organ for the development of the fetus. It is the only organ that enables the exchange of nutrients and oxygen from mother to fetus and that removes fetal waste products.[1] Placental lesions carry the risk of fetal hypoxia, neonatal morbidity, and even perinatal death.[2-6] Moreover, such lesions are associated with several neurological problems including intraventricular hemorrhage, white matter injury, cerebral palsy, and long-term neurodevelopmental problems.[7-13]

To date the mechanism whereby placental lesions lead to cerebral damage is unclear. One study hypothesized that chronic placental insufficiency could induce fetal hypoxia which in turn could result in cerebral hypoperfusion which leads to cerebral damage.[14] Longstanding placental hypoperfusion can result in a non-optimal intrauterine environment. The placental underperfusion can lead to a reduction of perfusion surface and, as a consequence, non-optimal oxygen delivery to the fetal circulation. This might result in some degree of intrauterine cerebral underperfusion, and as a consequence to a (transitional) effect on postnatal cerebral blood flow. On the other hand, cerebral hyperperfusion could also lead to cerebral damage.[15] Understanding the mechanism of placental lesions leading to neurodevelopmental problems is necessary to provide possible clues for early interventions aiming to improve neurological outcome. To determine whether disturbances in hemodynamics shortly after birth could be a possible mechanism underlying cerebral damage caused by placental lesions, it would be useful if we could measure cerebral tissue oxygen saturation and extraction. A non-invasive method of doing so is near-infrared spectroscopy (NIRS). It measures regional cerebral tissue oxygen saturation (r_cSO_2). From this value fractional cerebral tissue oxygen extraction (FTOE) can be calculated which reflects the balance between cerebral oxygen supply and cerebral oxygen consumption.[16]

Our objective was to determine whether placental lesions were associated with cerebral tissue oxygen saturation and extraction shortly after birth. We hypothesized that in the presence of placental lesions cerebral tissue oxygen saturation would be lower due to cerebral hypoperfusion.

Methods

Patient population

Our cohort consisted of 42 preterm, singleton infants that had been admitted to the neonatal intensive care unit of Beatrix Children's Hospital in Groningen, the Netherlands, between May 2006 and February 2008. The inclusion criteria were singleton birth and a gestational age (GA) of less than 32 weeks. Infants with major chromosomal and congenital abnormalities were not included. The review board of University Medical Center Groningen approved the study. Written, informed parental consent was obtained in all cases.

The majority of the infants included in this study were also part of another study concerning placental lesions and outcome.[17] In that study we determined the relation between placental lesions and early neurological outcome based on the quality of general movements.

Placental lesions

A perinatal pathologist (AT) examined the placentas in accordance with the guidelines of the Royal College of Obstetricians and Gynaecologists and the Royal College of Pathologists in Britain, and of the College of American Pathologists.[18-19] Apart from knowing the infants' GAs, the pathologist was blinded as to their clinical outcomes. We examined all placentas for lesions suspected of having an association with neurological impairment.[13-20] Such lesions are: placental pathology consistent with maternal vascular underperfusion (MVU),[21] ascending intrauterine infection (AIUI),[22] chronic villitis of unknown origin,[23] chronic deciduitis,[24] perivillous fibrinoid,[25] fetal thrombotic vasculopathy,[26] meconium-associated vascular necrosis,[27] chorioamniotic hemosiderosis,[28] elevated nucleated red blood cells (NRBCs),[29] chorangiosis,[30] and umbilical cord abnormalities.[31] A single placenta can have more than one lesion. All lesions presented in a single placenta were scored separately. In Table 1 we present the diagnostic terminology and definitions of these placental lesions. In addition to the placental lesions, we also collected data on placental weights and umbilical cord lengths.

Table 1: Diagnostic terminology and definition of the placental lesions

Diagnostic terminology	Definition and scoring criteria
Maternal vascular underperfusion	Decidual vasculopathy, e.g. incomplete or absent spiral artery remodelling, acute atherosis, fibrinoid necrosis, or thrombosis; parenchymal pathology such as placental hypoplasia, increased syncytial knotting, villous agglutination, increased perivillous fibrin, distal villous hypoplasia, infarction, retroplacental hematoma.[21]
Ascending intrauterine infection	Acute inflammation of the extraplacental membranes and chorionic plate. Acute chorioamnionitis and chorionitis represent the maternal response; chorionic or umbilical vasculitis represents the fetal response.[22]
Villitis of unknown etiology	Chronic lymphohistiocytic inflammation of the stem and chorionic villi, with or without obliterative vasculopathy of stem villus vessels.[23]
Chronic deciduitis	Chronic lymphohistiocytic or plasmacytic inflammation of placental decidua.[24]
Maternal floor infarction / massive perivillous fibrinoid deposition	Excessive perivillous fibrin deposition, either basally at a thickness of ≥3 mm on at least one slide (maternal floor infarction) or transmural encasing ≥50% of villi on at least one slide (massive perivillous fibrinoid deposition).[25]
Fetal thrombotic vasculopathy	Fetal vascular thrombosis, intimal fibrin cushions, fibromuscular sclerosis, hemorrhagic endovasculitis and groups of at least five avascular fibrotic villi without inflammation or mineralization and/or adherent thrombi in stem vessels.[26]
Meconium associated vascular necrosis	Meconium associated necrosis of smooth muscle cells in the wall of chorionic plate vessels.[27]
Chorioamniotic hemosiderosis	Presence of hemosiderophages in the amnion and chorion .[28]
Elevated nucleated red blood cells	Only rare NRBCs are normal after the first trimester. More than two NRBC in a randomly selected field of 4.5 mm^2, corresponding to 18 consecutive fields at 40x magnification, or one field at 10x magnification was considered as abnormal.[29]
Chorangiosis	Diffuse increase in the number of villous capillaries.[30]
Umbilical cord abnormalities	Obstruction or disruption of the umbilical cord blood flow (e.g. umbilical cord prolapse, entanglement, knots, disrupted velamentous vessels, hyper/hypo-coiling).[31]

Near-infrared spectroscopy

We used an INVOS 4100 near-infrared spectrometer (Somanetics Corporation, Troy, Michigan) in combination with the pediatric SomaSensor to obtain r_cSO_2 values. We placed the Somasensor on the left frontoparietal side of the infant's head and it was held in place by elastic bandaging. A more detailed description of the method was published previously.[32]

We measured r_cSO_2 within the first 24 hours after birth and subsequently on the second, third, fourth, and fifth days. On these days r_cSO_2 was measured over a clinically stable two-hour period. Fifteen minutes were allowed for stabilization of the measurement. Simultaneously, we measured arterial oxygen saturation (SpO_2) by pulse oximetry. We calculated FTOE with the equation FTOE = $(SpO_2 - r_cSO_2) / SpO_2$.[16]

Clinical variables

Prospectively, we collected details on perinatal and neonatal characteristics that might influence hemodynamics. These included GA, birth weight, small-for-gestational age (SGA), Apgar score, umbilical cord pH, birth asphyxia, early- and late-onset sepsis (culture proven), clinical infection, C-reactive protein (CRP), intraventricular hemorrhage, signs of circulatory failure, ventilatory status, patency of the ductus arteriosus, and medication. Clinical infection was defined as maternal fever during labor and/or fetal tachycardia and/or a CRP value ≥10 during the first 72 hours after birth, and/or positive blood cultures during the first 48 hours after birth. Maternal and pregnancy variables included anti-hypertensive medication (labetalol, $MgSO_4$, nifedipine), fetal growth restriction, preterm pre-labor rupture of the membranes (PPROM), pre-eclampsia, and mode of delivery.

The infants' heart rates, respiratory rates and mean arterial blood pressures were recorded simultaneously with the r_cSO_2 and SpO_2 measurements. Blood gas values, blood glucose, and hemoglobin concentrations were recorded on the day of NIRS measurements.

Statistical analysis

We used SPSS 20.0 software for Windows (SPSS Inc, Chicago, Illinois, USA) for the statistical analyses. The r_cSO_2 and SpO_2 values were collected every five seconds. The mean values for r_cSO_2, SpO_2, and FTOE were calculated for the 2-hour recording periods. We used the Kolmogorov-Smirnov test to determine the normality of the r_cSO_2 and FTOE values. Both showed a normal distribution. For the analyses of the relationships between placental lesions and NIRS parameters we used univariate linear regression. We included those placental lesions in our analyses which were 5 or more times present in our study group.

When determining associations between a specific placental lesion and cerebral oxygenation, the control group consisted of infants with no placental lesions and infants with other placental lesions than the one under study. We used backward multiple linear regression analyses to determine which variables were independently associated with

r_cSO_2 and FTOE throughout the analyses. For placental lesions we chose a univariate level of significance of $P \leq .05$ to be included into the multivariate analyses. Variables that were potential confounders and differed between the group with and without a placental lesion were included in the regression analyses at $P < .1$. A predetermined P value of $< .05$ was considered statistically significant.

Results

We present the patient characteristics in Table 2. No infants died during the first five days after birth. Four infants died between six and nineteen days after birth: three died of respiratory and circulatory insufficiency due to sepsis and one infant died of gastrointestinal perforation.

Placental lesions

Out of the 42 placentas we examined only three showed no lesions (Table 2). The largest group of placental lesions consisted of MVU (25 placentas). Sixteen placentas, representing the second largest group, showed signs of AIUI. A maternal response was present in 15 placentas, a fetal response in 13 placentas, a maternal and fetal response was present in 12 placentas. In 25 placentas we found more than one placental lesion.

Table 2. Patient characteristics. Data are given as median (range) or numbers (percentage).

Study population	N=42
Male/female	20/22 (48% / 52%)
Gestational age in weeks	29.4 (25-32)
Birth weight in grams	1230 (560-2250)
Small for gestational age (P<10)	7 (17%)
Apgar score at 5 minutes	8 (3-10)
Umbilical cord pH	7.22 (7.01-7.40)
Cerebral lesions	
Periventricular leukomalacia	17 (40%) (all grade 1)
Intracranial haemorrhage, grade 1-2	8 (19%)
Intracranial haemorrhage, grade 3-4	2 (5%)
Early-onset sepsis (culture proven)	2 (5%)
Late-onset sepsis (culture proven)	13 (31%)
Clinical infection[a]	8 (19%)
C-reactive protein (mg/L)[b]	1 (1-112)
Circulatory failure	
Fluid resuscitation	18 (43%)
Inotropes	2 (5%)
Artificial respiration needed	25 (60%)
Preterm pre-labour rupture of the membranes	13 (31%)
Caesarean section (elective and emergency)	23 (55%)
Placental weight in grams	260 (142-470)
Cord length in centimeters	28 (15-59)
Placental lesions[c]	39 (93%)
Maternal vascular underperfusion	25 (60%)
Ascending intrauterine infection	16 (38%)
Fetal thrombotic vasculopathy	6 (14%)
Villitis of unknown etiology	6 (14%)
Chronic deciduitis	11 (26%)
Chorioamniotic hemosiderosis	1 (2%)
Perivillous fibrinoid	1 (2%)
Placental markers	
Elevated nucleated red blood cells	20 (48%)
Chorangiosis	3 (7%)

[a] Clinical infection was defined as maternal fever during labor and/or fetal tachycardia and/or a CRP value ≥10 during the first 72 hours after birth, and/or positive blood cultures during the first 48 hours after birth

[b] Highest CRP value during the first 72 hours after birth for each infant. From 20 infants no CRP values were determined during the first 72 hours after birth.

[c] The numbers exceed totals, because a single placenta can have more than one lesion.

Relationship between placental lesions and r_cSO_2 and FTOE

On the first day after birth none of the placental lesions were associated with r_cSO_2 or FTOE.

On the second day the presence of AIUI was associated with lower r_cSO_2 and higher FTOE (*P*=.05 and *P*=.04, respectively). AIUI with a fetal response was associated with lower r_cSO_2 (*P*=.05) and higher FTOE (*P*=.06) although neither were statistically significant. AIUI with a maternal response was also associated with lower r_cSO_2 (*P*=.11) and higher FTOE (*P*=.07), but not significant. There was a trend towards an association between MVU and higher r_cSO_2 (*P*=.08) and lower FTOE (*P*=.06).

On the third and fourth days AIUI was still associated with lower r_cSO_2 (day 3 *P*=.008, day 4 *P*=.007) and higher FTOE (day 3 *P*=.01, day 4 *P*=.01). AIUI with a fetal response was also associated with lower r_cSO_2 (day 3 *P*=.009, day 4 *P*=.002) and higher FTOE (day 3 *P*=.02 day 4 *P*=.002). AIUI with a maternal response was associated with lower r_cSO_2 values (day 3 *P*=.05, day 4 *P*=.06) and higher FTOE values (day 3 *P*=.05 day 4 *P*=.09) although not statistically significant. On the fourth day a tendency was seen for an association between elevated NRBCs and lower r_cSO_2 (*P*=.09) and higher FTOE (*P*=.06).

On the fifth day after birth we found no association between AIUI and cerebral oxygenation. Figure 1 shows the relation between AIUI and r_cSO_2 (A) and FTOE (B) during the first five days after birth. SpO_2 did not differ in the presence or absence of AIUI. No other placental lesions were associated with r_cSO_2 or FTOE (Table 3) during the first five days after birth.

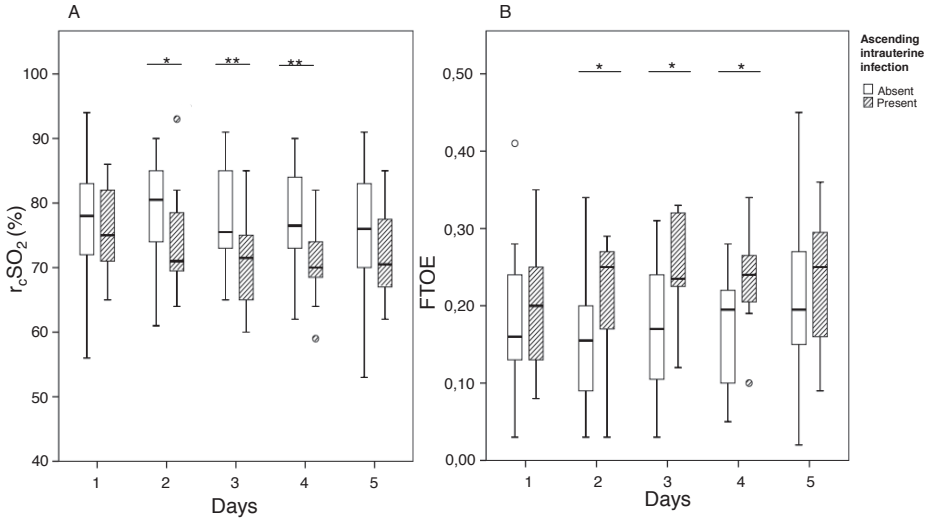

Figure 1: The course of r_cSO_2 (A) and FTOE (B) during the first five days after birth in the presence and absence of ascending intrauterine infection

Data are shown in box and whisker plots. Dots represent outliers.

Significant differences between the two groups are marked with asterisks (* *P*<.05 and ** *P*<.01).

Abbreviations: r_cSO_2 – regional cerebral tissue oxygen saturation; FTOE – fractional tissue oxygen extraction.

Table 3: Univariate regression model for placental lesions and rc_SO_2 and for placental lesions and FTOE

	r_cSO_2						FTOE					
Variable	B	*95% CI for B*	*Beta*	*t*	R^2	*P value*	*B*	*95% CI for B*	*Beta*	*t*	R^2	*P value*
Day 2												
MVU	4.33	-0.50 to 9.17	.29	1.82	8.2	.08	-0.05	-0.11 to 0.00	-.31	-2.00	9.8	.06
AIUI	-4.84	-9.68 to -0.00	-.32	-2.03	10	.05*	0.06	0.00 to 0.11	.33	2.15	11.1	.04*
VUE	-1.59	-9.75 to 6.57	-.07	-0.40	0.40	.70	0.05	-0.04 to 0.14	.20	1.22	3.9	.23
Chronic deciduitis	-1.01	-6.51 to 4.50	-.06	-0.37	0.40	.71	0.01	-0.05 to 0.07	.07	0.42	0.50	.68
FTV	-1.31	-9.48 to 6.85	-.05	-0.33	0.30	.75	0.00	-0.09 to 0.09	.01	0.06	0.00	.95
↑ NRBCs	0.48	-6.94 to 7.90	-.02	0.13	0.00	.90	0.00	-0.08 to 0.08	.00	0.02	0.00	.99
Day 3												
MVU	3.47	-2.34 to 9.28	.21	1.22	4.4	.23	-0.05	-1.10 to 0.01	-.26	-1.58	7.0	.13
AIUI	-7.74	-13.28 to -2.19	-.45	-2.84	20.1	.008*	0.08	0.02 to 0.13	.43	2.71	18.1	.01*
VUE	-0.28	-10.74 to 10.18	-.01	-0.05	0.00	.96	-0.00	-0.11 to 0.10	-.02	-0.09	0.00	.93
Chronic deciduitis	-0.61	-7.60 to 6.39	-.03	-0.18	0.10	.86	0.01	-0.06 to 0.09	.07	0.37	0.40	.71
FTV	-3.22	-12.35 to 5.92	-.13	-0.72	1.6	.48	0.00	-0.09 to 0.10	.00	0.00	0.00	.99
↑ NRBCs	0.01	-8.36 to 8.39	.00	0.00	0.00	.99	-0.02	-0.11 to 0.06	-.09	-0.54	0.90	.59
Day 4												
MVU	2.30	-3.18 to 7.78	.15	0.86	2.30	.40	-0.03	-0.08 to 0.03	-.17	-0.94	2.8	.35
AIUI	-7.27	-12.44 to -2.11	-.46	-2.87	21.0	.007*	0.07	0.02 to 0.12	.43	2.62	18.1	.01*
VUE	0.11	-11.37 to 11.60	.00	0.02	0.00	.98	-0.02	-0.13 to 0.09	-.06	-0.32	0.30	.75
Chronic deciduitis	-2.31	-8.96 to 4.33	-.13	-0.71	1.6	.48	-0.00	-0.07 to 0.06	-.01	-0.06	0.00	.93
FTV	-3.58	-11.87 to 4.71	-.16	-0.88	2.4	.39	0.01	-0.07 to 0.09	.04	0.24	0.20	.81
↑ NRBCs	-6.36	-13.63 to 0.92	-.31	-1.78	9.3	.09	0.07	-0.00 to 0.14	.33	1.93	10.7	.06

Abbreviations: rc_SO_2 – regional cerebral tissue oxygen saturation; FTOE – fractional tissue oxygen extraction; MVU- maternal vascular underperfusion; AIUI - ascending intrauterine infection; VUE - villitis of unknown etiology; FTV - fetal thrombotic vasculopathy; NRBCs - nucleated red blood cells.

* Indicates P≤.05. B indicates un-standardized coefficient, Beta indicates standardized coefficient.

Clinical variables

To test whether the clinical variables we collected had confounded our findings regarding AIUI and r_cSO_2 and FTOE, we performed multiple linear regressions. We first tested whether these variables differed between the groups of infants with and without AIUI ($P<.1$). Gestational age, birth weight, Apgar scores, umbilical cord pH, birth asphyxia, early- and late onset sepsis, CRP, intraventricular hemorrhage, signs of circulatory failure, ventilatory status, patency of the ductus arteriosus, medication (including antibiotic therapy for at least 48 hours after birth), and maternal anti-hypertensive medication were not significantly associated with AIUI in our group. The variables that differed were SGA, whether the mother had preeclampsia, PPROM, and whether the child was delivered by Caesarean section. On days three and four after birth, in the presence of AIUI, the infants' heart rates were higher: mean 155 versus 145.7 and 155.5 versus 148, i.e. $P=.007$ and $P=.08$, respectively. We entered these variables into the regression model; separately for each day.

On day two the parameters applied in our final model for r_cSO_2 and FTOE consisted of AIUI, whether the mother had preeclampsia, whether the infant was SGA, whether the mother had PPROM, and whether the child was delivered by Caesarean section. The final models for days three and four consisted of AIUI, whether the mother had preeclampsia, whether the infant was SGA, whether the mother had PPROM, whether the child was delivered by Caesarean section, and the infant's heart rate.

On day two only preeclampsia remained significant in the regression model with r_cSO_2 and FTOE. On day three AIUI remained significant in the model for r_cSO_2. For FTOE only SGA remained significant in the model. On day four only AIUI remained significant in the regression model for r_cSO_2 (Table 4). AIUI, PPROM, and the infant's heart rate remained significant in the model for FTOE (Table 5).

The presence of a clinical infection was also associated with placentas showing signs of AIUI. We did not adjust for this because the relation between AIUI and clinical infection is interdependent and can therefore falsely affect our results. In a univariate analysis, clinical infection was not associated with NIRS values during the first five days after birth (independent *t*-test, $P>.1$)

Table 4. Univariate and multiple linear regression model for AIUI and r_cSO_2.

Variable	B	95% CI for B	beta	*t*	R^2	*P* value
Day 2						
Univariate						
AIUI	-4.84	-9.68 to -0.00	-.32	-2.03	10	.05*
Multivariate[a]						
AIUI	-3.67	-8.67 to -2.47	-.24	-1.49	15.6	.15
Pre-eclampsia	4.38	-1.39 to 10.15	.25	1.54	15.6	.13
Day 3						
Univariate						
AIUI	-7.74	-13.28 to -2.19	-.45	-2.84	20.1	.008*
Multivariate[b]						
AIUI	-5.98	-11.6 to -0.28	-.35	-2.14	28	.04*
SGA	6.44	-0.71 to 13.59	.30	1.84	28	.08
Day 4						
Univariate						
AIUI	-7.27	-12.44 to -2.11	-.46	-2.87	21	.007*
Multivariate[b]						
AIUI	-7.27	-12.44 to -2.11	-.46	-2.87	21	.007*

Abbreviations: r_cSO_2 – regional cerebral tissue oxygen saturation; AIUI - ascending intrauterine infection; SGA - small-for-gestational age.

* Indicates $P \leq .05$. B indicates un-standardized coefficient, Beta indicates standardized coefficient.
[a] corrected for potential confounders: whether the mother had pre-eclampsia, whether the child was small-for-gestational age, whether there was preterm pre-labor rupture of the membranes, whether the infant was delivered by Caesarean section.
[b] corrected for potential confounders: whether the mother had pre-eclampsia, whether the child was small-for-gestational age, whether there was preterm pre-labor rupture of the membranes, whether the infant was delivered by Caesarean section, and the infant's heart rate.

Table 5. Univariate and multiple linear regression model for AIUI and FTOE.

Variable	B	95% CI for B	beta	*t*	R^2	*P* value
Day 2						
Univariate						
AIUI	0.06	0.00 to 0.11	.33	2.15	11.1	.04*
Multivariate[a]						
AIUI	0.04	-0.01 to 0.09	.23	1.48	21.3	.15
Pre-eclampsia	-0.07	-0.13 to -0.00	-.34	-2.16	21.3	.04*
Day 3						
Univariate						
AIUI	0.08	0.02 to 0.13	.43	2.71	18.1	.01*
Multivariate[b]						
AIUI	0.04	-0.02 to 0.10	.22	1.36	36.8	.19
Pre-eclampsia	-0.05	-0.11 to 0.02	-.24	-1.48	36.8	.15
SGA	-0.08	-0.15 to -0.01	-.36	-2.30	36.8	.03*
Day 4						
Univariate						
AIUI	0.07	0.02 to 0.12	.43	2.62	18.1	.014*
Multivariate[b]						
AIUI	0.11	0.06 to 0.17	.72	4.02	37.9	<.001*
PPROM	-0.06	-0.12 to -0.00	-.37	-2.15	37.9	.04*
Heart rate	-0.00	-0.01 to -0.00	-.44	-2.73	37.9	.01*

Abbreviations: FTOE – fractional tissue oxygen extraction; AIUI - ascending intrauterine infection; SGA - small-for-gestational age; PPROM – preterm pre-labor rupture of the membranes.

* Indicates P≤.05. B indicates un-standardized coefficient, Beta indicates standardized coefficient.
[a] corrected for potential confounders: whether the mother had pre-eclampsia, whether the child was small-for-gestational age, whether there was preterm pre-labor rupture of the membranes, whether the infant was delivered by Caesarean section.
[b] corrected for potential confounders: whether the mother had pre-eclampsia, whether the child was small-for-gestational age, whether there was preterm pre-labor rupture of the membranes, whether the child was delivered by Caesarean section and the infant's heart rate.

Subanalysis of the ascending intrauterine infection group

Of the 16 infants with AIUI, one had a culture proven early onset sepsis and three infants had signs of a clinical infection. In the group of 16 infants with AIUI no difference was found in cerebral tissue oxygen saturation and oxygen extraction in the presence or absence of clinical / culture proven infection (*P*>.10).

Discussion

Our study indicated that AIUI was associated with lower r_cSO_2 and higher FTOE on the second, third, and fourth days after birth. SpO_2 did not differ in the presence or absence of AIUI. During the first five days after birth we found no other placental lesions that associated with r_cSO_2 and FTOE. Therefore, in the case of AIUI, our hypothesis that cerebral oxygen saturation is lower in the presence of placental lesions was confirmed, albeit not for other placental lesions.

The lower r_cSO_2 and higher FTOE in the presence of AIUI may be due either to reduced cerebral oxygen supply or to higher cerebral oxygen consumption.[33] Firstly, the reduced cerebral oxygen supply might be the result of lower cerebral blood flow. Due to the presence of AIUI, several immune-derived cytokines may be induced: interleukin (IL) -1, IL -6, and tumor necrosis factor (TNF)–α.[34] These cytokines are major initiators of the acute-phase liver response that leads to an increase in chemokines, cytokines, and prostaglandins. In turn, prostaglandin activation leads to vasodilatation.[35] Such systemic vasodilatation may lead to lower cerebral blood flow. We would expect to find lower blood pressures in the presence of vasodilatation. Systemic blood pressure, however, did not differ between the group with and without AIUI. We did find higher heart rates in the presence of AIUI. It is possible that blood pressure is maintained through a higher heart rate. Conversely, it is known that blood pressure in preterm infants is not a reliable measure of cardiac output and, therefore, low cerebral blood flow.[36] This means that in the presence of adequate blood pressure microcirculation might be disturbed and end-organ perfusion is reduced. As a consequence, it might be that in the presence of AIUI blood pressure is adequate, but that the microcirculation is reduced. This could result in lower end-organ perfusion and, therefore, lower cerebral oxygen supply, which explains higher FTOE. This is, however, highly speculative. It is, for example, not supported by clinical findings as clear signs of circulatory failure were absent in the infants with AIUI.

A second possible explanation for lower r_cSO_2 and higher FTOE was higher cerebral oxygen consumption. Higher cerebral oxygen consumption may reflect increased cerebral metabolic activity.[33] We surmise that increased metabolic activity might be due to cytokine activation in the presence of AIUI.

Our results could also be explained by higher r_cSO_2 and lower FTOE in the group **without** AIUI compared to the group with AIUI. Even though our cohort consisted of preterm infants, the etiology of their preterm births differed. Some infants were born preterm after PPROM, while others were born following maternal or fetal indications such as preeclampsia or fetal growth restriction. Indeed, we found a higher rate of preeclampsia

and SGA in the group without AIUI compared to the group with AIUI. It was suggested that maternal anti-hypertensive drugs, often prescribed in cases of preeclampsia, are associated with a decrease in cerebral oxygen consumption (↓FTOE).[37] Nevertheless, we did not find a difference in anti-hypertensive drug use between the group with and the group without AIUI. Other factors that are presumed to be associated with a decrease in cerebral oxygen consumption, e.g. medication for the infant like morphine and midazolam, did not differ on the research days between the group with and without AIUI.[37-38] Although we were unable to find a difference in clinical variables that could affect cerebral oxygenation between the group with and without AIUI, we could not completely exclude this option.

Another possibility is that the effect of AIUI on r_cSO_2 and FTOE is secondary to a systemic inflammatory response in early onset sepsis. We did not find a relation between the presence of AIUI and culture proven early onset sepsis (EOS). This can be due to the small number of infants with EOS (n=2). We did find a relation between AIUI and clinical infection. Clinical infection, however, was not associated with r_cSO_2 and FTOE.

Ascending intrauterine infection is known to be associated with neonatal morbidity, like low Apgar scores shortly after birth, a higher incidence of neonatal infections, necrotizing enterocolitis, and bronchopulmonary dysplasia.[39-42] In addition, AIUI is also associated with neurological problems such as intraventricular hemorrhages, periventricular leukomalacia, cerebral palsy, and poorer neurodevelopmental outcomes at toddler and school ages.[7,13,42,43] We now add the association between lower cerebral oxygen saturation, higher cerebral oxygen extraction, and the presence of AIUI. To the best of our knowledge only one other study investigated the relation between AIUI with a fetal response (fetal vasculitis) and cerebral tissue oxygen saturation and extraction shortly after birth.[44] These authors found no difference in cerebral oxygenation in the presence or absence of AIUI with a fetal response. In their study, however, cerebral oxygenation was only measured during the first 24 hours after birth. Likewise, in our study we also found no relation between AIUI and cerebral oxygenation on the first day. During this transitional day, other factors might exert more influence on cerebral oxygenation than AIUI. We did, however, find an association on days two, three, and four.

It was suggested that during the first two weeks after birth cerebral oxygenation is associated with neurodevelopmental outcome. Lower r_cSO_2 and higher FTOE are associated with poorer neurodevelopmental outcome at two to three years of age.[45] Ascending intrauterine infection is also known to be associated with poorer neurodevelopmental outcome.[43] The status of cerebral oxygenation shortly after birth might be the mediating factor for AIUI to lead to neurodevelopmental problems.

The strength of this study was that we investigated the relation between a broad spectrum of placental lesions and cerebral oxygenation. This might contribute towards gaining insight into the pathogenesis of placental lesions leading to neurological problems. Nevertheless, we need to point out several limitations of our study. Firstly, only three children in our group had no placental lesions. The others all had one or more placental lesions. When determining associations between placental lesions and cerebral oxygenation, the

control group consisted partly of infants with other placental lesions than the one studied. Because of the high incidence of placental lesions in a premature group, it is difficult to include a large control group with no placental lesions. Secondly, we performed multiple testing in the univariate analyses. We chose not to adjust our significance level, as this was an explorative study. Thirdly, we only included singletons so as to be certain that each infant was linked to its own placenta. Placental lesions might also differ between twins, e.g. twin-to-twin transfusion. Finally, we studied r_cSO_2 and FTOE values during a 2-hour stable period each day. These values, however, might be different during other moments of the day. Mean arterial blood pressures were also studied during a 2-hour stable period, and might therefore not be sufficient for the interpretation of hemodynamics.

Conclusion

Our study indicated that ascending intrauterine infection was associated with lower regional cerebral tissue oxygen saturation and higher cerebral oxygen extraction on the second, third, and fourth days after birth. Both ascending intrauterine infection and lower cerebral oxygen saturation and a higher oxygen extraction shortly after birth are associated with neurodevelopmental problems. The effect ascending intrauterine infection has on cerebral oxygenation might be the mechanism that causes it to lead to neurodevelopmental problems.

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