Persistent pulmonary hypertension of the newborn after fetomaternal hemorrhage

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BACKGROUND: Newborns with anemia are at increased risk of persistent pulmonary hypertension of the newborn (PPHN), yet reports on the association between fetomaternal hemorrhage (FMH) and PPHN are rare. To optimize care for pregnancies complicated by FMH, clinicians should be aware of the risks of FMH and the possible diagnostic and therapeutic options. To increase the current knowledge, the incidence of PPHN and short-term neurologic injury in FMH cases were studied.

STUDY DESIGN AND METHODS: We included all FMH cases (≥30 mL fetal blood transfused into the maternal circulation) admitted to our neonatal unit between 2006 and 2018. First, we evaluated the incidence of PPHN and short-term neurologic injury. Second, we studied the potential effect of intrauterine transfusion (IUT).

RESULTS: PPHN occurred in 37.9% of newborns (11 of 29), respectively, 14.3% (one of seven) and 45.5% (10 of 22) in the IUT group and no-IUT group (p = 0.20). The mortality rate was 13.8% (4 of 29). Severe brain injury occurred in 34.5% (10 of 29), respectively, and 14.3% (one of seven) and 40.9% (nine of 22) in the IUT group and no-IUT group (p = 0.37).

CONCLUSION: Awareness should be raised among perinatologists and neonatologists about the possible life-threatening consequences of FMH, as more than one-third of neonates with anemia due to FMH experience PPHN and suffer from severe brain injury. Antenatal treatment with IUT seems to reduce these risks. Specialists should therefore always consider fetal anemia in FMH cases and refer patients to a fetal therapy center. If anemia is present at birth, it should be corrected promptly and neonatologists should be aware of signs of PPHN.

In fetomaternal hemorrhage (FMH), fetal blood cells leak into the maternal circulation. Risk factors for FMH are trauma, preeclampsia, placental tumors, or vascular abnormalities and monochorionicity, but most cases occur in otherwise uncomplicated pregnancies.[1] Clinically insignificant fetal-to-maternal blood transfer occurs in the majority of pregnancies,[2] but moderate to severe FMH is an uncommon event with an estimated incidence of three per 1000 live births.[3] Severe FMH can be responsible for unexplained stillbirths, severe neonatal anemia, and neonatal morbidity and mortality.[4]

Another life-threatening condition in the neonatal period is persistent pulmonary hypertension of the newborn (PPHN),[5] which has an estimated incidence of two per 1000 live births.[6] The disease results from abnormal cardiopulmonary transition after birth. Elevated pulmonary vascular resistance in the newborn causes shunting of nonoxygenated blood from the pulmonary to the systemic circulation through the ductus arteriosus, leading to severe hypoxemia.[5] Hypoxia in turn is a known risk factor for PPHN. Hypoxia can result from anemia, as cardiac output and hemoglobin are key elements in determining

ABBREVIATIONS: CTG = cardiotocogram; FMH = fetomaternal hemorrhage; IUT = intrauterine transfusion; LUMC = Leiden University Medical Center; PPHN = persistent pulmonary hypertension of the newborn.

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systemic oxygen transport. This explains the increased incidence of PPHN in case of anemia at birth.[7-9]

Although there is an increased risk of PPHN in anemic newborns, reports on the association between FMH and PPHN are limited. It is unknown whether treatment of fetal anemia by intrauterine transfusions (IUTs) in cases of FMH affects the risk of PPHN at birth. To optimize care for pregnancies possibly complicated by FMH, clinicians should be aware of the risks of FMH and the possible diagnostic and therapeutic options. To increase the current knowledge, we first evaluated the incidence of PPHN and short-term neurologic injury in FMH cases. Second, we studied the potential protective effect of IUTs.

MATERIALS AND METHODS

Data on the neonates admitted to the neonatal intensive care unit of the Leiden University Medical Center (LUMC) are collected prospectively and consecutively entered into a medical database, as described previously.[10,11] We extracted all cases with FMH from this database admitted between January 2006 and January 2018. Inclusion criteria were 1) singleton live birth; 2) a diagnosis of FMH, defined as a calculated loss of more than 30 mL of fetal blood transfused into the maternal circulation, using the Kleihauer-Betke test[4] and 3) absence of a major structural heart defect or lung hypoplasia. This study was approved by the Medical Ethics Committee of the LUMC.

We recorded the presence of PPHN. Symptoms of PPHN were signs of respiratory distress (tachypnea, retractions, and grunting) and cyanosis. PPHN was then defined as severe hypoxemia (PaO_2 < 37.5–45 mm Hg in an FiO_2 of 1.0) requiring mechanical ventilation and inhaled nitric oxide treatment (selective pulmonary vasodilator).[12] Diagnosis of PPHN was only reached if right-to-left shunting in the ductus arteriosus was observed by echocardiography, in the absence of a structural heart defect or severe lung hypoplasia.[13] In addition, the following perinatal data were collected: maternal preeclampsia, maternal selective serotonin reuptake inhibitor use during pregnancy, IUTs, ultrasound data prior to IUT, preterm premature rupture of membranes, place of birth, gestational age at birth, birth weight, sex, mode of delivery, Apgar score at 5 minutes, (umbilical cord) blood gas analysis within 1 hour postnatally (pH, base excess, lactate), meconium aspiration syndrome, early-onset sepsis, perinatal asphyxia, severe brain damage, and mortality within 1 month after birth. The LUMC is the national referral center for fetal therapy; therefore, all IUTs are performed in this hospital. Early-onset sepsis was defined as a positive blood culture 72 hours or less postpartum (proven sepsis). Perinatal asphyxia was defined as the presence of three or more of the following criteria: nonreassuring cardiotocogram (CTG) patterns (sinusoidal, late decelerations, or loss of variability), umbilical cord artery pH of less than 7.10 and base deficit of 16 mmol/L or higher or lactate of greater than10 mmol/L, a 5-minute Apgar score of less than 5, failure of spontaneous breathing 5 minutes after birth, and onset of multiple organ failure. Severe brain injury was defined as moderate to severe hypoxic ischemic injury to the basal ganglia, thalamus, and/or cerebral cortex; severe white matter injury; periventricular leukomalacia Grade 2 or higher; infarction; intraparenchymal hemorrhage; intraventricular hemorrhage Grade 2 or higher; or cerebellar hemorrhage, as confirmed by cranial ultrasound and/or magnetic resonance imaging.

TABLE 1. Baseline characteristics of all FMH cases*

IUT	7 (24%)
Cesarean delivery	24 (83%)
Kleihauer-Betke test, cc	215 (129–300)
GA at birth, wk	36 (33–40)
Birth weight, g	2458 (1820–3096)
SGA	2 (7%)
Female gender	17 (59%)
Apgar ≤ 5 at 5 min	13 (45%)
Umbilical cord pH	7.1 (0.15)
Umbilical cord BE, mmol/L	−7.5 (−13.8 to −1.3)
Lactate, mmol/L	7.1 (1.6–12.6)
Hemoglobin at birth, g/L	3.6 (2.0–5.3)

*Values are presented as number (%) or median (interquartile range).
GA = gestational age; SGA = small for gestational age; BE = base excess.

Data were analyzed using computer software (SPSS version 23, IBM) and are reported as n (%) or median (interquartile range), as appropriate. We compared the groups treated with (IUT group) and without IUT (no-IUT group). Statistical analysis was performed using the Fisher's exact test or chi-square test for categorical variables and Mann–Whitney U test for continuous variables. A p value of less than 0.05 was considered significant. Because of the explorative character of the study, no power analysis for sample size calculations was performed.

RESULTS

A total of 29 singletons diagnosed with FMH were admitted to our neonatal intensive care unit between January 2006 and January 2018. None of the cases had lung hypoplasia. Severe PPHN occurred in 11 of the 29 (37.9%) newborns with FMH. The baseline characteristics of all FMH cases are depicted in Table 1. None of the following risk factors for PPHN were present: selective serotonin reuptake inhibitor use, preeclampsia, preterm premature rupture of membranes, or meconium aspiration syndrome. 26 of 29 patients reported reduced fetal movements, of whom three had a history of abdominal trauma and one had an external cephalic version earlier in pregnancy. Of the remaining three patients in whom fetal movements were not reduced, two had a forceps delivery (delayed second stage of labor and fetal distress, head entrapment at vaginal breech delivery) and one had a cesarean section because of an abnormal CTG prior to a planned

TABLE 2. Comparison between the IUT group and no-IUT group*

	All cases (n = 29)	IUT (n = 7)	No-IUT (n = 22)	p value
Cesarean delivery	24 (83%)	7 (100%)	17 (77%)	0.30
GA at birth, wk	36 (33–40)	31 (29–33)	37 (35–39)	0.00
Birth weight, g	2458 (1820–3096)	1710 (1313–2108)	2813 (2328–3296)	0.00
Apgar ≤ 5 at 5 minutes	13 (45%)	0	13 (59%)	0.01
Hemoglobin at birth, g/L	3.6 (2.0–5.3)	11.9 (10.23–13.6)	2.1 (1.8–5.0)	0.00
RBCTx at birth	27 (93%)	5 (71%)	22 (100%)	0.05
Perinatal asphyxia	9 (31%)	0	9 (41%)	0.07
Early onset sepsis	1 (3%)	1 (14)	0	0.24
PPHN	11 (38%)	1 (14%)	10 (46%)	0.20
Seizures	8 (28%)	0	8 (37%)	0.14
Outcomes				
Severe brain injury	10 (35%)	1 (14%)	9 (41%)	0.37
Mortality < 1 month	4 (14%)	0	4 (18%)	0.55

*Values are presented as the number (%) or median (interquartile range).
GA = gestational age; RBCTx = red blood cell transfusion.

external cephalic version. Seven cases (41%) were treated by at least one IUT. Thirteen neonates were born in the LUMC (44.8%), and 16 were born elsewhere (55.2%). Delivery by cesarean section occurred in 82.8% of the cases, in 21 of 24 because of a suboptimal CTG. Approximately one-half of the Kleihauer-Betke tests were performed before birth (55.2%). Four of 16 (25%) infants of mothers tested before birth developed PPHN, as compared to seven of 13 (53.8%) tested after birth (p = 0.14). Five of 17 females (29.4%) and six of 12 males (50%) developed PPHN (p = 0.26). One-third of neonates had perinatal asphyxia (9 of 29), of whom five developed PPHN (55.6%). One neonate had early-onset sepsis. Severe brain injury occurred in 10 of 29 (34.5%) newborns, and five of 11 (45.5%) and five of 18 (27.8%) in the group with and without PPHN, respectively (p = 0.43).

Table 2 shows the differences between the IUT group and the no-IUT group. The median gestational age at birth was 5 weeks earlier in the IUT group (31 vs. 37 weeks; p = 0.00). The hemoglobin level at birth was significantly higher in the IUT group; two of seven neonates did not need a red blood cell (RBC) transfusion at birth. The risk of PPHN in the group with and without IUT treatment was 14.3% (1 of 7) and 45.5% (10 of 22), respectively (p = 0.20). None of the neonates in the IUT group had perinatal asphyxia, as compared to nine of 22 (40.9%) in the non-IUT group (p = 0.07). Severe brain injury occurred in one of seven (14.3%) and nine of 22 (40.9%) newborns in the IUT group and no-IUT group, respectively (p = 0.37). The mortality rate was 13.8% (four of 29); none of the four were treated with an IUT.

Table 3 shows a detailed description of all FMH cases with IUT treatment. One patient had three IUTs, and the other six patients had one. All patients had a high peak systolic velocity of the middle cerebral artery in combination with an abnormal CTG (reduced variability or sinusoidal pattern), three patients had fetal hydrops, and one patient presented with fetal pleural effusion and cardiomegaly. In six patients, antenatal corticosteroid treatment for fetal lung maturation was administrated. The patient who did not receive steroids had an IUT at 32 + 5 weeks and delivered 3 days later by cesarean section because of a reduced variability on CTG. The interval between IUT and delivery varied between 1 and 6 days. In the patient with multiple IUTs, the time to delivery since the first and last IUT was 10 days and 1 day, respectively. In five patients, a cesarean section was performed because of signs of persistent fetal anemia (either a high peak velocity in the middle cerebral artery or a sinusoidal CTG). One patient had a suspected partial placental abruption on ultrasound, for which the pregnancy was terminated. One patient with FMH in the IUT group developed cystic periventricular leukomalacia.

Table 4 shows a detailed description of all FMH cases without IUT treatment. Four patients delivered before 34 weeks of gestation. Of these patients, all four received

TABLE 3. Detailed characteristics of all FMH cases with IUT treatment

Case	Mode of delivery	GA at birth (weeks)	BW (g)	Apgar ≤ 5 at 5 min	Hb at birth (g/L)	Number of RBCTx	EOS	Perinatal asphyxia	PPHN	Seizures	Severe brain damage	Alive after 1 month
1	CS	31	2080	No	3.5	2	No	No	Yes	No	No	Yes
2	CS	28	935	No	9.99	2	Yes	No	No	No	No	Yes
3	CS	28	1285	No	13.37	0	No	No	No	No	No	Yes
4	CS	30	1510	No	12.9	1	No	No	No	No	No	Yes
5	CS	32	2375	No	15.15	0	No	No	No	No	No	Yes
6	CS	32	1887	No	11.92	1	No	No	No	No	No	Yes
7	CS	33	1710	No	10.8	3	No	No	No	No	Cystic PVL	Yes

BW = birth weight; CS = cesarean section; EOS = early-onset sepsis; GA = gestational age; Hb = hemoglobin; PVL = periventricular leukomalacia; RBCTx = red blood cell transfusion.

TABLE 4. Detailed characteristics of all FMH cases without IUT treatment

Case	Mode of delivery	GA at birth (weeks)	BW (g)	Apgar ≤ 5 at 5 min	Hb at birth (g/L)	Number of RBCTx	EOS	Perinatal asphyxia	PPHN	Seizures	Severe brain damage	Alive after 1 month
1	CS	30	1336	No	2.6	4	No	No	Yes	No	No	Yes
2	CS	34	2680	Yes	1.9	2	No	Yes	Yes	Yes	Hypoxic ischemic injury to basal ganglia and thalami	Yes
3	CS	35	2280	Yes	3.1	1	No	Yes	Yes	No	Hypoxic ischemic injury to basal ganglia and thalami	Yes
4	CS	35	3000	Yes	2.9	2	No	No	Yes	No	No	Yes
5	CS	37	3340	Yes	6.5	3	No	No	Yes	No	No	Yes
6	CS	37	2635	Yes	2.7	2	No	Yes	Yes	Yes	Hypoxic ischemic injury to basal ganglia and thalami, cortex, white matter	No
7	Vaginal	38	3180	No	6.5	2	No	No	Yes	No	No	Yes
8	CS	39	3500	Yes	4.7	2	No	Yes + hypothermia	Yes	Yes	Hypoxic ischemic injury to basal ganglia and thalami, cortex, white matter	No
9	CS	39	2820	No	3.4	3	No	No	Yes	No	No	Yes
10	CS	40	3720	Yes	2.9	3	No	Yes + hypothermia	Yes	No	Hypoxic ischemic injury to cortex	Yes
11	CS	29	1435	Yes	2.9	3	No	No	No	No	No	Yes
12	CS	32	1850	No	3.54	2	No	No	No	No	No	Yes
13	CS	32	1732	No	3.54	3	No	No	No	No	No	Yes
14	CS	36	2950	Yes	3.22	2	No	No	No	No	No	Yes
15	Vaginal	36	2000	No	3.71	1	No	Yes	No	Yes	No	Yes
16	CS	37	3000	No	5.48	1	No	No	No	No	No	Yes
17	CS	38	2700	Yes	2.9	3	No	No	No	No	No	Yes
18	Vaginal	38	2805	No	5.32	3	No	No	No	No	No	Yes
19	CS	39	3180	Yes	3.54	2	No	Yes	No	Yes	Hypoxic ischemic injury to basal ganglia and thalami, cortex, white matter	Yes
20	Vaginal	39	2370	No	7.25	2	No	No	No	Yes	Hypoxic ischemic injury to basal ganglia and thalami, cortex, white matter	No
21	CS	39	3285	Yes	9.35	1	No	Yes + hypothermia	No	Yes	Hypoxic ischemic injury to basal ganglia and thalami, cortex, white matter	No
22	Vaginal	40	2950	Yes	12.41	2	No	Yes + hypothermia	No	Yes	Large bilateral cerebellar hemorrhage	Yes

BW = birth weight; CS = cesarean section; EOS = early onset sepsis; GA = gestational age; Hb = hemoglobin; RBCTx = red blood cell transfusion.

one dose of betamethasone (12 mg), three were referred to the LUMC but delivered before an IUT could be performed due to CTG tracings that urged immediate delivery, and one was delivered elsewhere. All neonates with severe brain injury (nine of 22) suffered from perinatal asphyxia.

DISCUSSION

To our knowledge, this is the first large case series reporting on the neonatal outcome after severe FMH in which we found a strong association between FMH and PPHN. The incidence of PPHN after birth in our study population of FMH newborns was strikingly high (11 of 29; 37.9%), which is almost 200 times higher compared with the reported incidence of 0.2% in live-born singleton neonates in the literature.[6] This finding supports the two previous case reports addressing the association between FMH and PPHN.[14,15]

The pathogenesis of PPHN is multifactorial and includes maternal and neonatal causes. Earlier studies report an increased risk in infants of mothers with preeclampsia, after fetal exposure to selective serotonin reuptake inhibitors, and in cases of neonatal sepsis, meconium aspiration syndrome, or perinatal asphyxia.[16-18] Neonatal anemia is also suggested to be a risk factor for PPHN.[7,8,11] This hypothesis is strongly supported by the findings of this study. In our cohort, in which almost all infants received an RBC transfusion after birth, there was a greatly increased risk of PPHN as compared to the general population. Anemia at birth may provoke PPHN through the cascade of hypoxia and neonatal asphyxia. Acute hypoxia as a result of anemia causes smooth muscle contraction in pulmonary arteries through a direct effect on intracellular calcium levels. Sustained hypoxia causes reduced activity of nitric oxide synthase at the level of pulmonary endothelium, leading to a reduction in nitric oxide synthesis.[19] Animal models have shown an increase in pulmonary vascular resistance following acute hypoxia.[9] The risk of PPHN is possibly even further increased if both anemia and perinatal asphyxia are present in the infant, as both conditions may lead to hypoxia and PPHN. The data of this study suggest, although not statistically significant due to a low number of patients, that treatment with IUT might have a protective effect for PPHN in cases of fetal anemia.

In addition, this study also shows that besides the risk of PPHN, FMH may have other serious consequences for neonates. The incidence of perinatal asphyxia and severe brain injury in our case series was 31% (nine of 29) and 35% (10 of 29), respectively. Both perinatal asphyxia and PPHN are known causes for adverse neurodevelopmental outcome.[20-22] In PPHN, the physiological delivery of oxygen to the brain and systemic organs is hampered because of right-to-left shunting. Therefore, we hypothesize that infants with asphyxia as a result of FMH, accompanied by PPHN, are likely to be exposed to a greater degree of disrupted brain perfusion and are therefore at greater risk of adverse neurologic outcome compared with those without PPHN. Severe brain injury occurred in 46% and 28% of cases with and without PPHN, respectively ($p = 0.43$). To prevent brain injury in asphyxiated newborns, therapeutic hypothermia is the only available treatment.[23,24] However, this treatment has been inconsistently reported to possibly worsen PPHN by inhibiting hypoxic pulmonary vasoconstriction in newborns.[24,25]

To avert these effects and the possible long-term sequelae of FMH, FMH should possibly be detected and receive prompt and adequate antenatal treatment. If FMH is suspected, either because of a history of abdominal trauma during the pregnancy or because of reduced fetal movements since most cases of FMH occur spontaneously, a Kleihauer-Betke test should be performed to measure the level of fetal erythrocytes in the maternal circulation. The fact that almost one-half of the Kleihauer-Betke tests were performed after birth could imply that fetal anemia due to FMH is poorly recognized by clinicians. Neonates could benefit from early recognition of anemia, a statement arguably substantiated by our finding that only in one-third of PPHN cases a Kleihauer-Betke test was performed before birth, implicating late recognition of anemia in the cases with adverse outcomes. Fetal condition is often assessed by CTG, but fetal anemia should be ruled out by cerebral Doppler (middle cerebral artery peak systolic velocity[26]) even if the CTG is reassuring.[27] If there are signs of fetal anemia, an IUT should be considered to correct the hemoglobin level before birth. If the pregnancy can be prolonged and the gestational age is below 34 weeks, corticosteroids are recommended. This approach for the antenatal management of suspected FMH is also suggested by others.[4] To our knowledge, our study is the first to indicate the possible protective effect of IUT for PPHN. Intrauterine correction of fetal anemia could facilitate cardiopulmonary transition after birth and may prevent acute hypoxia. As hypoxia is a known risk factor for PPHN, an IUT could result in a lower risk of PPHN. In addition, this study shows a trend toward a reduction in the risk of perinatal asphyxia and severe brain injury in the group treated with IUT. In our cohort, neonates who received an IUT were born 5 weeks earlier than neonates without IUT treatment. IUTs were generally not considered at advanced gestational age, mainly because these infants do not benefit from prolonging the pregnancy per se to provide antenatal corticosteroid treatment. Management of fetal anemia after 32 weeks of gestation also remains a matter of concern because of the good prospects of alternative extrauterine treatment. Results from this study do suggest, however, that IUTs could be beneficial to prevent complications from FMH. Another possible explanation for a better outcome in the IUT group could be that fetuses who experience FMH earlier in pregnancy have a better outcome because of their greater adaptive ability than fetuses near term. This may be supported by the finding of better outcomes in younger fetuses in the no-IUT group (three of four born before 34 weeks did not show signs of PPHN, asphyxia, or severe brain damage). Future (multicenter)

studies should investigate the protective effect of IUT for PPHN, perinatal asphyxia, and brain injury, which may result from fetal or neonatal anemia.

This case series has limitations due to the rarity of the disease. Because of its single-center design with a limited sample size, the comparative analyses are underpowered. It highlights the importance, however, of recognizing the presence of anemia as a result of FMH as a cause or at least a significant contributing factor for PPHN, by itself or along with other known factors. We advise that all patients with possible FMH be examined for fetal anemia by cerebral Doppler, and if possible treated by an IUT. Treatment with IUT might reduce the risk of PPHN and severe brain injury. Because the development of PPHN is difficult to predict and severe FMH may cause serious harm to newborns, we also advise that in cases of severe FMH, neonates should be delivered in a tertiary care center with inhaled nitric oxide treatment options.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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