Cardiovascular compromise in monochorionic twins

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PART III

POSTNATAL CIRCULATION

CHAPTER 6

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN IN TWIN-TWIN TRANSFUSION SYNDROME: A CASE-CONTROL STUDY

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ABSTRACT

Background: Persistent pulmonary hypertension of the newborn (PPHN) is associated with severe morbidity and mortality. Twin-twin transfusion syndrome (TTTS) is suggested to increase the risk of PPHN.

Objectives: To describe the incidence of PPHN in TTTS twins and to identify risk factors in TTTS twins for the development of severe PPHN.

Methods: Cases with severe PPHN were extracted from our monochorionic twin database (2002-2016). Severe PPHN was defined as severe hypoxemia requiring mechanical ventilation and inhaled nitric oxide (iNO) treatment, confirmed by strict echocardiographic criteria. A case-control comparison within TTTS survivors was conducted to identify risk factors for PPHN.

Results: The incidence of PPHN in TTTS twins was 4% (24/598, 95% confidence interval [CI] 2.7-5.9%) and 0 4% (2/493, 95% CI 0.1-1.5%) in uncomplicated monochorionic twins (odds ratio [OR] 10.3, 95% CI 2 4-43.9, p = 0.002). Two risk factors were independently associated with PPHN: severe prematurity (OR 3.3, 95% CI 1.0-11.4) and recipient status (OR 3.9, 95% CI 1 4-11.0). In TTTS recipients, another risk factor for PPHN is anemia at birth (OR 7 2, 95% CI 1.8-29.6).

Conclusion: Clinicians caring for neonates with TTTS should be aware of the 10-fold increased risk of PPHN compared to uncomplicated monochorionic twins. PPHN occurs more often in case of premature delivery and in recipient twins, particularly in the presence of anemia at birth. As the development of severe PPHN is difficult to predict, we advise that all TTTS twins should be delivered in a tertiary care center with iNO treatment options.

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is the result of failure of the normal circulatory transition after birth. An inadequate decrease in pulmonary vascular resistance (PVR) leads to a high right-ventricular pressure and the shunting of non-oxygenated blood from the pulmonary to the systemic circulation, resulting in systemic arterial hypoxaemia.[1] Severe PPHN has an estimated incidence of two per 1,000 live births[2] and is associated with significant morbidity and mortality.[1]

The pathogenesis of PPHN is multifactorial and includes maternal and neonatal causes. There is an increased risk in the infants of mothers with asthma, diabetes or obesity, and in case of fetal exposure to certain drugs.[3] Known effects are the early closure of the ductus arteriosus due to exposure to non-steroidal anti-inflammatory drugs,[4] and pulmonary vascular remodeling due to exposure to selective serotonin re-uptake inhibitors.[5, 6]

Another cardiovascular disorder that is suggested to increase the risk of PPHN is twin-twin transfusion syndrome (TTTS).[7, 8] TTTS affects 10-15% of monochorionic twin pregnancies and results from unbalanced intertwin blood transfusion through placental vascular anastomoses, that leads to hypovolemia and oligohydramnios in the donor and hypervolemia and polyhydramnios in the recipient.[8, 9] Two small case series reported an incidence of severe PPHN of 26-30/1,000 TTTS newborns, most of which were recipients.[10, 11] Up to 70% of recipients show echocardiographic signs of anatomical or functional cardiac compromise at the time of diagnosis of TTTS, as a result of both increased PVR from vasoactive substances and volume overload.[12, 13] This chronic volume loading might cause remodeling of the pulmonary vasculature, which could result in neonatal PPHN.

The objectives of this study were to describe the incidence of PPHN in TTTS twins and to identify risk factors for the development of PPHN in TTTS survivors, and in recipient twins in particular.

METHODS

All live born monochorionic twins (single or double live births) delivered at our center between March 2002 and September 2016 were eligible for this study. The Leiden University Medical Center (LUMC) is the national referral center for TTTS in the Netherlands. All monochorionic twins admitted to our neonatal intensive care unit (NICU) are prospectively entered into a dedicated medical database, as described previously.[10] We excluded triplets, acardiac twins, twin pairs with spontaneous twin anemia polycythemia sequence (TAPS) or selective fetal growth restriction (defined as a birth weight discrepancy > 25%), twin pairs in which selective feticide was performed, neonatal demises, and those with a major structural heart defect (including right ventricular outflow tract obstruction) or severe lung hypoplasia.

We searched our database for all neonates who were affected by severe PPHN. Severe PPHN was defined as severe hypoxemia (PaO_2 < 37.5-45 mmHg in a FiO_2 of 1.0) requiring mechanical ventilation and inhaled nitric oxide (iNO) treatment. A diagnosis of PPHN was only reached if right-to-left shunting in the ductus arteriosus was observed on echocardiography in the absence of a structural heart defect or severe lung hypoplasia.[14] Echocardiography is performed routinely in all infants admitted to our NICU with severe hypoxemia and the suspicion of PPHN. In order to make a clear distinction between primary PPHN and PPHN secondary to lung injury and prolonged mechanical ventilation in extreme premature neonates with bronchopulmonary dysplasia, our study included only cases of PPHN detected on the first day of life.

The following data concerning TTTS were retrieved from the database: Quintero stage at diagnosis, recipient or donor status, type of treatment for TTTS (expectant management/ amniodrainage/ fetoscopic laser surgery [FLS]/ selective feticide), gestational age (GA) at the time of FLS and the occurrence of post-laser TAPS. A diagnosis of TTTS was based on standard European diagnostic ultrasound criteria.[15] The following neonatal data was recorded: GA at birth, anemia at birth requiring a red blood cell transfusion within 24 hours postpartum, and perinatal asphyxia. Perinatal asphyxia was defined as the presence of ≥ 3 of the following criteria: non-reassuring cardiotocogram patterns, umbilical cord artery pH < 7.10 and base deficit ≥ 16 mmol/L or lactate > 10 mmol/L, a 5-min Apgar score of < 5, failure to achieve spontaneous breathing 5 min after birth, and the onset of multiple organ failure. In TTTS cases, the status of the donor or the recipient was recorded according to the status in utero, and remained registered as such, also in post-laser TAPS cases. Therefore, in case of reversal of the intertwin transfusion after laser (in post-laser TAPS cases), the initial recipient was still recorded as the recipient after birth.

Statistical analysis

First, an analysis was performed to estimate the incidence of PPHN in both TTTS and uncomplicated monochorionic twins. Second, a case-control comparison was conducted to identify risk factors for PPHN in neonates with TTTS. TTTS neonates with PPHN were considered as cases and those without PPHN were considered as controls. Since recipient twins are already known to be at an increased risk of PPHN, we also performed risk analyses within the subgroup of recipients. The data were analyzed using SPSS v23 (IBM, USA) and reported as n (%) or median (interquartile range [IQR]). An analysis of risk factors possibly predicting PPHN was conducted using univariate and multivariate logistic regression models with a generalized estimating equation approach to account for the fact that observations of twin pairs are not independent. The following potential predictors for severe PPHN were studied in a univariable logistic regression model: Quintero stage, recipient status (compared with donor), treatment for TTTS, GA at the time of FLS, post-laser TAPS, severe prematurity (GA at birth < 32 weeks), anemia at birth, and perinatal asphyxia. The multivariate logistic regression model included all variables that showed a significant association in the univariate analyses. The results are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). The level of significance was set at $p < 0.05$. This study was approved by the Medical Ethics Committee of the LUMC.

RESULTS

A total of 1,347 live born monochorionic twins were delivered in our obstetrical department and admitted to our NICU between March 2002 and September 2016. A total of 1,091 newborns were included for analyses; 598 were TTTS twins and 493 were uncomplicated monochorionic twins (Figure 1). A total of 39 TTTS twins and 10 uncomplicated monochorionic twins were single survivors after the fetal demise of the co-twin. Severe PPHN occurred in 26 of the 1,091 (2.4%) liveborn monochorionic twins. The incidence of severe PPHN was 4% (24/598, 95% CI 2.7-5.9%) in the TTTS twins and 0.4% (2/493, 95% CI 0.1-1.5%) in the uncomplicated monochorionic twins (OR 10.3, 95% CI 2.4-43.9, p = 0.002).

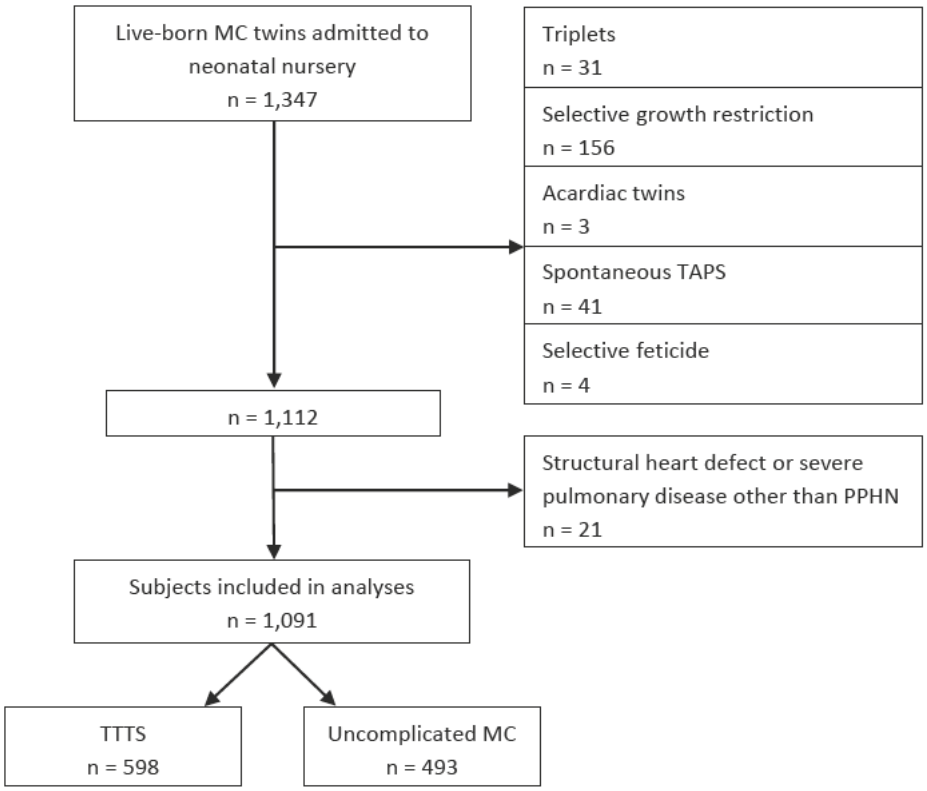

Figure 1. Flow chart showing the derivation of the study population. TAPS, twin anaemia polycythaemia sequence; MC, monochorionic

Table 1 shows possible risk factors for PPHN in TTTS newborns. The 24 TTTS newborns with PPHN were considered as cases and the 574 without PPHN as controls. We found no differences in Quintero stage at diagnosis, type of TTTS treatment, GA at the time of FLS, post-laser TAPS, or the occurrence of asphyxia between cases and controls. More recipients were affected by PPHN than donors; 75% of twins in the group of TTTS twins with PPHN were recipients versus 49% in the group without PPHN (OR 3.1, 95% CI 1.3-7.3). PPHN occurred more often in cases of severe prematurity (83 vs. 43%; OR 6.7, 95% CI 2.2-20.0) and with anemia at birth (25 vs. 8%; OR 3.8, 95% CI 1 4-10.4). The multivariable model only confirmed a significant independent association between PPHN and severe prematurity (OR 3.3, 95% CI 1.0-11 4) and recipient status (OR 3.9, 95% CI 1.4-11.0). The median length of the period from FLS to birth was 2 weeks less in the group with PPHN (10 vs. 12 weeks; crude OR 1.82 for each week younger, 95% CI 1.7-1.9, p = 0.006). In the TTTS recipients, post-laser TAPS (indicating incomplete FLS) contributed to a higher risk of PPHN in the univariate analysis (35 vs. 13% of recipients treated by FLS; OR 3.8, 95% CI 1 4-10.4). No difference in GA at the time of FLS was found. We found an independent association between PPHN and severe prematurity (OR 4.4, 95% CI 1.4-13.7) and between PPHN and anemia at birth (OR 7 2, 95% CI 1.8-29.6). One third of anemic ex-recipients developed PPHN (Table 2).

Table 3 shows the characteristics of all PPHN cases. All PPHN cases with post-laser TAPS were anemic at birth, demonstrating a reversal of the intertwin transfusion after laser. One (untreated) recipient was anemic because of acute peri-mortem transfusion after the intrauterine demise of the donor twin.

Table 1. Possible risk factors associated with PPHN in TTTS newborns

Risk factors	**PPHN (n = 24)**	**No PPHN (n = 574)**
Quintero stage		
I	4 (17)	103 (18)
II	8 (33)	169 (29)
III	11 (46)	270 (47)
IV	1 (4)	30 (5)
V	0 (0)	2 (0)
Recipient status	18 (75)	283 (49)
Treatment		
Fetoscopic laser surgery	21 (88)	496 (86)
Amniodrainage	1 (4)	47 (8)
Expectant management	2 (8)	31 (5)
GA at laser, weeks	19 (17 - 21)	20 (18 - 23)
Post-laser TAPS	6 (29[a])	65 (13[a])
Gestational age at birth		
< 32 weeks	20 (83)	246 (43)
≥ 32 weeks	4 (17)	328 (57)
Anemia at birth	6 (25)	46 (8)
Asphyxia	1 (4)	4 (1)

Data are presented as n (%) or median (IQR). PPHN, persistent pulmonary hypertension of the newborn; OR, odds ratio; CI, confidence interval; GA, gestational age;
[a] In TTTS twins treated by FLS.

Table 2. Possible risk factors associated with PPHN in TTTS recipients

Risk factors	**PPHN (n = 18)**	**No PPHN (n = 283)**
GA at laser, weeks	19 (17 - 21)	20 (18 - 23)
Post-laser TAPS	6 (35[a])	32 (13[a])
Gestational age at birth		
< 32 weeks	14 (78)	118 (42)
≥ 32 weeks	4 (22)	165 (58)
Anemia at birth	6 (33)	13 (5)

Data are presented as n (%) or median (IQR). PPHN, persistent pulmonary hypertension of the newborn; OR, odds ratio; CI, confidence interval; GA, gestational age;
[a] In TTTS twins treated by FLS.

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
	-	0.86	-	-
	3.1 (1.3 - 7.3)	**0.01**	3.9 (1 4 - 11.0)	**0.01**
	-	0.77	-	-
	0.9 (0.8 - 1.0)	0.20	-	-
	2.5 (1.0 - 6.5)	0.06	-	-
	6.7 (2.2 - 20.0)	**<0.01**	6.0 (1.9 - 19.1)	**<0.01**
	3.8 (1.4 - 10.5)	**0.01**	3.3 (1.0 - 11 4)	0.06
	6.2 (0.6 - 64 4)	0.13	-	-

TAPS, twin anemia polycythemia sequence.

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
	0.9 (0.8 - 1.1)	0 25	-	-
	3.8 (1 4 - 10.4)	**0.01**	1.4 (0.4 - 4.9)	0.64
	4.9 (1.6 - 15.1)	**0.01**	4.4 (1 4 - 13.7)	**0.01**
	10.4 (3.4 - 32.2)	**<0.01**	7 2 (1.8 - 29.6)	**0.01**

TAPS, twin anemia polycythemia sequence.

Table 3. PPHN cases in TTTS and uncomplicated monochorionic twin pregnancies

	Donor or Recipient	Quintero stage	Treatment	GA at laser, weeks
1	Recipient	Q2	FLS	23
2	Recipient	Q2	FLS	18
3	Recipient	Q2	FLS	19
4	Recipient	Q3	FLS	19
5	Recipient	Q2	FLS	20
6	Recipient	Q3	FLS	27
7	Recipient	Q3	FLS	16
8	Recipient	Q3	FLS	18
9	Recipient	Q1	FLS	17
10	Recipient	Q2	FLS	17
11	Recipient	Q1	FLS	21
12	Recipient	Q2	FLS	16
13	Recipient	Q3	FLS	23
14	Recipient	Q3	FLS	18
15	Recipient	Q3	FLS	16
16	Recipient	Q4	FLS	20
17	Recipient	Q3	FLS	20
18	Donor	Q2	FLS	19
19	Donor	Q3	FLS	18
20	Donor	Q2	FLS	17
21	Donor	Q3	FLS	23
22	Recipient	Q1	Expectant	-
23	Donor	Q1	Expectant	-
24	Donor	Q3	Amniodrainage	-
25	Normal MC	-	-	-
26	Normal MC	-	-	-

GA, gestational age; TAPS, twin anemia polycythemia sequence; Q, Quintero stage; FLS, fetoscopic laser surgery; alive, alive at time of discharge/transfer to secondary care center; MC, monochorionic twin.

GA at birth, weeks	Post-laser TAPS	Anemia at birth	Outcome
26	Yes	Yes	Neonatal death
27	Yes	Yes	Alive
27	No	No	Alive
27	No	No	Alive
28	Yes	Yes	Neonatal death
28	No	No	Neonatal death
28	No	No	Alive
28	No	No	Alive
29	No	No	Alive
29	No	No	Alive
30	No	No	Alive
31	No	No	Alive
31	No	No	Alive
33	Yes	Yes	Neonatal death
33	No	No	Alive
33	Yes	Yes	Alive
33	No	No	Alive
27	No	No	Alive
28	No	No	Alive
29	No	No	Alive
29	No	No	Alive
29	-	Yes	Alive
24	-	No	Neonatal death
30	-	No	Neonatal death
30	-	No	Alive
32	-	Yes	Alive

DISCUSSION

In our cohort of TTTS twins, the incidence of severe PPHN requiring iNO at birth was increased 10-fold compared to in monochorionic twins without TTTS (4 vs. 0.4%). This study confirms the previously noted association between PPHN and TTTS, although the incidence of 4% was slightly higher than the previously reported incidence of 2.6-3%.[10, 11] Differences across studies may be due to methodological differences including variations in the criteria for PPHN and small sample sizes. The strict diagnostic criteria for severe PPHN in our study and the large sample size meant that the incidence could be estimated more accurately.

We found two risk factors that were independently associated with severe PPHN: a younger GA at birth and a recipient status. Previous studies already identified recipient twins as being at an increased risk of PPHN.[10, 11] The relatively high incidence of PPHN in TTTS found in this study, particularly in preterm deliveries and in recipients, could have several explanations. First, preterm delivery and severe anemia are common problems in TTTS.[16, 17] Severe anemia is often present in TTTS cases after incomplete laser surgery due to persistent intertwin blood transfusion through residual anastomoses. Severe anemia at birth may lead to acute hypoxia, which leads to vascular remodeling and increased PVR[18] that result in PPHN. The association with severe prematurity and PPHN is less clear. Although the incidence of PPHN in premature newborns is thought to be lower than in term or near-term newborns,[19] a recent study showed a higher risk of PPHN in late preterm infants than in term infants.[20] In TTTS twins, preterm birth comprises a higher risk of PPHN. Importantly, association does not mean causation. As the GA at laser was similar in the cases and the controls, and prematurity correlated strongly with PPHN, a shorter period from FLS to birth could also explain the higher risk of PPHN observed. In our cohort, the median length of this period was two weeks less in the group with PPHN. It might take several months for damaged pulmonary vasculature to recover from high volume-load damage, so an early birth could lead to high PVR and PPHN. Other factors linked to preterm birth such as premature prolonged rupture of the membranes, inflammation due to chorioamnionitis, or perinatal sepsis may be related to the development of PPHN. This could also explain the increased occurrence of PPHN in recipients after FLS, as these twins are at increased risk of iatrogenic rupture of the membranes, chorioamnionitis, and sepsis.[21, 22] Unfortunately, due to the retrospective nature of this study, we did not systematically record the presence of these factors.

Another explanation for the high incidence is based on the cardiac adaptation to TTTS. In TTTS, cardiac function is especially compromised in recipients. Chronic volume loading causes remodeling of the pulmonary vasculature, which contributes to the development of PPHN.[12, 13] Although cardiac function usually improves within a few weeks after FLS, abnormalities of the pulmonary vasculature may persist despite complete laser surgery being performed, and this could lead to PPHN. As an analogy, right ventricular outflow tract obstruction also occurs in recipients despite complete laser surgery and can result in abnormal development of the pulmonary valve and subsequent pulmonary stenosis or atresia.[24] In cases of incomplete laser surgery and the existence of residual anastomoses, the cardiac burden may be prolonged. As shown in this study, incomplete laser surgery was identified as a risk factor for PPHN in TTTS recipients, with one-third of the recipients who were anemic at birth developing PPHN after post-laser TAPS. We propose a 'double hit theory' for anemic recipients after post-laser TAPS: the baseline increased risk of PPHN due to increased PVR is further increased by acute hypoxia as a result of anemia at birth. Therefore, in cases of detected or suspected post-laser TAPS, clinicians should be aware of the extremely increased risk of PPHN in anemic recipients.

We found an increased incidence of PPHN in donors (2%) versus in uncomplicated MC twins (0.4%) or all live births (0.2%). In donor twins, cardiac output is reduced as a result of hypovolemia. Since cardiac output is essential in determining systemic oxygen transport, hypovolemia could cause hypoxia and lead to pulmonary endothelial adaptation.[18] We excluded twin pairs with a birth weight discrepancy of > 25%, so the supposed hypothesis of a higher risk of PPHN as a result of lower arginine levels in growth-restricted donors[25, 26] cannot be substantiated by this study.

This study has certain strengths and limitations. The LUMC is the national referral center for TTTS in the Netherlands. As a result, a large database of TTTS twins has been created, in which rare outcomes can be investigated. Nevertheless, the absolute number of PPHN cases was still relatively small, so some of the risk factor analyses may be underpowered. We only included severe PPHN cases, since such infants require prompt treatment. Mild PPHN cases without the need for iNO treatment were not included. No additional prenatal findings were recorded, e.g. flow velocities over the aorta and pulmonary artery. These findings might predict the development of PPHN and could be a subject of further research.

CONCLUSIONS

Clinicians caring for neonates with (treated) TTTS should be aware of the 10-fold increased risk of PPHN compared to in uncomplicated monochorionic twins. PPHN occurs more often in recipients and after premature delivery. As the development of severe PPHN is difficult to predict, we advise that all TTTS twins should be delivered in a tertiary care center with iNO treatment options.

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CHAPTER 7

CONGENITAL HEART DEFECTS IN MONOCHORIONIC TWINS:
A SYSTEMATIC REVIEW AND META-ANALYSIS

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