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Increased Risk of Persistent Pulmonary Hypertension of the Newborn in Twin Anaemia Polycythaemia Sequence Donors

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Keywords
Twin anaemia polycythaemia sequence · Persistent pulmonary hypertension of the newborn · Severe foetal anaemia · Respiratory complications

Abstract

Introduction: This study aimed to describe the prevalence and risk factors for respiratory complications in monochorionic twins with twin anaemia polycythaemia sequence (TAPS). ***Methods:*** All neonates diagnosed with postnatal TAPS at our center between 2002 and 2023 were included in this retrospective study. The primary outcome was the prevalence of respiratory complications, including respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), and persistent pulmonary hypertension of the newborn (PPHN). Secondary outcomes included need of respiratory support during admission and a risk factor analysis for adverse respiratory outcome. ***Results:*** In our study of 100 postnatally diagnosed TAPS pregnancies, 32% (62/199) experienced RDS and 13% (25/199) had BPD, with no difference between donors and recipients. PPHN occurred in 7% of cases, more frequently in donors (11%, 11/100) than in recipients (3%, 3/100) (OR = 1.3, 95% CI: 0.2–2.6). Lower gestational age at birth and severe foetal anaemia were found to be significant independent risk factors associated with PPHN in TAPS twins (OR = 0.3, 95% CI: 0.1–0.5), respectively (OR = 1.9, 95% CI: 0.8–3.1). ***Conclusion:*** TAPS donor twins have a fourfold increased risk of PPHN due to anaemia compared to recipient twins. Given the life-threatening nature of PPHN, TAPS twins should be born in hospitals equipped to treat it.

Plain Language Summary

Twin anaemia polycythaemia sequence (TAPS) is a condition in identical twins, occurring in the womb and causing one twin to have too little blood (known as anaemia) and the other to have too much (known as polycythaemia). This can lead to various health problems in TAPS newborns from blood issues up to severe brain damage and even death. Breathing problems could occur due to their abnormal blood conditions. In our study, the prevalence of several adverse neonatal breathing conditions like persistent pulmonary hypertension of the newborn (PPHN), bronchopulmonary dysplasia (BPD), and respiratory distress syndrome (RDS) were studied. PPHN is a condition where blood vessels in the lungs of babies do not open properly, making it hard for babies to get enough oxygen into their blood. In BPD, the neonate's lungs get inflamed and damaged, most often because of a prolonged time of ventilation. RDS happens because the baby's lungs are not fully

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developed and cannot make enough surfactant, a substance that helps the lungs expand and stay open. This study aimed to investigate these breathing problems in TAPS twins and to identify potential risk factors for the development of these respiratory complications.

Introduction

Twin anaemia polycythaemia sequence (TAPS) results from chronic unbalanced feto-foetal transfusion through minuscule placental anastomoses in monochorionic twin pregnancies, leading to anaemia in the donor and polycythaemia in the recipient twin [1]. Neonatal morbidity in TAPS may vary from haematologic complications up to severe cerebral injury and perinatal death [2].

In TAPS, not much is known about the respiratory condition of the neonates. Aside from the respiratory problems related to prematurity, both TAPS donors and recipients might have an increased risk for respiratory complications due to their abnormal haemoglobin values. In TAPS donors, anaemia-induced hypoxia in donor twins may cause pulmonary vasoconstriction in the lungs, which may lead to persistent pulmonary hypertension of the newborn (PPHN) [3–5]. In TAPS recipients on the other hand, polycythaemia may lead to sluggish blood flow in the small pulmonary vessels, impairing adequate exchange of oxygen and carbon dioxide in the alveoli [6]. As a result, TAPS recipients may experience respiratory distress or other breathing difficulties after birth. Aside from the respiratory effects of anaemia, TAPS donors may also be more prone to developing bronchopulmonary dysplasia (BPD) due to foetal growth restriction, which affects approximately 50% of TAPS donor twins [7].

Owing to the low incidence of TAPS, data on respiratory neonatal outcome are scarce. As severe respiratory complications can greatly impact short- and long-term outcome, more studies are needed to improve our knowledge and future perinatal care. To investigate respiratory outcome in TAPS, we set up a study to assess the prevalence of respiratory complications, comparing outcomes between donors and recipients, and identify potential risk factors for adverse respiratory outcome.

Methods

For this study, all monochorionic twins diagnosed with TAPS postnatally at the Leiden University Medical Centre (LUMC) between 2002 and 2023 were considered eligible. Cases were included when they met the postnatal criteria for TAPS, defined as an intertwin haemoglobin difference >8 g/dL, together with either a reticulocyte ratio >1.7 or the presence of miniscule anastomoses (diameter <1 mm) on the placental surface identified through colour dye injection [8]. TAPS cases with lacking records on respiratory outcome, were considered lost to follow-up and were excluded from this study.

Data on maternal, foetal, and neonatal outcome were retrospectively collected from patient records. The following obstetric data were retrieved: gravidity, parity, antenatal stage of TAPS, type of TAPS (spontaneous or post-laser), antenatal management for TAPS, gestational age (GA) at birth and type of delivery (vaginal birth or caesarean section). Antenatal TAPS was staged according to the previously published staging system by Slaghekke et al. [9]. For antenatal TAPS management, the type of management was registered: expectant management, preterm delivery, intrauterine transfusion (IUT) with or without partial exchange transfusion (PET), fetoscopic laser surgery, selective foeticide or termination of pregnancy.

Neonatal characteristics that were collected included birth weight, small-for-gestational age (SGA; birth weight <10th percentile) and foetal growth restriction (FGR; birth weight <3rd centile) according to the charts of Hoftiezer et al. [10], Apgar score (after 1, 5, and 10 min), arterial umbilical cord pH and presence of severe foetal anaemia defined as the need for blood transfusion within the first 24 h after birth.

Respiratory complications included RDS, BPD, or PPHN. RDS was diagnosed based on the need of mechanical ventilation and/or surfactant administration. Diagnosis of RDS was confirmed by a chest X-ray [11]. The definition of BPD varies based on GA. For infants born at a GA less than 32 weeks, BPD was defined as the need for more than 21% oxygen for at least 28 days, followed by an assessment at 36 weeks post-menstrual age or at discharge, whichever occurs first. In infants born at a GA greater than 32 weeks, BPD was defined as the requirement for supplemental oxygen (<21%) for at least 28 days but fewer than 56 days postnatal age or until discharge, whichever comes first. BPD was classified as mild (no oxygen requirement), moderate (<30% oxygen requirement) or severe (<30% oxygen requirement or the need for positive pressure ventilation/continuous positive pressure) [12]. Diagnosis of PPHN was reached if signs of respiratory distress and cyanosis were present requiring mechanical ventilation and inhaled nitric oxide (iNO) treatment. PPHN was then defined as severe hypoxaemia (PaO2 <37.5–45 mm Hg in a FiO2 of 1.0) and was confirmed by echocardiography if right-to-left shunting

in the patent ductus arteriosus was observed, in the absence of a structural heart defect or severe lung hypoplasia [13]. Other echocardiographic signs that were used to evaluate the severity of PPHN included tricuspid regurgitation, right ventricular dilatation, and leftward deviation of the interventricular septum.

To evaluate these respiratory complications in TAPS neonates after birth, the following data were collected: the respiratory support needed after birth, the need for surfactant application and the need for iNO treatment during NICU admission. Respiratory support during NICU admission was categorized into two main types: invasive and non-invasive. Invasive respiratory support refers to the requirement for conventional ventilation or high frequency oscillation ventilation (HFOV). Non-invasive respiratory support is characterized by the need for low flow, high flow, or continuous positive airway pressure.

Primary outcome was the prevalence of respiratory complications, including RDS, BPD, and PPHN. Secondary outcomes included need of respiratory support during NICU admission and a risk factor analysis for adverse respiratory outcome.

Statistical analysis was performed using SPSS version 25 (IBM, Armonk, NY, USA). Data are reported as *n* (%) or median (interquartile ranges [IQR]). TAPS donors were compared to recipients using generalized estimating equations module for categorical data and paired *t*-test for continuous variables. Analysis of potential risk factors predicting adverse respiratory outcome in TAPS twins was conducted using univariate logistic regression model with a generalized estimating equation approach to adjust for the fact that observations in twin pairs are not independent. These risk factors were checked for correlation using Pearson's square (*r*). An *r* value of >0.7 or <−0.7 was considered to indicate a strong relationship between factors. A multivariate logistic regression model was applied to the variables that showed significant association in the univariate analysis. Results are expressed as odds ratios (OR) with 95% confidence intervals. A *p* value of 0.05 or lower was regarded as statistically significant. For this study protocol, the Medical Research Ethics Committee Leiden Den Haag Delft stated that the Medical Research Involving Human Subjects Act does not apply to the above mentioned study and is therefore exempted from review.

Results

Of the 176 TAPS pregnancies between 2002 and 2023, 62 did not meet the postnatal TAPS criteria and were consequently excluded. In 8% (14/176) of TAPS pregnancies, there was a lack of information regarding the respiratory outcome or the cases were lost to follow-up. The derivation of the study population is presented in Figure 1. Baseline characteristics of the study population are shown in Table 1. In 76% (76/100) of the included pregnancies, TAPS was diagnosed antenatally. Antenatal therapy for TAPS consisted of expectant management in 51% (39/76), intrauterine transfusion with or without PET in 33% (25/76), unsuccessful fetoscopic laser surgery in 9% (7/76), and immediate delivery in 7% (5/76). Median GA at birth was 32.4 weeks (IQR: 29.7–34.6). 39% (39/100) of the donors were affected by foetal growth restriction (birth weight <3rd percentile) compared to 8% (8/100) of the recipients. Severe foetal anaemia occurred in 74% (74/100) of donors and 0% (0/100) of the recipients.

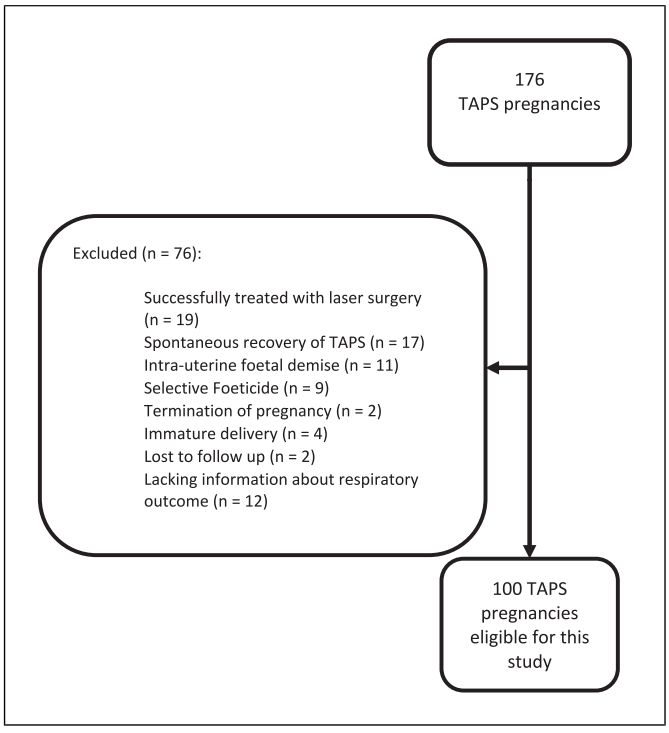

Fig. 1. Flowchart showing derivation of study population. TAPS, twin anaemia polycythaemia sequence.

Respiratory Complications

Overall, PPHN was found in 7% (14/200) of TAPS twins and occurred significantly more often in donors than in recipients, 11% (11/100) versus 3% (3/100), respectively ($p = 0.028$) (Table 2). Tricuspid regurgitation, right ventricular dilatation, and leftward deviation of the interventricular septum were measured in 13/14 twins with PPHN and in 85% (11/13) of them, these

Table 1. Baseline characteristics of the 100 TAPS pregnancies included in this study

	Total (*N* = 100 pregnancies, *N* = 200 foetuses)	TAPS donors (*N* = 100)	TAPS recipients (*N* = 100)
Gravidity	2 (1–3)		
Parity	1 (0–1)		
Sex (female)	45/100 (45)		
GA at diagnosis, weeks	25.3 (21.9–28.4)		
TAPS diagnosed antenatally	76/100 (25)		
Antenatal TAPS stage			
Stage 1	32/76 (21)		
Stage 2	42/76 (55)		
Stage 3	15/76 (20)		
Stage 4	3/76 (4)		
Type of TAPS			
Spontaneous	54/100 (54)		
Post-laser	47/100 (47)		
Antenatal management			
Expectant management	39/76 (51)		
IUT (with or without PET)	25/76 (33)		
Fetoscopic laser surgery	7/76 (9)		
Immediate delivery	5/76 (7)		
Caesarean section	44/100 (56)		
GA at birth, weeks	32.4 (29.7–34.6)		
Birth weight, g	1,608 (1,169–1,980)	1,480 (1,068–1,848)	1,750 (1,284–2,145)
Birth weight <p3[a]	47/200 (23)	39/100 (39)	8/100 (8)
Birth weight <p10[a]	84/200 (42)	62/100 (62)	22/100 (22)

Data are presented as median (IQR) or *n*/*N* (%). TAPS, twin anaemia polycythaemia sequence; IUT, intrauterine transfusion; PET, partial exchange transfusion; GA, gestational age. [a]2 missing values: 1 TAPS donor and 1 TAPS recipient with lacking data about birth weight.

echocardiographic findings were observed. A total of 31% (62/199) of TAPS twins developed RDS, and in 13% (25/199) of TAPS twins BPD was diagnosed. There was no significant difference in prevalence of RDS and BPD between TAPS donors and recipients.

Respiratory Support

After birth, TAPS donors had a significant lower Apgar score compared to recipients, both at 1 and 5 min (7; IQR 4–8 vs. 8; IQR 6–9, $p < 0.001$) and (8; IQR 7–9 vs. 9; IQR 7–9, $p = 0.031$), respectively. Table 3 shows data regarding respiratory support in TAPS twins during NICU admission. There was no statistical difference found in need for respiratory support ($p = 0.100$) or duration of respiratory support ($p = 0.368$) between TAPS donors and recipients. In terms of mechanical ventilation, TAPS donors more often needed HFOV (14%, 14/100), compared to their recipient co-twins (6%, 6/100) ($p = 0.024$).

Risk Factors for PPHN

Table 4 summarizes the characteristics of TAPS twins with PPHN. Among the cohort of 14 TAPS twins diagnosed with PPHN, the observed death rate was approximately 29% (4/14). Importantly, all instances of mortality involved donor twins, resulting in a mortality rate of 36% (4/11) among donors with PPHN. In one of these cases, the neonate died due to severe PPHN, which was refractory to both to iNO and sildenafil treatment. In two other cases, despite treatment with iNO for PPHN, the neonates did not improve. These cases were complicated by multiple factors, including respiratory failure associated with severe BPD and intracranial haemorrhage. After considering the poor prognosis due to the multiple severe underlying conditions, the decision was made to discontinue supportive care. The fourth case involved a neonate who developed PPHN shortly after birth and responded well to iNO treatment. Despite this

Table 2. Respiratory complications in TAPS twins during NICU admission

	Total (*N* = 200)	TAPS donors (*N* = 100)	TAPS recipients (*N* = 100)	*p* value
RDS	63/199[a] (32)	29/99 (29)	34/100 (34)	0.291
BPD	25/199[a] (13)	13/99 (13)	12/100 (12)	0.730
Mild	15/25 (60)	8/13 (62)	7/12 (58)	
Moderate	5/25 (20)	2/13 (15)	3/12 (25)	
Severe	5/25 (20)	3/13 (23)	2/12 (17)	
PPHN	14/200 (7)	11/100 (11)	3/100 (3)	**0.028**

Data are presented as *n*/*N* (%). RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; PPHN, persistent pulmonary hypertension of the newborn. [a]1 missing value: 1 TAPS donor with lacking data about prevalence of RDS and BPD.

Table 3. Respiratory support in TAPS twins during NICU admission

	Total (*N* = 200)	TAPS donors (*N* = 100)	TAPS recipients (*N* = 100)	*p* value
Apgar score				
After 1 min	8 (5–9)	7 (4–8)	8 (6–9)	<**0.001**
After 5 min	8 (7–9)	8 (7–9)	9 (7–9)	**0.031**
After 10 min	9 (9–10)	9 (8–9)	9 (8–10)	0.060
Intubation at birth	12/199[a] (6)	6/99 (6)	6/100 (6)	0.992
CPAP to NICU	107/199[a] (54)	51/99 (52)	56/100 (56)	0.326
Respiratory support	140/199[a] (70)	66/99 (67)	74/100 (74)	0.100
Respiratory support, days	6 (1–17)	8 (2–24)	7 (1–16)	0.368
Non-invasive respiratory support	126/200 (63)	60/100 (60)	66/100 (66)	0.141
Non-invasive respiratory support, days	5 (1–18)	5 (1–23)	5 (1–19)	0.322
Mechanical ventilation	58/200 (29)	29/100 (29)	29/100 (29)	0.928
Mechanical ventilation, days	4 (2–8)	5 (3–8)	3 (2–7)	0.255
Conventional ventilation	48/199[a] (24)	22/99 (22)	26/100 (26)	0.456
Conventional ventilation, days	3 (2–5)	3 (2–5)	2 (1–5)	0.825
HFOV	20/200 (10)	14/100 (14)	6/100 (6)	**0.024**
HFOV, days	5 (3–11)	7 (4–15)	3 (3–9)	0.161

Data are presented as median (IQR) or *n*/*N* (%). Non-invasive respiratory support is defined as need of low flow, high flow, or CPAP during NICU admission. Mechanical ventilation is defined as need of conventional ventilation or HFOV during NICU admission. CPAP, continuous positive airway pressure; HFOV, high frequency oscillation ventilation; NICU, neonatal intensive care unit. [a]1 missing value: 1 TAPS donor with lacking data about respiratory support needed during NICU admission.

improvement, the neonate ultimately passed away due to complications from pulmonary interstitial emphysema. All other cases with PPHN were discharged without medication.

To identify potential risk factors for PPHN in TAPS twins, we performed a risk factor analysis (Table 5), with GA at birth, severe foetal anaemia, donor status, and arterial umbilical cord pH. Univariate logistic regression analysis revealed that PPHN was significantly associated with GA at birth (OR = 0.3, 95% CI: 0.1–0.4, $p = 0.001$), donor status (OR = 1.3, 95% CI: 0.2–2.6, $p = 0.028$), and severe foetal anaemia (OR = 1.9, 95% CI: 0.7–3.1, $p = 0.002$). As severe foetal anaemia was strongly correlated with donor status ($R = 0.758$, $p < 0.001$), donor status was

Table 4. Overview of TAPS twins with PPHN in this study

	Donor or recipient	Antenatal TAPS stage	GA at diagnosis, weeks	Therapy for TAPS	GA at birth, weeks	Hb at birth, g/dL	Outcome	Echocardiography
1	Donor	Stage 2	21	Expectant	28	7.4	Neonatal death	TR: no RVD: no LD-IVS: no
2	Donor	Stage 4	27	Delivery	27	2.6	Neonatal death	TR: no RVD: no LD-IVS: no
3	Donor	Stage 1	24	FLS	27	10.4	Alive	TR: yes RVD: yes LD-IVS: yes
4	Donor	Stage 1	24	FLS	30	9.3	Neonatal death	TR: yes RVD: yes LD-IVS: yes
5	Donor	Stage 3	19	IUT	33	11.1	Neonatal death	TR: yes RVD: yes LD-IVS: yes
6	Donor	Stage 1	30	Delivery	30	3.1	Alive	TR: yes RVD: yes LD-IVS: yes
7	Donor	NA[a]	NA[a]	NA[a]	33	9.7	Alive	TR: yes RVD: yes LD-IVS: yes
8	Donor	Stage 3	22	IUT	28	9.8	Alive	TR: yes RVD: yes LD-IVS: yes
9	Recipient	Stage 3	22	IUT	28	19.3	Alive	TR: yes RVD: yes LD-IVS: yes
10	Donor	NA[a]	NA[a]	NA[a]	27	10.0	Alive	TR: yes RVD: yes LD-IVS: yes
11	Recipient	Stage 2	23	FLS	25	23.2	Alive	TR: yes RVD: yes LD-IVS: yes
12	Donor	Stage 2	28	IUT	33	4.8	Alive	TR: yes RVD: yes LD-IVS: yes
13	Recipient	Stage 2	25	IUT	30	28.2	Alive	TR: yes RVD: yes LD-IVS: yes
14[b]	Donor	NA[a]	NA[a]	NA[a]	32	5.5	Alive	NA[b]

NA, non-applicable; FLS, fetoscopic laser surgery; IUT, intrauterine transfusion; TR, tricuspid regurgitation; RVD, right ventricular dilatation; LD-IVS, leftward deviation of the interventricular septum. [a]These neonates were postnatally diagnosed with TAPS. [b]This donor was diagnosed with persistent pulmonary PPHN in the absence of echocardiography; nevertheless, the clinical progression exhibited such a strong correlation with PPHN that this donor was included in the study.

Table 5. Univariate and multivariate analysis of possible risk factors associated with PPHN in TAPS twins

	PPHN (N = 14)	No PPHN (N = 186)	Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Donor status	11/14 (79)	89/186 (48)	1.3 (0.2–2.6)	**0.028**	NA	NA
GA at birth	29 (28–33)	32 (30–35)	0.3 (0.1–0.4)	**0.001**	0.3 (0.1–0.5)	**0.006**
pH art. UC	7.18 (7.17–7.27)	7.24 (7.17–7.30)	2.5 (–5.6–10.6)	0.546	NA	NA
Severe foetal anaemia	11/14 (79)	64/186 (34)	1.9 (0.7–3.1)	**0.002**	1.9 (0.8–3.1)	**0.001**

Data are presented as median (IQR) or n/N (%). Values are odds ratios (OR) (95% confidence intervals [CI]) and p value. Severe foetal anaemia is defined as the need for blood transfusion within the first 24 h after birth. GA, gestational age; Hb, haemoglobin; art., arterial; UC, umbilical cord.

excluded from the multivariate analysis. There was no strong correlation with severe foetal anaemia and GA at birth (R <0.001, p = 1.000), so these parameters were both included in the multivariate analysis. In the multivariate analysis, GA at birth (OR = 0.3 per week, 95% CI: 0.1–0.5, p = 0.006) and severe foetal anaemia (OR = 1.9, 95% CI: 0.8–3.1, p = 0.001) were identified as independent risk factors for PPHN.

Discussion

This is the first study investigating the neonatal respiratory condition of TAPS twins. We found a high prevalence of PPHN in TAPS twins (7%), with donor twins having fourfold higher odds for developing PPHN compared to recipients.

PPHN is a severe cardio-pulmonary condition characterized by elevated pulmonary vascular resistance, leading to impaired gas exchange and systemic hypoxaemia, occurring at a rate of 0.1–0.2% in live births [14]. In uncomplicated monochorionic twins, PPHN is found in 0.2% of infants, and in twin-to-twin transfusion syndrome (TTTS) twins, PPHN can develop in up to 4% [14, 15]. In contrary to TAPS, TTTS is characterized by imbalanced blood flow through large placental anastomoses, leading to significant amniotic fluid differences between the twins. In our study, we identified a higher prevalence of 7% of PPHN among TAPS twins, with lower GA at birth and severe anaemia being important risk factors for its development. Prematurity has been identified before as a strong risk factor for PPHN [3, 16]. In premature infants, pulmonary vessels are not fully developed, making them more prone to vasoconstriction and elevated pulmonary vascular resistance. Secondly, premature infants may also have reduced levels of vascular endothelial nitric oxide, which is a signalling molecule involved in vasodilation. Decreased nitric oxide availability can lead to persistent vasoconstriction in pulmonary blood vessels, contributing to PPHN [17, 18].

The high prevalence of PPHN in TAPS twins can be predominantly attributed to the higher PPHN rate in donor twins, who are more prone to develop this condition due to their severe anaemia. Previous studies in TTTS twins and infants suffering from anaemia due to feto-maternal transfusion already established a correlation between anaemia and the development of PPHN [19, 20]. It is important to note that foetal anaemia might not be a direct cause of PPHN, but the physiological responses and adaptations to foetal anaemia can contribute to the development of PPHN. In foetal anaemia, the decreased number of red blood cells can result in a diminished oxygen-carrying capacity of the blood. This leads to systemic foetal hypoxia, a condition in which the body tissues receive insufficient oxygen supply. In response, the body employs a compensatory mechanism to prioritize blood flow to vital organs, such as the brain and heart. This is achieved by constricting blood vessels in non-essential areas, including the lungs [21]. Prolonged pulmonary vasoconstriction may result in pulmonary hypertension, leading to the onset of PPHN.

Additionally, anaemia-induced hypoxia can trigger the generation of reactive oxygen species (ROS) [22]. ROS are highly reactive molecules, including oxygen radicals, that are produced as by-products of normal cellular metabolism. In the context of hypoxia, the usual oxygen-dependent reactions that help neutralize ROS become impaired, leading to an accumulation of ROS levels. ROS can trigger the activation of signalling pathways that accelerate the breakdown of nitric

oxide, resulting in reduced availability for vasodilatation [23]. The diminished availability of nitric oxide can subsequently contribute to vasoconstriction in the pulmonary vasculature, thereby increasing the risk of developing PPHN [18]. Another factor that can aggravate the onset of PPHN in TAPS donors is neonatal lactate acidosis. In a previous study, we found that 49% of TAPS donors show lactate acidosis in the first day after birth, likely due to chronic foetal anaemia [24]. Elevated levels of lactic acid in the blood can directly affect the smooth muscle cells lining the pulmonary arteries, triggering vasoconstriction [25]. This neonatal pulmonary vasoconstriction, coupled with the effects of intrauterine vasoconstriction and depleted nitric oxide levels, can create a vicious cycle of inadequate oxygenation, pulmonary hypertension, and worsening systemic hypoxaemia.

Furthermore, chronic hypoxia in PPHN can potentially induce structural modifications in the pulmonary vasculature, such as muscularisation of the small pulmonary arteries. This remodelling process can involve thickening and narrowing of the blood vessels, making them less responsive to vasodilators like nitric oxide (NO). Moreover, as the vascular remodelling progresses, there is a potential loss of the endothelial cells' capacity to generate NO within the pulmonary arteries. This phenomenon might offer a partial explanation for the notably high mortality risk (36%) observed among TAPS donors with PPHN, as 75% of these cases were non-responders on iNO treatment.

In this study, we found a prevalence of 31% of RDS, which was comparable between donors and recipients. These findings align with a previous report examining RDS in TAPS [26]. In contrast to our initial hypothesis, we did not observe an increased risk of BPD in TAPS donors compared to recipients, despite approximately 40% of TAPS donors was being identified as growth restricted. A previous study showed that in monochorionic twins with selective foetal growth restriction, the smaller twin has an increased susceptibility to developing BPD [27]. However, in TAPS, the birth weight discordance between the donor and recipient twin is smaller compared to monochorionic twin pregnancies with selective foetal growth restriction. This smaller discrepancy in birth weight among TAPS twins could explain the comparable prevalence of BPD between these twin pairs.

With the high prevalence of PPHN in TAPS donors, we add yet another complication to the already compromised neonatal outcome in TAPS donor twins. Previous studies have showed that TAPS donors more often suffer from haematological issues (such as anaemia and lymphocytopenia), renal insufficiency, and metabolic complications (including hypoglycaemia, lactate acidosis, hypoalbuminaemia, and hypoproteinaemia) [28]. Importantly, besides neonatal complications, TAPS donors also have significantly higher rates of severe neurodevelopmental impairment, including bilateral deafness during childhood than TAPS recipients [29]. Although the precise underlying mechanisms responsible for these long-term impairments in donors remain a puzzle, the high prevalence of PPHN may potentially contribute to this. A study conducted by Konduri et al. [30] demonstrated that approximately 25% of infants with PPHN develop neurodevelopmental impairment later in life. Future research is necessary to investigate whether neurodevelopmental problems in TAPS donors is associated with PPHN.

The results of this study should be interpreted with care, due to the retrospective character of the study design, which may have introduced selection bias into the study population. Since the LUMC serves as the national referral centre for TAPS pregnancies, it is possible that this could result in an increased representation of severe TAPS cases, leading to a potential overestimation of the prevalence of PPHN. However, most of the TAPS twins with PPHN in our study, presented with TAPS stage I or II (n = 7). In some instances, TAPS was not even diagnosed antenatally (n = 3). Only one TAPS twin with PPHN presented with TAPS stage IV antenatally. The distribution of TAPS stages among twins with PPHN aligns with previously published data from the international TAPS registry, which indicated that approximately 80% of TAPS cases were classified as stage I or II antenatally [31].

Additionally, the relatively small absolute number of PPHN cases among TAPS twins raises the possibility of underpowered risk factor analyses. Nevertheless, it is worth noting that we were able to include a relatively large sample size, particularly considering the low incidence of TAPS.

In conclusion, this research shows that TAPS donor twins may develop PPHN in more than 1 out of 10 pregnancies, leading to neonatal mortality in 1 out of 3 of them. Given the life-threatening nature of PPHN, which necessitates immediate and adequate interventions such as mechanical ventilation and nitric oxide therapy, neonatologists should be aware of this complication. Considering the potential for lack of availability of iNO and HFOV ventilation in many hospitals, caregivers should be aware of the importance of delivering TAPS pregnancies in hospitals equipped with these therapeutic resources.

Statement of Ethics

For this study protocol, the Medical Research Ethics Committee Leiden Den Haag Delft stated that the Medical Research Involving Human Subjects Act does not apply to the above mentioned study and is therefore exempted from review. Written informed consent for data collection was obtained prior to the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Margot J.A. van de Sande, MD, and Lisanne S.A. Tollenaar, MD, PhD, were responsible for conceptualization, (monitoring and interpreting) data collection, wrote the statistical analysis plan, analysed the data, and drafted and revised the final manuscript. Femke Slaghekke, MD, PhD, and Enrico Lopriore, MD, PhD, were responsible for the conceptualization, supervised in the data interpretation, and reviewed and edited the final manuscript. Arjan B. te Pas, MD, PhD, and Ruben S.G.M. Witlox, MD, PhD, supervised in data interpretation and reviewed the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participant but are available from the corresponding author (Margot J.A. van de Sande) upon reasonable request.

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