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Necrotizing enterocolitis in monochorionic twins: Insights from an identical twin model

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ABSTRACT

Necrotizing enterocolitis (NEC) is a major cause of neonatal morbidity and mortality in preterm neonates, yet its pathophysiology remains unclear. The aim of this study is to evaluate risk factors for NEC using an identical twin model. In this case-control study, all monochorionic twin pairs born in our center in 2002–2020 were retrospectively reviewed for NEC. Potential risk factors for NEC were studied. For within-pair comparison, outcomes were compared between affected and unaffected twins. Within-pair analyses showed that the twin with NEC had a lower birth weight compared to its unaffected co-twin (1100 (913–1364) vs. 1339 (1093–1755) grams). Median gestational age at birth and birth weight were lower in twin pairs in the NEC-group compared to the no-NEC group, 29.1 weeks (27.8–30.8) versus 33.6 (30.7–36.0) and 1221 g (1010–1488) versus 1865 (1356–2355) respectively. Twin pregnancies in the NEC-group were more often complicated by twin-to-twin transfusion syndrome compared to the no-NEC-group (70 % (14/20) vs. 49 % (472/962)), particularly when treated with amnioreduction. This unique population of identical twins confirms that preterm neonates with a relatively lower birth weight are more prone to develop NEC compared to their co-twin, regardless of other genetic, maternal and obstetrical factors.

1. Introduction

Necrotizing enterocolitis (NEC) is a life-threatening inflammatory disease of the intestines affecting 1–5 % of preterm neonates and is considered to be a major cause of neonatal morbidity and mortality in the neonatal intensive care unit [1]. Neonates with NEC requiring surgery have mortality rates up to 20–30 % and studies have shown an association with long-term complications, such as gastrointestinal problems, failure to thrive and neurodevelopmental delay [2,3]. Current treatment strategies generally include broad-spectrum antibiotics, bowel rest, and ionotropic and fluid support to maintain cardiorespiratory function [2]. Surgical intervention may be required in advanced stages to perform drain placement, resection of affected bowel and enterostomy [2,4].

The pathophysiology of NEC remains unclear, though clinical observations strongly suggest a complex, multifactorial nature relating to impaired blood flow or oxygen delivery, immaturity of the intestines and an overactive immune response [1,2,5]. Preterm birth, enteral or formula feeding and being born small for gestational age (SGA) have been reported to be important risk factors for NEC development [5–8]. Many other reported risk factors remain controversial [9]. Furthermore, risk assessment is broadly based on singletons with NEC, yet limited by bias due to differences in genetic, maternal and obstetrical factors.

Hence, research using twin models is needed to conduct a more comprehensive analysis of risk factors associated with NEC development and develop a clinical profile of the neonate most at risk for NEC. Studies on the determinants of NEC in identical twins are limited [10,11]. Due to identical genetic, maternal and obstetrical factors, monochorionic (MC) twins offer a natural experiment to examine differences between a twin with and a twin without NEC within twin pairs and identify risk factors for NEC.

Better insight into prognostic factors is needed to enable optimal

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identification or earlier diagnosis of neonates at risk for developing NEC. Consequently, treatment can be started earlier, and progression of NEC can be prevented. The aim of this study is to describe the overall occurrence of NEC in the MC twin population and evaluate risk factors for NEC by comparing the clinical features of one twin affected by NEC with its co-twin unaffected by NEC.

2. Methods

2.1. Study design and participants

This is a nested case-control study describing NEC in a MC twin population and comparing within-pair differences between the affected and unaffected twin in MC twin pairs. We included all consecutive live-born MC twins born between 2002 and 2020 at the Leiden University Medical Center (LUMC) in the Netherlands, the national referral center for complicated MC twin pregnancies and fetal therapy. Cases were reviewed for the presence of NEC, defined as NEC ≥ stage IIA according to Bell's criteria [12]. Twin pairs with twin reversed arterial perfusion (TRAP) and other congenital abnormalities were excluded. MC twin pairs with incomplete information on NEC were excluded as well. Neonatal outcomes and pre-existing clinical features were compared in twin pairs with at least one NEC case (defined as the NEC-group) versus twin pairs without NEC (no-NEC-group). To explore risk factors for developing NEC, we compared clinical characteristics in a twin with NEC versus the co-twin without NEC within the same twin pair. The Medical Ethical Committee Leiden-The Hague-Delft has waived the requirement of informed consent due to the retrospective design (G20.004).

2.2. Baseline characteristics

The following maternal, obstetrical and neonatal characteristics were collected from the medical records: delivery mode, sex, gestational age at birth, birth weight, SGA (defined as birth weight < 10th percentile [13]) and birth weight discordance (BWD) calculated as ([birth weight larger twin–birth weight smaller twin]/birth weight larger twin) x 100 %.

The following MC twins complications were recorded: twin-to-twin transfusion syndrome (TTTS), treatment with laser surgery or amnioreduction for TTTS, successful or unsuccessful laser treatment (based on the presence of residual anastomoses determined with placental injection after birth), twin anemia polycythemia sequence (TAPS) and selective fetal growth restriction (sFGR).

TTTS was diagnosed by the presence of oligo-polyhydramnios and classified according to the Eurofetus criteria [14–16]. TAPS was diagnosed by large discordance in middle cerebral artery peak systolic velocity (MCA-PSV) with cut-off values of >1.5 multiples of the median (MoM) in the donor and <1.0 MoM in the recipient according to Slaghekke et al. until 2019 [17]. Since then, TAPS was defined as delta MCA-PSV >0.5 MoM and classified according to Tollenaar et al. [14,18]. sFGR was defined as BWD ≥20 % and classified according Gratacós et al. based on the umbilical artery Doppler flow in the smaller twin [14,19].

2.3. Neonatal morbidity and mortality

The following neonatal outcomes were recorded: the presence of NEC, NEC staging, NEC treatment, other severe neonatal morbidities including severe cerebral injury (defined as intraventricular hemorrhage ≥ Grade 3, cystic periventricular leukomalacia ≥ Grade 2, ventricular dilatation >97th percentile, arterial or venous infarction or porencephalic or parenchymal cysts) and neonatal mortality (defined as death within 28 days after birth).

Severe neonatal morbidity was defined as at least one of the following: perinatal asphyxia, respiratory distress syndrome (RDS, respiratory failure requiring mechanical ventilation or surfactant) and patent ductus arteriosus (PDA) requiring medical treatment or surgical closure [20,21]. Perinatal asphyxia was diagnosed in presence of at least one of the following criteria: [1] 5 min Apgar score ≤ 5; [2] respiratory failure requiring resuscitation during at least 10 min postpartum; [3] arterial pH <7.0 and BE ≤-16 mmol/L in umbilical artery or blood gas sample within 1 h of life; [4] lactate >10 mmol/L in umbilical artery or blood gas sample within 1 h of life [22].

2.4. Risk assessment

The following potential risk factors for NEC based on current literature were used for within-pair comparison: birth weight, smaller twin status (i.e. twin with the lower birth weight), SGA, TTTS or TAPS donor status and amount of RBC transfusions [2,6,23–26]. Since current research describes RBC transfusions as possible risk factor for NEC development, the amount of RBC transfusions prior to NEC development as well as the amount of RBC transfusions within 48 h before developing NEC in affected twins was recorded [26,27]. The same observation time was applied for the co-twin without NEC.

2.5. Statistical analysis

Data was analyzed using IBM SPSS Statistics version 25.0 (SPSS, Inc., an IBM company, Chicago, IL, USA). Data are presented as n/N (%) and median (interquartile range [IQR]). Differences in clinical characteristics between twin pairs with and without at least one NEC case were analyzed using Mann-Whitney-*U* tests for numerical data and Chi-square tests for categorical data. For within-pair comparison, Generalized Estimated Equations (GEE) were performed to test the association between neonatal characteristics and NEC. A *p*-value <0.05 was considered as statistically significant.

3. Results

Between 2002 and 2020, a total of 902 live-born MC twin pairs were delivered at the LUMC (Fig. 1). After exclusion of aforementioned criteria ($n = 29$ twin pairs), 873 twin pairs (1746 neonates) were eligible for analysis comparing characteristics in twin pairs with and without NEC. To assess the within-pair risk difference for NEC, 17 twin pairs in which only one neonate developed NEC were included. Three out of 20 twin pairs were excluded for within pair analysis since both twins developed NEC.

Maternal, obstetrical and neonatal characteristics are presented in Table 1. Median gestational age at birth was significantly lower in the NEC-group as opposed to the no-NEC-group (29.1 weeks (27.8–30.8) vs. 33.6 weeks (30.7–36.0), $p < 0.01$). The NEC group had lower birth weight compared to the no-NEC-group (1221 g (1010–1488) vs. 1856 g (1356–2355), $p < 0.01$).

TTTS had occurred more often in the NEC-group (70 %, 14/20) compared to the no-NEC-group (46 %, 392/853) ($p = 0.01$), particularly when treated with amnioreduction (14 % (2/14) vs. 7 % (26/392), $p = 0.01$) and in case of acute peripartum TTTS (7 % (1/14) vs. 2 % (6/392), $p = 0.01$). In the NEC-group, 71 % (10/14) had received laser treatment at a median gestational age of 19.0 (17.6–22.5) weeks. The majority of these laser treatments (89 %, 8/9) were successful and did not show residual anastomoses after color dye injection. One placenta could not be examined due to placenta rupture during birth. In the no-NEC-group, 88 % (344/853) received laser treatment for TTTS of which 79 % (251/316) were successful.

Neonatal morbidity and mortality in the NEC-group were compared with the no-NEC-group. In the NEC-group, 26 % (6/23) was classified as Bell's stage IIA, 61 % (14/23) as stage IIB, 4 % (1/23) as stage IIIA and 9 % (2/23) as stage IIIB. A total of 50 % (10/20) was eligible for surgery. In three affected neonates, it was unknown whether they were eligible for surgery. More than half (58 % (23/40)) of the NEC-group simultaneously had other severe neonatal morbidity, while this was the case for

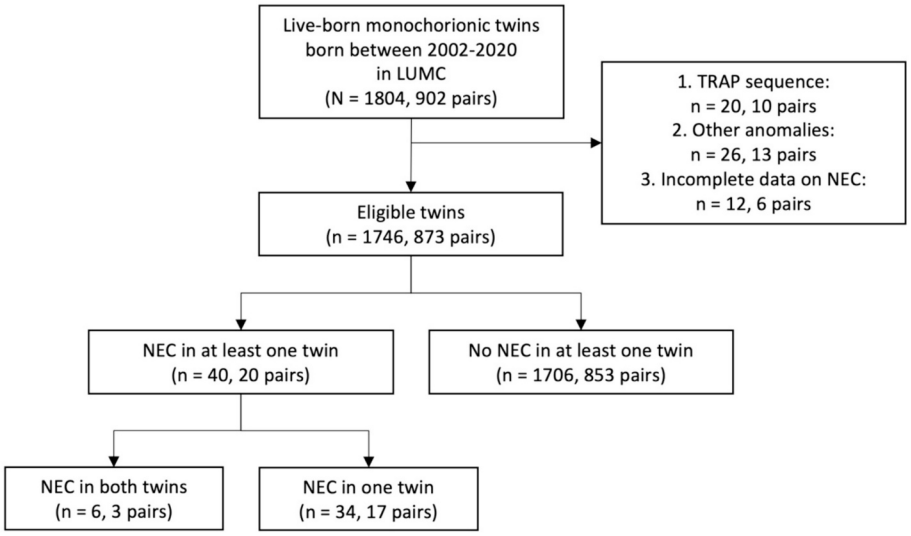

Fig. 1. Flowchart patient inclusion. LUMC: Leiden University Medical Center, TRAP: twin reversed arterial perfusion, NEC: necrotizing enterocolitis.

Table 1
Maternal, obstetrical and neonatal characteristics for the included MC twins with and without NEC.

	Twin pairs with at least one NEC (n = 40; 20 pairs)	Twin pairs without NEC (n = 1706; 853 pairs)	*p*-Value
MC twin complications			
TTTS	14/20 (70)	392/853 (46)	**0.003**
Laser	10/14 (71)	344/392 (88)	0.207
Amnioreduction	2/14 (14)	26/392 (7)	**0.014**
No therapy	1/14 (7)	16/392 (4)	0.158
Acute peripartum	1/14 (7)	6/392 (2)	**0.003**
TAPS	0/20 (0)	47/853 (6)	0.127
sFGR	4/20 (20)	113/853 (13)	0.215
Uncomplicated	2/20 (10)	301/853 (35)	**0.001**
Caesarean delivery	24/40 (60)	823/1697 (49)	0.150
Female	13/20 (65)	839/1702 (49)	0.050
Gestational age at birth, weeks	29.1 (27.8–30.8)	33.6 (30.7–36.0)	**<0.0001**
Birth weight, g	1221 (1010–1488)	1856 (1356–2355)	**<0.0001**
Smaller twin	1083 (796–1323)	1700 (1200–2160)	
Larger twin	1346 (1079–1808)	1995 (1540–2510)	
SGA	16/40 (40)	660/1696 (39)	0.889
Smaller twin	14/20 (70)	504/847 (60)	
Larger twin	2/20 (10)	156/849 (18)	
BWD, %	16.7 (6.6–30.4)	11.7 (5.5–22.8)	0.148

Data are presented as n/N (%) and median (IQR). MC: monochorionic, NEC: necrotizing enterocolitis, TTTS: twin-to-twin transfusion syndrome, TAPS: twin anemia polycythemia sequence, sFGR: selective fetal growth restriction, SGA: small for gestational age, BWD: birth weight discordance. *P*-values <0.05 are highlighted in bold.

only 24 % (323/1374) in the no-NEC-group ($p < 0.01$). The prevalence of RDS was significantly higher in the NEC-group compared to the no-NEC-group (55 % (22/40) vs. 19 % (306/1586), $p < 0.01$). PDA was more often present in the NEC-group as opposed to the no-NEC-group as well (20 % (8/40) vs. 3 % (43/1578), $p < 0.01$). Neonatal mortality rate in the NEC and no-NEC-group was 15 % (6/40) and 4 % (66/1696) respectively ($p < 0.01$). All mortality cases in the NEC-group occurred in twins who developed NEC.

3.1. Within-pair comparison: twin with NEC versus co-twin without NEC

Differences in possible risk factors for developing NEC were examined within-twin pairs (Table 2). The twin with NEC had lower birth weight compared to its unaffected co-twin (1100 g (913–1364) vs. 1339 g (1093–1755), $p = 0.01$). In 71 % (5/7) of twin pairs receiving at least one RBC transfusion, amount of RBC transfusions was higher in the twin with NEC compared to its unaffected co-twin. In 67 % (4/6) of the affected neonates receiving at least one RBC transfusion, NEC had occurred within 48 h. No within-pair differences were found for smaller twin status, SGA, TTTS donor status and amount of RBC transfusions.

4. Discussion

The results in this study originate from a unique natural experiment in identical twins, evaluating important clinical characteristics in twin pairs with at least one NEC case and offering a within-pair comparison to explore risk factors for developing NEC while eliminating potential confounders. This model substantiated that twins born with a relatively lower birth weight are more prone to develop NEC as opposed to their larger co-twin, regardless of genetic constitution or other maternal/obstetrical factors.

Table 2
Within-pair differences in risk factors between affected twins with NEC compared to their unaffected co-twin.

	Twin with NEC *(n = 17)*	Co-twin without NEC *(n = 17)*	*p*-Value
Birth weight, g	1100 (913–1364)	1339 (1093–1755)	**0.008**
Smaller twin	11/17 (65)	6/17 (35)	0.232
SGA	8/17 (47)	4/17 (24)	0.205
TTTS donor status	6/11 (55)[a]	5/11 (46)[a]	0.763
Amount of RBC transfusions			0.814
1	2/11 (18)[a]	1/11 (9)[a]	
>1	4/11 (36)[a]	2/11 (18)[a]	

Outcomes are presented as n/N (%) and median (IQR). MC: monochorionic, NEC: necrotizing enterocolitis, SGA: small for gestational age, TTTS: twin-to-twin transfusion syndrome, RBC: red blood cell. The amount of RBC transfusions prior to NEC development was recorded and same observation time was applied for the co-twin without NEC. *P*-values <0.05 are highlighted in bold.

[a] In 6 twin pairs, data on TTTS donor status and amount of RBC transfusions was missing.

The findings in our twin model are in accordance with cohort studies describing the highest incidence of NEC among neonates with lower birth weight, a decline in NEC incidence with increasing birth weight and birth weight being independently associated with the increased risk of mortality as a consequence of NEC [7,28–30]. Moreover, twin pairs in whom one member suffered from NEC had a lower gestational age at birth compared to twin pairs without NEC which favors the widely proposed hypothesis in NEC pathophysiology, with prematurity as a primary risk factor. According to this hypothesis, immaturity of intestinal epithelium facilitates bacterial translocation and, consequently, a violent inflammatory storm leading to intestinal necrosis [3,31].

Since both lower gestational age and lower birth weight were found to be significant risk factors for developing NEC in this study, SGA may be a relevant prognostic factor in clinical practice. Being born SGA is associated with increased neonatal mortality and morbidity including gastrointestinal dysfunction [32]. However, studies show conflicting results: some report that SGA neonates are at increased risk for developing NEC compared to neonates born appropriate for gestational age (AGA) while others observe a similar incidence of NEC for both SGA and AGA neonates [6,33]. In our within-pair comparison, the twin with NEC was SGA twice as often as its co-twin without NEC. However, this association did not show a statistically significant difference, presumably due to our small sample size.

When comparing MC twin complications during pregnancy, our study showed that NEC occurred more frequently in TTTS twin pairs, particularly when treated with amnioreduction or when acute peripartum TTTS was present. Previous studies have shown that pregnancies complicated by TTTS are at higher risk for developing NEC due to persistent hypoperfusion of the gastrointestinal tract in donor twins or hyperviscosity causing vascular accidents in recipient twins [23–25,34]. Our finding is in accordance with a previous study by Lopriore et al., which examined incidence of TTTS in a similar cohort at our center from 2002 to 2021 and also reported an increased NEC incidence in TTTS twins without laser treatment [10]. Noteworthy, the successfulness of TTTS laser treatments should be taken into account when investigating the association between TTTS and NEC, since untreated or unsuccessfully treated TTTS casus show a more severe neonatal course including higher morbidity rates resulting in higher NEC prevalence [35]. In our study, the majority of TTTS laser treatments were successful in both the NEC-group and no-NEC-group. However, our results must be taken with caution as it was limited by our sample size. Additionally, TTTS pregnancies are associated with lower gestational age at birth and birth weight compared to uncomplicated MC twins [36–38]. Hence, increased incidence of NEC in TTTS twins may be explained by preterm birth due to TTTS rather than by TTTS itself.

Current research in NEC also discusses red blood cell transfusion as a possibly important risk factor for NEC development, particularly transfusion-associated NEC (TANEC), defined as NEC arising within 48 h after receiving blood transfusion due to increasing inflammatory cytokines [26,27]. We found, although not significant, that the amount of RBC transfusions before NEC development was higher in the twin with NEC compared to the unaffected co-twin and most of the NEC twins receiving RBC transfusions, developed NEC within 48 h. The lack of significant association may be due to small sample size; thus, larger cohort studies are needed to further explore the relationship between neonatal RBC transfusions and the pathogenesis of NEC.

Although nutrition is reported as one of the significant predictors for developing NEC, data concerning the type of milk feeding and feeding regimen prior to NEC onset was largely unavailable from our medical records. According to broad recent research, human milk is linked to a lower risk of NEC compared to formula feeding or enteral nutrition, as a result of its prebiotic and immunomodulatory properties [8,39]. It is important to take this missing information into account when interpreting our results.

The main limitation in our study was the small study population which should be considered when interpreting the results. This can be explained by NEC being a rare neonatal complication and occurring in only 1–5 % of preterm neonates which resulted in a small number of NEC cases in the MC twin population. Yet, our results are strengthened by the extensive documentation of maternal, obstetrical and neonatal data as well as the fact that NEC cases had to be confirmed before inclusion.

In conclusion, our study contributes to further understanding the pathogenesis of NEC by using a unique identical twin model, showing that twins with a lower birth weight are more prone to develop NEC regardless of gestational age at birth and regardless of genetic, maternal and obstetrical factors. These findings contribute to the development of a clinical profile of the neonate most susceptible to NEC, allowing clinicians to make an adequate and timely risk assessment to take preventative measures in an early stage.

CRediT authorship contribution statement

Nour Rebai: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Enrico Lopriore:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Vincent Bekker:** Writing – review & editing, Methodology, Formal analysis. **Femke Slaghekke:** Writing – review & editing, Methodology, Formal analysis. **Michiel H.D. Schoenaker:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sophie G. Groene:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

None declared.

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