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Spekman, J.A.; Emrani, S. el; Schalij-Delfos, N.E.; Slaghekke, F.; Klink, J.M.M. van; Lopriore, E.; Groene, S.G.

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CLINICAL RESEARCH ARTICLE

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Association between fetal growth-restriction and retinopathy of prematurity using a unique identical twin model

Jip A. Spekman[1]✉, Salma El Emrani[1,2], Nicoline E. Schalij-Delfos[2], Femke Slaghekke[3], Jeanine M. M. van Klink[1], Enrico Lopriore[1] and Sophie G. Groene[1]

BACKGROUND: Research in singletons identified fetal growth restriction (FGR) as a risk factor for retinopathy of prematurity (ROP), but is generally subject to confounding by genetic, obstetric, and maternal factors. We investigated the effect of FGR on ROP in growth-discordant identical twins, thereby controlling for confounding factors.
METHODS: All data of monochorionic (MC) twin pairs with a birth weight discordance ≥20% born in our center between 2010 and 2021 were retrospectively reviewed for the presence of ROP. Potential risk factors for ROP were analyzed. Outcomes were compared between the smaller and larger twin.
RESULTS: We included 88 MC twin pairs with growth discordance. In 34% (30/88), both neonates were at risk of ROP. Prevalence of ROP was higher among the smaller twin compared to the larger twin, 30% (9/30) versus 13% (4/30), respectively (OR 2.8, 95% CI: 1.2–6.6). The smaller twin had a longer duration of mechanical ventilation (8 (1–20) versus 2 (1–4) days) and received their first red blood cell transfusion at an earlier postmenstrual age (29.6 (28.1–31.6) versus 30.4 (29.7–32.6) weeks).
CONCLUSIONS: In this identical twin model, FGR is associated with almost tripled odds of ROP development, suggesting that both unfavorable antenatal growth conditions and adverse neonatal outcomes affect postnatal retinal vascular proliferation.

Pediatric Research; https://doi.org/10.1038/s41390-023-02670-7

IMPACT:

- Fetal growth restriction in growth-discordant identical twins is associated with almost tripled odds of developing retinopathy of prematurity in the smaller twin.
- Since these twins do not only differ in birth weight but also duration of mechanical ventilation and timing of the first red blood cell transfusion, both unfavorable antenatal growth conditions and adverse neonatal outcomes can affect postnatal retinal vascular proliferation.
- More attention for preventing retinopathy of prematurity is needed in those with fetal growth restriction who received prolonged duration of mechanical ventilation, oxygen supplementation, or a first red blood cell transfusion <32 weeks postmenstrual age.

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the developing and incompletely vascularized retina in preterm neonates. After preterm birth, the placental supply of growth factors such as insulin-like growth factor 1 (IGF-1) is suddenly interrupted. Abrupt change from hypoxic in utero fetal condition to hyperoxic milieu after birth leads to suppression of vascular endothelial growth factor (VEGF), induces retinal vessel obliteration, and halts retinal vessel outgrowth, initiating phase I of ROP development.[1,2] As a result, the poorly vascularized retina becomes hypoxic. In phase II of ROP, VEGF levels increase in response to hypoxia and IGF-1 levels rise, facilitating retinal vessel outgrowth. In approximately 30%, an abundance of growth factors induces ROP, resulting in retinal detachment and visual impairment, or even blindness in severe cases.[3]

Previous research identified fetal growth restriction (FGR) as a risk factor for ROP, although results vary between studies.[4–6] However, research on the association between FGR and ROP has mostly been conducted in singletons and is therefore subject to confounding by genetic, obstetric, and maternal factors influencing the risk of ROP development. In addition, heterogeneity in the definition of FGR and concomitant neonatal morbidities also influence this risk. Conclusive evidence to clarify how FGR contributes to the risk of ROP is still lacking. Since monochorionic (MC) twins have the same maternal factors and gestational age (GA) at birth, part of these substantial confounders are automatically eliminated, making these twins an ideal model.

Although genetically identical, MC twins can experience environmental differences in utero inherent to sharing a single placenta.[7–9]

[1]Neonatology, Willem-Alexander Children's Hospital, Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands. [2]Department of Ophthalmology, Leiden University Medical Center, Leiden, The Netherlands. [3]Fetal Therapy, Department of Obstetrics, Leiden University Medical Center, Leiden, The Netherlands.
✉email: J.A.Spekman@lumc.nl

Received: 9 January 2023 Revised: 24 April 2023 Accepted: 16 May 2023
Published online: 31 May 2023

Selective fetal growth restriction (sFGR), caused by unequal placental sharing, or twin–twin transfusion syndrome (TTTS), resulting from intertwin blood flow imbalances, occurs in approximately 15–20% of MC pregnancies. Subsequently, unequally distributed nutrients and oxygen can lead to large intertwin growth discrepancy, ultimately resulting in a birth weight discordance (BWD).[10–12] These twin pairs constitute an ideal population to study the association between FGR and ROP. To date, only three studies have examined ROP development in growth-discordant twin pairs.[13–15] However, these studies used various definitions of sFGR and often lacked a distinction in chorionicity.

This study aims to investigate the effect of FGR on ROP development in a large cohort of MC twin pairs with discordant growth by performing a within-pair comparison, thereby controlling for confounding factors. In addition, we aim to analyze factors contributing to ROP development, thereby identifying neonates at risk.

METHODS

All live-born MC twin pairs delivered at the Leiden University Medical Centre (LUMC) between 2010 and 2021 were eligible for inclusion in this retrospective study. Twin pairs were reviewed for the presence of discordant growth, defined as BWD of ≥20% (calculated as (birth weight larger twin – birth weight smaller twin) / birth weight larger twin × 100%).[8] Exclusion criteria were: triplets, pregnancies complicated by TTTS who underwent treatment other than fetoscopic laser surgery (no treatment or amnioreduction) or in which laser surgery was incomplete (either recurrent TTTS or post-laser twin anemia polycythemia sequence (TAPS)),[16,17] pregnancies complicated by spontaneous TAPS,[18] pregnancies complicated by twin reversed arterial perfusion sequence[19] or other congenital abnormalities. After applying these inclusion and exclusion criteria, twin pairs with sFGR and TTTS with discordant growth and complete fetoscopic laser surgery were eligible for inclusion.[8] In case of complete laser surgery for TTTS, discordant growth resulting from flow imbalances is eliminated, leaving the underlying placental share discordance as the primary cause of the discordant growth in these twin pairs.[20,21] All placentas were injected with colored dye to determine whether laser surgery for TTTS was complete. In addition, we excluded twin pairs when neonatal mortality (defined as death within 28 days after birth) in either one or both twins occurred, since ROP starts at a later age, or if ROP data was missing. The ethics committee of the LUMC waived the requirement for written informed consent (protocol number G20.004).

The following baseline characteristics were collected from our local medical records: maternal age, gravidity, parity, Gratacós classification for cases with isolated sFGR (type I defined as positive end-diastolic flow, type II defined as persistent absent or reversed end-diastolic flow and type III defined as intermittent absent or reversed end-diastolic flow),[22] the occurrence of TTTS (including GA at diagnosis and GA at laser surgery), GA at birth, sex, delivery mode, birth weight, BWD, and proportion of neonates born small for gestational age (SGA) (birth weight <10th centile).[23]

According to the national screening protocol, routine ophthalmological examination was performed in twins who met the screening criteria of ROP (GA at birth <30 weeks and/or birth weight <1250 g; GA at birth 30–32 weeks and/or birth weight 1250–1500 g with at least one of the following neonatal risk factors: the need for mechanical ventilation, neonatal sepsis, necrotizing enterocolitis (NEC), postnatal corticosteroids or cardiotonic drugs).[24] Screening started from the fifth week after birth or at postmenstrual age (PMA) of 31 weeks, whichever came first. Diagnosis of ROP was based on the second International Classification of Retinopathy of Prematurity, describing the abnormal vascular response of the retina in preterm neonates according to five stages of severity, location of retinal involvement by zone and presence of plus disease.[25] We recorded the highest stage, with severe ROP being a composite outcome of at least one of the following conditions: ROP ≥stage 3, (laser) treatment, aggressive-posterior ROP, and/or plus disease. Treatment is generally considered for eyes with type 1 ROP according to the Early Treatment for ROP criteria: any stage of ROP in zone I with plus disease, stage 3 ROP in zone I without plus disease, and stage 2 or 3 ROP in zone II with plus disease.[26]

In addition, risk factors for ROP development were analyzed in a subgroup of twin pairs who were both at risk of ROP development and were both screened to prevent screening bias, since birth weight is part of the screening criteria. These risk factors consisted of the need for mechanical ventilation (including duration in days), supplemental oxygen therapy of >21% (including duration in days), red blood cell transfusion (including the number of transfusions and PMA at first transfusion), postnatal corticosteroids, neonatal sepsis (defined as a clinically ill neonate with a positive blood culture) and NEC ≥stage 2.[27] We reported the long-term ophthalmic sequelae in this subgroup of twins at risk of ROP development. Outcomes and risk factors were compared between the smaller and larger twin within each twin pair.

Statistical analyses were performed with IBM SPSS Statistics Version 25.0 (IBM, Armonk, New York). Continuous data are reported as median (interquartile ranges) and categorical data as *n/N* (%). For continuous and categorical data, we used the generalized estimating equations (GEE) to analyze within-pair differences and to account for the fact that observations between co-twins are not independent. Since the GEE cannot be used when an outcome event does not occur in one of the groups (i.e., smaller or larger twin), an alteration was applied to the data changing an unaffected twin (i.e., outcome not present) to an affected twin (i.e., outcome present) in both groups, resulting in more conservative *p* values of outcomes in which this adjustment was applied (severe ROP, plus disease, laser surgery for ROP and NEC ≥stage 2). No uni- or multivariate risk factor analysis was performed as the low number of observed ROP cases precluded a reliable analysis. A *p* value of <0.05 was considered statistically significant.

RESULTS

In total, 643 live-born MC twin pairs were born during the study period. After exclusion according to the aforementioned criteria ($n = 555$), a total of 88 twin pairs (176 neonates) with discordant growth were included. In 34% (30/88) of twin pairs, both twins were at risk of and screened for ROP development (Fig. 1).

sFGR was diagnosed in 67% (59/88) of twin pairs and TTTS with discordant growth and complete fetoscopic laser surgery in 33% (29/88) of twin pairs (Table 1). Median GA at birth was 33.0 (30.6–35.7) weeks. The smaller twin had a median birth weight of 1395 (954–1834) g and the larger twin of 1986 (1493–2570) g, with a median BWD of 29.9% (25.0–38.1).

The prevalence of ROP was higher in the smaller twin as opposed to the larger twin (14% (12/88) versus 5% (4/88), $p = 0.005$) (Table 2). Four (9%) smaller twins were diagnosed with severe ROP. The smaller twin was screened for ROP more frequently than the larger twin, 49% (43/88) versus 34% (30/88), respectively ($p < 0.0001$).

In 30/88 twin pairs, both twins were at risk of ROP development and were both screened. In this subgroup, the smaller twin had a higher prevalence of ROP than the larger twin, 30% (9/30) versus 13% (4/30), respectively ($p = 0.019$) (Table 3). The odds of developing any stage of ROP for the smaller twin were almost tripled (OR 2.8 (95% CI 1.2–6.6)). The two smaller twins with plus disease underwent ophthalmic laser surgery (ROP stage 3 and stage 4 in posterior zone II) and these children suffered from long-term ophthalmic sequelae at a later age. The observed ophthalmic sequelae in the smaller twins consisted of a correction of −6.0 adequately corrected with lenses in the smaller twin, myopia with a correction of −10.0 with bilateral astigmatism and a unilateral coloboma with macular involvement. In the larger twin, the long-term ophthalmic sequela was strabismus requiring treatment.

Regarding outcomes of risk factors for ROP development in the twin pairs at risk of ROP, 40% (12/30) of the smaller twins and 60% (18/30) of the larger twins received mechanical ventilation ($p = 0.049$). The median duration of mechanical ventilation was 8 (1–20) days in the smaller twin and 2 (1–4) days in the larger twin ($p = 0.018$). The median duration of supplemental oxygen therapy for the smaller twin was 15 (6–39) days as opposed to 9 (3–21) days in the larger twin ($p = 0.010$). The smaller twin received red blood cell transfusions at a lower PMA compared to the larger twin, 29.6 (28.1–31.6) versus 30.4 (29.7–32.6) weeks, respectively ($p = 0.020$)). Other risk factors (need for supplemental oxygen therapy, need for red blood cell transfusion, number of transfusions, postnatal corticosteroids, neonatal sepsis and NEC ≥stage 2) did not significantly differ within the twin pairs.

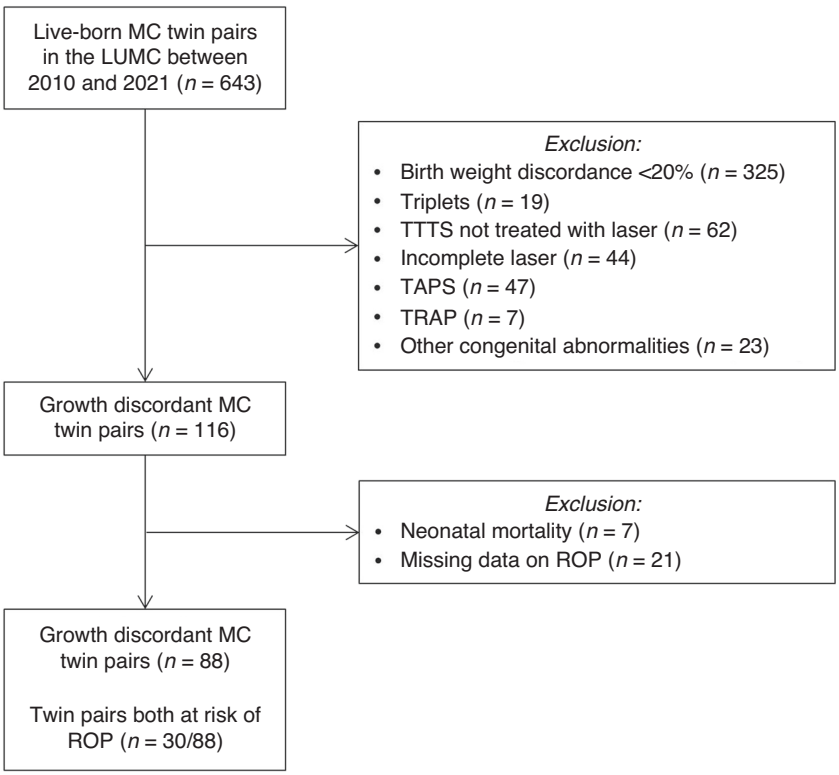

Fig. 1 Flowchart of study inclusion. MC monochorionic, LUMC Leiden University Medical Center, TTTS twin-twin transfusion syndrome, TAPS twin anemia polycythemia sequence, TRAP twin reversed arterial perfusion sequence, ROP retinopathy of prematurity.

DISCUSSION

In a unique model of identical twins discordant for fetal growth, within-pair comparison demonstrated a significantly higher prevalence of ROP in the smaller twin compared to the larger twin. Although being genetically identical, FGR is associated with almost tripled odds of developing any stage of ROP. Since these twins do not only differ in birth weight but also duration of mechanical ventilation, duration of oxygen supplementation and timing of the first red blood cell transfusion, both unfavorable growth conditions in utero and adverse neonatal conditions may influence postnatal retinal vascular proliferation.

Several pathophysiological mechanisms may underlie the observed within-pair difference in ROP between the smaller and larger twin. Firstly, FGR was previously identified as a risk factor for ROP by way of lower circulatory IGF-1 level, which can contribute to postnatal arrest of retinal vascular growth (phase I).[6,28] Consequently, the retina becomes hypoxic and VEGF will increase, resulting in poorly perfusing neovascularization (phase II), as sufficient levels of IGF-1 are required for appropriate vascular growth.[1,29] This suggests that unfavorable growth conditions in utero may emphasize the adverse effect of reduced IGF-1 levels on postnatal retinal vascular proliferation.

Another possible explanation for the higher prevalence of ROP in the smaller twin is related not only to lower birth weight, but also to the additional neonatal morbidities associated with FGR.[10,11] We found that the smaller twin of twin pairs at risk of ROP development had a significantly longer duration of mechanical ventilation and supplemental oxygen therapy, in line with previous results from our research group in the same cohort.[12] Prolonged mechanical ventilation is a well-known risk factor for ROP.[30] The association between prolonged duration mechanical ventilation and ROP development may be influenced by a confounding variable, namely prolonged use of supplemental oxygen.[31] Supplemental oxygen can lead to additive hyperoxia, an important cause of suppression of oxygen-regulated growth factors, particularly erythropoietin and VEGF.[1] As a consequence, retinal vascular growth ceases (phase I), the retina becomes hypoxic and VEGF will increase again (phase II).

In addition, red blood cell transfusion is considered a significant risk factor for ROP development.[30] Adult hemoglobin in red blood cell transfusions has a lower affinity for oxygen than fetal hemoglobin, leading to an increased transfer of oxygen to the retina.[32] This may induce hyperoxia and phase I of ROP development. In contrast to other literature, in our cohort, no association between the amount of blood transfusions and the risk of ROP development was found.[33,34] However, the PMA at first red blood cell transfusion appears to be of importance, considering the physiology of retinal vascularization. Recent studies suggest that hyperoxia up to a PMA of approximately 32 weeks (phase I) increases the risk of ROP development, whereas prevention of hypoxia beyond the PMA of approximately 32–34 weeks (phase II) decreases the risk of ROP development.[1,2,35] In our cohort, the smaller twin received red blood cell transfusions at a lower PMA compared to the larger twin, increasing the probability of hyperoxia during phase I and thus the risk of ROP development. This may imply that the timing of red blood cell transfusions, and to a lesser extent, the amount of red blood cell transfusions, could be associated with the risk of ROP development in preterm neonates.

It is important to acknowledge that the above hypothesized pathophysiological mechanisms of ROP development are in close relation to FGR. So, it is difficult to determine through which mechanisms the association between FGR and ROP actually runs as they share pathophysiological mechanisms which are closely intertwined. Nevertheless, we have shown an association between FGR and ROP that should be considered in clinical practice when attempting to prevent ROP development or progression in neonates with FGR.

Table 1. Baseline maternal and neonatal characteristics for MC twins with discordant growth.

Characteristics	Twins with discordant growth ($n = 88$ pregnancies; 176 neonates)
Maternal age (years)	31 (28–35)
Gravidity	2 (1–3)
Parity	0 (0–1)
sFGR[a]	59/88 (67)
Type I	29/59 (49)
Type II	8/59 (14)
Type III	18/59 (31)
TTTS with discordant growth	29/88 (33)
Gestational age at diagnosis (weeks)	17.9 (16.0–19.7)
Gestational age at laser (weeks)	18.6 (16.6–20.2)
Gestational age at birth (weeks)	33.0 (30.6–35.7)
Female	80/176 (46)
Cesarean delivery	110/176 (63)
Birth weight (g)	
Smaller twin	1395 (954–1834)
Larger twin	1986 (1493–2570)
Birth weight discordance (%)	29.9 (25.0–38.1)
Small for gestational age	
Smaller twin	84/88 (96)
Larger twin	10/88 (11)

Outcomes are presented as median (interquartile range (IQR)) or *n/N* (%).
sFGR selective fetal growth restriction, *type I* positive end-diastolic flow, *type II* absent or reversed end-diastolic flow, *type III* intermittent absent or reversed end-diastolic flow, *TTTS* twin–twin transfusion syndrome.
[a]In 4/59 cases, the Gratacós type was unknown due to the unavailability of antenatal ultrasound images.

Table 2. ROP outcomes for the smaller and larger twin in growth-discordant twin pairs.

	Smaller twin ($n = 88$)	Larger twin ($n = 88$)	*p* value
ROP screening	43/88 (49)	30/88 (34)	**<0.0001**
ROP	12/88 (14)	4/88 (5)	**0.005**
ROP severity			0.632
Stage 1	4/12 (33)	3/4 (75)	
Stage 2	4/12 (33)	1/4 (25)	
Stage 3	3/12 (25)	0/4 (0)	
Stage 4	1/12 (8)	0/4 (0)	
Severe ROP	4/12 (33)	0/4 (0)	0.208
Plus disease	2/12 (17)	0/4 (0)	0.579
Laser surgery for ROP	2/12 (17)	0/4 (0)	0.579

Outcomes are presented as median (interquartile range (IQR)) or *n/N* (%).
ROP retinopathy of prematurity.
P values <0.05 are highlighted in bold.

Our findings are in line with two previous twin studies regarding ROP development in growth-discordant twins.[13,14] The retrospective cohort study by Zloto et al. studied preterm-born twin pairs ($n = 45$) with a GA at birth <34 weeks and

Table 3. Risk factors and long-term visual impairment compared for the smaller and larger twin in twin pairs at risk for ROP.

	Smaller twin ($n = 30$)	Larger twin ($n = 30$)	*p* value
ROP	9/30 (30)	4/30 (13)	**0.019**
ROP severity			0.879
Stage 1	3/9 (33)	3/4 (75)	
Stage 2	2/9 (22)	1/4 (25)	
Stage 3	3/9 (33)	0/4 (0)	
Stage 4	1/9 (11)	0/4 (0)	
Severe ROP	4/9 (44)	0/4 (0)	0.225
Plus disease	2/9 (22)	0/4 (0)	0.451
Laser surgery for ROP	2/9 (22)	0/4 (0)	0.451
Risk factors for ROP			
Mechanical ventilation (%)	12/30 (40)	18/30 (60)	**0.049**
Duration of mechanical ventilation (days)	8 (1–20)[a]	2 (1–4)[a]	**0.018**
Supplemental oxygen (%)	24/30 (80)	26/30 (87)	0.314
Duration of supplemental oxygen (days)	15 (6–39)[b]	9 (3–21)[b]	**0.010**
Red blood cell transfusion (%)	11/30 (37)	12/30 (40)	0.781
Number of red blood cell transfusions	2 (1–5)[c]	1 (1–1)[c]	0.228
1	3/30 (10)	10/30 (33)	
≥2	8/30 (27)	2/30 (7)	
PMA at first transfusion (weeks)	29.6 (28.1–31.6)	30.4 (29.7–32.6)	**0.020**
Postnatal corticosteroids	3/30 (10)	1/30 (3)	0.336
Sepsis	8/30 (27)	8/30 (27)	1.000
NEC ≥stage 2	1/30 (3)	0/30 (0)	0.320
Long-term ophthalmic sequelae	3/24[d] (13)	1/24[d] (4)	0.335

Outcomes are presented as median (interquartile range (IQR)) or *n/N* (%).
ROP retinopathy of prematurity, *PMA* postmenstrual age, *NEC* necrotizing enterocolitis.
P values <0.05 are highlighted in bold.
[a]Among those who received at least 1 day of mechanical ventilation.
[b]Among those who received at least 1 day of supplemental oxygen therapy.
[c]Among those who received at least 1 red blood cell transfusion.
[d]Among those of at least 2 years of age.

described a higher rate of ROP for the smaller twin compared to the larger twin (9% versus 0%, respectively).[13] Petricli et al. focused on discordant twin pairs ($n = 52$) born <32 weeks GA and also found that the incidence of any stage ROP was higher in the smaller twin than the larger twin (35% versus 13%).[14] Both studies concluded that birth weight, independent of GA, contributes to the development of ROP. In addition, the latter demonstrated that being born SGA was independently associated with any stage of ROP. Conversely, Woo et al. did not find significant differences in ROP between smaller and larger twins in a retrospective cohort study of discordant twin pairs ($n = 55$) who underwent ROP screening and thereby concluded that GA is a better predictor of ROP than birth weight.[15] The reason for their conflicting results may be the lower BWD threshold that

was used (14%). Yet, all three studies lacked a distinction of chorionicity or zygosity.

When interpreting our data, certain limitations should be taken into account. Firstly, the retrospective design may introduce bias. Secondly, smaller twins were screened more often than larger twins, which potentially introduced screening bias. Nevertheless, none of the larger twins who were screened without fulfilling the ROP screening criteria presented with ROP, indicating that the risk of screening bias in this study was probably low. Lastly, excluding twin pairs in which neonatal death occurred could have led to a selection of twins with milder postnatal course. Nevertheless, we described ROP development in a relatively large cohort of identical twin pairs, in which major confounders, such as maternal factors and GA at birth, are eliminated by performing a within-pair comparison. Larger prospective studies are warranted to provide more conclusive evidence.

In conclusion, our data show that FGR is associated with more than tripled odds of ROP development, suggesting that both adverse growth conditions in utero and adverse neonatal conditions negatively affect postnatal retinal vascular proliferation. This finding stresses the importance of close monitoring to recognize possible risk factors for ROP development or progression after FGR in an early stage, even before the first screening for ROP. In particular, more attention for preventing ROP is needed in those with FGR who received prolonged duration of mechanical ventilation, oxygen supplementation, or a red blood cell transfusion during phase I (<32 weeks PMA) of ROP development.

DATA AVAILABILITY

The dataset generated and analyzed during the current study is available from the corresponding author on reasonable request. The request will be reviewed by the research team and the ethics committee of the LUMC.

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AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study. J.A.S., E.L., and S.G.G. contributed to data acquisition and contributed to data analysis. All authors were involved with the data interpretation. J.A.S. contributed to the draft formation. S.E.E., N.E.S.-D., F.S., J.M.M.v.K., E.L., and S.G.G. revised it critically for important intellectual content. All authors approved with the final version.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The ethics committee of the LUMC waived the requirement for written informed consent (protocol number G20.004).

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Jip A. Spekman.

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