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Prevalence and Risk Factors of Cerebral Lesions in Neonates After Laser Surgery for Twin-Twin Transfusion Syndrome

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Abstract

Objective—To identify risk factors for cerebral lesions among survivors of TTTS treated with laser surgery.

Study Design—A multilevel regression analysis examined risk factors for neonatal cerebral lesions identified by imaging. Imaging was routine in “high-risk survivors”, defined as those delivered at <32 weeks' gestation, and by clinical indications if born later. Severe lesions were defined as: intraventricular hemorrhage grade III–IV, cystic periventricular leukomalacia, ventriculomegaly and/or hydrocephalus, microcephaly, infarctions, porencephalic/Dandy-Walker cysts, or bilateral other cysts.

Results—For 262 consecutive laser-treated TTTS patients, 18 neonates had severe lesions identified among 427 individual survivors (4.2%) and 242 “high-risk survivors” (7.4%). Forty-six newborns had any cerebral lesion, resulting in lesion rates of 10.8%–19.0%. Delivery <32 weeks' (OR=4.95, $p<0.001$) and <28 weeks' (OR=6.25, $p<0.001$) gestation were associated with increased likelihood of any cerebral lesion.

Conclusions—This cohort showed low rates (4–7%) of severe neonatal cerebral lesions, with prematurity being the primary risk factor.

Keywords

cerebral lesions; imaging; neurological; outcome; twin-twin transfusion syndrome

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INTRODUCTION

Twin-twin transfusion syndrome (TTTS) occurs in monochorionic twin gestations due to unbalanced exchange of blood through placental vascular communications. The optimal treatment for TTTS is selective laser photocoagulation of communicating vessels (SLPCV), which has led to improved single and dual twin survival.^{1–3} With this improvement in survival, concern exists regarding risk factors to neonatal neurological status and later neurodevelopmental outcomes.

There is a relative paucity of data regarding neurological outcomes after laser surgery, particularly involving U.S. patients. In a systematic review and meta-analysis of neurodevelopmental outcomes after laser therapy for TTTS published in 2011, seven articles were identified that described neonatal neurological outcomes.⁴ Overall, the prevalence of neurologic morbidity, defined as cerebral injury on imaging, cerebral palsy, blindness, and/or deafness, was 6.1%.⁴ Studies with particular emphasis on neonatal cerebral imaging have shown rates of severe cerebral lesions of 5–14%.^{5–7} The 2011 meta-analysis also showed that the prevalence of long-term neurodevelopmental impairment was 11.1%,⁴ with rates of cerebral palsy in the range of 4–6%.^{8–9} Thus, counseling of prospective TTTS patients contemplating laser surgery must take into account survival statistics as well as potential neurological morbidity. Elucidation of the types of cerebral lesions and the antecedent factors would enhance parental counseling and decisions regarding treatment.

The aim of this study was to determine the prevalence of neonatal cerebral lesions and risk factors among TTTS survivors treated with laser surgery in a large cohort of U.S. patients.

MATERIALS AND METHODS

Study population

All consecutive patients that were treated for TTTS between March 2006 and May 2011 were considered eligible for this retrospective study. TTTS was diagnosed at initial assessment at Los Angeles Fetal Therapy (University of Southern California) if the monochorionic-diamniotic multiple gestation had a maximum vertical pocket of fluid 8 cm in the recipient's sac and 2 cm in the donor's sac. Each case was prospectively classified according to the Quintero staging system.¹⁰ Patients were not offered laser surgery if preoperative ultrasound revealed abnormal intracranial findings, including intraventricular hemorrhage, porencephalic cysts, hydrocephalus, isolated ventriculomegaly (atrium >20 mm), or congenital anomaly including Dandy-Walker syndrome, holoprosencephaly, and agenesis of the corpus callosum. All cases were exclusively treated via selective laser photocoagulation of communicating vessels (SLPCV) with or without sequential technique, as described in detail previously.¹¹ Umbilical cord occlusion is not a treatment option for TTTS at this center.

After laser surgery, the patients were referred back to their perinatologists for further pregnancy management. Delivery and 30-day survival information were collected at their respective intervals. Placental pathological evaluation and injection studies were performed using previously reported methodology.¹² Medical records of delivery, neonatal course, and all identified imaging reports were retrieved and reviewed. With few exceptions, neonates with a gestational age (GA) < 32 weeks had routine cerebral imaging, and neonates with a GA ≥ 32 weeks had cerebral imaging when clinically indicated or deemed appropriate by the NICU team. “High-risk survivors” were defined as 1) those delivered at a GA < 32 weeks, and 2) those born later for whom cerebral imaging was performed because of a clinical indication. Cerebral imaging was defined as a post-natal intracranial ultrasound, CT scan, and/or MRI. Reported results defaulted to the confirmatory scans. This study was

approved by the Institutional Review Board of the Health Sciences Campus of the University of Southern California.

Measures

Potential risk factors measured at the individual (i.e., fetal) level included donor status (1=donor, 0=recipient) and birth weight (kg). Potential risk factors measured at the pregnancy level (i.e., measurements that would be identical within a pair of twin fetuses) included Quintero stage (ordinal with range 1 to 4); gestational ages at diagnosis, surgery, and birth (in weeks); existence of a triplet (1=triplet pregnancy, 0=no triplet); co-twin intrauterine fetal demise (1=co-twin fetal demise, 0=no fetal demise); and presence of residual vascular anastomoses via placental injection studies (1=residual anastomoses, 0=no residual anastomoses). Gestational age at birth was also recoded into a binary indicator of prematurity under 32 weeks (1=age < 32 weeks, 0=age ≥ 32 weeks) and under 28 weeks (1=age < 28 weeks, 0=age ≥ 28 weeks). All “singletons” of triplet gestations (i.e. the triplet not involved in the fetio-fetal transfusion) were excluded from the analysis; however, the analysis did include twin survivors of triplet gestations.

For the cerebral lesion outcomes, “any lesions” were defined as: intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (PVL), ventriculomegaly and/or hydrocephalus, microcephaly, single or multiple infarctions, congenital anomalies, porencephalic or Dandy-Walker cysts, nonspecific echogenicity, and bilateral/multiple subependymal, pseudo-, or choroid plexus cysts identified on neonatal imaging (coded 1=any lesion, 0=no lesion). “Severe lesions” excluded cases with only grade I–II IVH and/or nonspecific echogenicity.^{13–15} Unilateral subependymal, pseudo-, and choroid plexus cysts were not included in “any lesions” and excluded from the analysis as incidental findings.¹⁶

Statistical analyses

SPSS (version 19) was used for data management and reporting of univariate statistics. Mplus software (version 6) was used to perform multilevel logistic regression analysis,¹⁷ also known as hierarchical linear modeling or hierarchical regression analysis,^{18–21} with twins grouped or “nested” within pregnancy. In the present study, a multilevel approach accounts for shared variance within twin pairs, which is created by pregnancy and family factors that are equivalent among the twins, as well as for heterogeneity between pregnancies and families. In this way, multilevel analysis allows us to simultaneously model the effects of both individual (i.e., fetus-level) and pregnancy-level risk factors on the likelihood of cerebral lesion development.

Regression models initially included donor status and birth weight at the individual level and Quintero stage, gestational ages at diagnosis, surgery, and birth, existence of a triplet, co-twin demise, and presence of residual vascular anastomoses at the pregnancy level. Due to the very low incidence of severe cerebral lesions among neonatal survivors in this cohort, risk factors to severe lesion development were not investigated further. Thus, only the presence of any lesion was regressed on the individual- and pregnancy-level risk factors. Risk factors to any lesion development were first tested individually (unadjusted model) and then simultaneously (adjusted model), and non-significant predictors were systematically removed from the adjusted model.

RESULTS

A total of 262 consecutive TTTS cases were treated via SLPCV between March 2006 and May 2011. Of the 262 twin gestations, 242 (92%) had at least one neonatal survivor and 185 (71%) had dual survivors at 30 days. All demises prior to 30 days after birth, whether

intrauterine (N=78) or in the neonatal period (N=19), were excluded from the analysis. Of the 427 “total survivors”, 137 were delivered at a gestational age of less than 32 weeks, and 134 of those had routine cranial ultrasounds. Of the remaining 290 30-day survivors that were born at or beyond 32 weeks' gestation, 108 had cerebral imaging due to other clinical indications, and 182 had no clinical indication for imaging and thus did not undergo an imaging procedure. Thus, among our sample, 242 “high-risk survivors” had delivery, demographic, 30-day survivorship, and imaging information available for analysis (see Figure 1).

Among the entire cohort of 427 survivors, 46 (10.8%) had a documented cerebral lesion and 18 (4.2%) had a documented severe lesion if survivors with only grade I–II IVH and/or nonspecific echogenicity were excluded. All survivors with a documented cerebral lesion (N=46) had a cranial ultrasound except for one who had magnetic resonance imaging only. Of the 45 survivors with a cranial ultrasound, 12 had an additional follow-up magnetic resonance imaging and 2 others had follow-up computed tomography scan. Among the 242 “high-risk survivors” indicated for cerebral imaging, the rates for any cerebral lesion and severe cerebral lesion were 19.0% and 7.4%, respectively. In this sub-group of “high-risk survivors”, the prevalence of any cerebral lesion and severe cerebral lesion in the survivors born between 24 to <28 weeks was 44.7% and 18.4%; between 28 and <32 weeks was 20.8% and 7.3%; and 32 weeks or greater was 8.3% and 3.7%, respectively (see Figure 2).

Table 1 presents descriptive statistics for the risk factors and outcomes by donor/recipient status and overall for the “high-risk survivors”. Multiple lesions were found in several of these survivors. Documented severe lesions included: grade III or IV IVH (N=6; 2.5%), PVL (N=7; 3%), ventriculomegaly/hydrocephalus (N=6; 2.5%), microcephaly (N=1; 0%), Dandy-Walker cyst (N=1; 0%), and bilateral or multiple choroid plexus cysts (N=1; 0%). No survivors were diagnosed with single or multiple infarctions. There were seven survivors with residual anastomoses; among these, two had grade I–II IVH and one had a co-twin with an intrauterine fetal demise (IUFD) but no lesions. None of the survivors with residual anastomoses had severe lesions. No significant difference in the rate of any cerebral lesion were noted in the sub-group of “high-risk survivors” with an IUFD (7.7%) compared to those with dual survivors (20.4%, $p=0.18$). Similarly, no difference in prevalence of severe cerebral lesions were detected in these two sub-groups (3.8% vs. 7.9%, $p=0.70$, respectively).

Using the multilevel modeling approach, it is possible to compute an intraclass correlation that represents the proportion of total variation in the outcome present at each level of the model. The intraclass correlation of the empty model for any lesion (i.e., a multilevel model with no predictors) was 0.259, indicating that roughly a quarter of the variation in any lesion development outcome was attributable to pregnancy-level, rather than individual-level, effects, demonstrating the need to account for both sources of variation in modeling survivor outcomes. A series of multilevel logistic regression models were then conducted in Mplus to investigate the relationships, if any, between individual- and pregnancy-level risk factors and likelihood of any lesion. Table 2 presents the unadjusted regression model results from a series of analyses in which each risk factor for any lesion was tested in the model one-at-a-time. Higher birth weight (kg) (OR=0.12, 95% CI=[0.04,0.34], $p<0.001$) and later gestational age at birth (OR=0.73, 95% CI=[0.63,0.85], $p<0.001$) were protective. The binary indicator of prematurity defined as birth <32 weeks (OR=4.95, 95% CI=[1.91,12.81], $p=0.001$) and < 28 weeks (OR=6.25, 95% CI=[2.16–18.07], $p=0.001$) were significant risk factors for development of any lesion in the “high-risk survivors”.

Subsequently, the effects of all potential individual- and pregnancy-level risk factors were modeled simultaneously in a multivariate multilevel regression model. Separate models

were run including either gestational age at birth or the prematurity indicator. In the multivariate model, only birth weight (OR=0.11, 95% CI=[0.04,0.31], $p<0.001$) remained a significant risk factor for any lesion development. Curiously, triplet pregnancy (OR=0.20, 95% CI=[0.04,0.98], $p<0.05$) became significantly associated with a lower odds of any lesion after controlling for the variance associated with low birth weight. After accounting for the variance explained by these predictors in the adjusted model, 18.4% of the variation in the occurrence of any lesion remained at the pregnancy rather than individual level.

COMMENT

This US cohort of TTTS twins treated with laser surgery showed rates of severe neonatal cerebral lesions between 4% (entire cohort) and 7% ("high-risk survivors"). Preterm birth and low birth weight were the primary risk factors associated with the detection of any cerebral lesion. This study supports the contention of previous reports that have suggested that neurological morbidity after laser surgery for TTTS results primarily from prematurity related complications.²² These findings suggest that optimization of length of pregnancy may be a key factor to avoiding cerebral lesions in TTTS survivors.

While not deterministic, studies have shown an increased risk of abnormal neurodevelopmental outcomes with the presence of severe cerebral lesions. A meta-analysis among preterm infants found that after a specific abnormality is identified on cranial ultrasound, there was a higher post test probability for the presence of cerebral palsy or neuromotor impairment for grade III IVH (26%), grade IV hemorrhage (53%), cystic PVL (74%), ventricular dilation (22%), and hydrocephalus (27%).²³ Despite these increased risks, multiple factors influence neurodevelopmental outcomes, making cerebral imaging part of an overall risk profile.²⁴ Formal neurodevelopmental testing of the individuals in this cohort at two years of age is ongoing.

There were several pertinent negative results in this study. The intrauterine demise of one twin did not put the surviving co-twin at an increased risk of a cerebral lesion, as would be the case in a monochorionic twin gestation that did not undergo laser surgery.²⁵ This would lead to the speculation that SLPCV may be protective in the surviving co-twin, but this study lacked the power and appropriate study design to test this hypothesis. Assuming all vascular communications have been successfully occluded, the laser surgery transforms the pregnancy into a functional dichorionic twin gestation, thereby rendering the circulatory systems of the twins independent of one another. The rate of residual anastomoses was relatively low in this cohort (3%). However, there were seven survivors that had a residual anastomosis after laser surgery; fortunately, none had a severe cerebral lesion, though two showed less significant grade I–II IVH. Second, the lack of effect of Quintero stage was surprising based on previous long-term studies.⁴ Finally, this study did not find donor/recipient status, or gestational age at diagnosis or surgery, to be significant risk factors.

The primary methodological strength of this study was the relatively large sample size available for analysis. The extensive prospectively collected data of prenatal and postnatal risks were used to determine clinically relevant factors to these immediate neurological outcomes. However, there are several important weaknesses of this study. First, cerebral lesions were not common, thus this study may overemphasize the significance of risk factors common to the few participants who suffered lesions. A larger cohort may indeed identify further risk factors for cerebral lesions (other than prematurity and birth weight) that may be clinically important. Second, the study used clinical data from the various birth hospitals, which could have led to misclassification or omission of lesions based on the expertise of the radiologist. Third, scans were not available on the 182 late preterm or term survivors who had no clinical indication for imaging. Thus, the regression models for any cerebral

lesions were performed in the “high-risk survivors”, which may underestimate the final odds ratio for prematurity in this model. On the other hand, there is the possibility that cerebral lesions were not detected in this sub-group. These could lead to over- or underestimation of the prevalence of lesions. We tried to take this into account by reporting a range of severe cerebral lesion rates of 4%, which includes the entire cohort, and 7%, which includes only the “high risk survivors” with clinically indicated imaging. Fourth, data were not available to document the timing of these lesions. Fifth, limitations in the study methodology cannot take into account survivorship bias, or those individuals who may have died with cerebral lesions. Finally, unmeasured covariates could have led to confounding and played a role in creating worse outcomes for some participants.²⁶

In summary, we found a relatively low prevalence (4 to 7%) of severe cerebral lesions in neonatal survivors of TTTS after laser surgery. The primary risk factor for these lesions appears to be prematurity and low birth weight. The clinical relevance of these lesions must be seen in the correlation with later neurodevelopmental outcomes. Further investigation of the presence of cerebral lesions as a risk factor to later neurodevelopmental outcomes is ongoing.

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REFERENCES

1. Rossi AC, D'Addario V. Laser therapy and serial amnioreduction as treatment for twin-twin transfusion syndrome: a metaanalysis and review of literature. *Am J Obstet Gynecol.* Feb; 2008 198(2):147–52. [PubMed: 18068144]
2. Ahmed S, Luks FI, O'Brien BM, Muratore CS, Carr SR. Influence of experience, case load, and stage distribution on outcome of endoscopic laser surgery for TTTS--a review. *Prenat Diagn.* Apr; 2010 30(4):314–9. [PubMed: 20101672]
3. Chmait RH, Kontopoulos EV, Korst LM, Llanes A, Petisco I, Quintero RA. Stage-based outcomes of 682 consecutive cases of twin-twin transfusion syndrome treated with laser surgery: the USFetus experience. *Am J Obstet Gynecol.* May; 2011 204(5):393, e1–6. [PubMed: 21411051]
4. Rossi AC, Vanderbilt D, Chmait RH. Neurodevelopmental outcomes after laser therapy for twin-twin transfusion syndrome: a systematic review and meta-analysis. *Obstet Gynecol.* Nov; 2011 118(5):1145–50. [PubMed: 22015883]
5. Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. *N Engl J Med.* Jul 8; 2004 351(2):136–44. [PubMed: 15238624]
6. Quarello E, Molho M, Ville Y. Incidence, mechanisms, and patterns of fetal cerebral lesions in twin-to-twin transfusion syndrome. *J Matern Fetal Neonatal Med.* Aug; 2007 20(8):589–97. [PubMed: 17674276]
7. Lopriore E, van Wezel-Meijler G, Middeldorp JM, Sueters M, Vandenbussche FP, Walther FJ. Incidence, origin, and character of cerebral injury in twin-to-twin transfusion syndrome treated with fetoscopic laser surgery. *Am J Obstet Gynecol.* May; 2006 194(5):1215–20. [PubMed: 16647903]
8. Sago H, Hayashi S, Saito M, Hasegawa H, Kawamoto H, Kato N, et al. The outcome and prognostic factors of twin-twin transfusion syndrome following fetoscopic laser surgery. *Prenat Diagn.* Dec; 2010 30(12-13):1185–91. [PubMed: 21064193]
9. Quintero RA, Dickinson JE, Morales WJ, Bornick PW, Bermudez C, Cincotta R, et al. Stage-based treatment of twin-twin transfusion syndrome. *Am J Obstet Gynecol.* May; 2003 188(5):1333–40. [PubMed: 12748508]
10. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. *J Perinatol.* Dec; 1999 19(8 Pt 1):550–5. [PubMed: 10645517]

11. Chmait RH, Khan A, Benirschke K, Miller D, Korst LM, Goodwin TM. Perinatal survival following preferential sequential selective laser surgery for twin-twin transfusion syndrome. *J Matern Fetal Neonatal Med.* Jan; 2010 23(1):10–6. [PubMed: 19626566]
12. Chmait RH, Assaf SA, Benirschke K. Residual vascular communications in twin-twin transfusion syndrome treated with sequential laser surgery: frequency and clinical implications. *Placenta.* Jul; 2010 31(7):611–4. [PubMed: 20451248]
13. Rosier-van Dunne FM, van Wezel-Meijler G, Bakker MP, de Groot L, Odendaal HJ, de Vries JI. General movements in the perinatal period and its relation to echogenicity changes in the brain. *Early Hum Dev.* Feb; 2010 86(2):83–6. [PubMed: 20153941]
14. Hines N, Mehta T, Romero J, Levine D. What is the clinical importance of echogenic material in the fetal frontal horns? *J Ultrasound Med.* Dec; 2009 28(12):1629–37. [PubMed: 19933475]
15. Yamamoto N, Utsu M, Serizawa M, Ohki S, Murakoshi T, Seguchi M, et al. Neonatal periventricular leukomalacia preceded by fetal periventricular echodensity. *Fetal Diagn Ther.* Jul-Aug; 2000 15(4):198–208. [PubMed: 10867479]
16. Fernandez Alvarez JR, Amess PN, Gandhi RS, Rabe H. Diagnostic value of subependymal pseudocysts and choroid plexus cysts on neonatal cerebral ultrasound: a meta-analysis. *Arch Dis Child Fetal Neonatal Ed.* 2009; 94:F443–F446. [PubMed: 19321510]
17. Muthén, LK.; Muthén, BO. *Mplus User's Guide*; Sixth Edition. Los Angeles, CA: Muthén & Muthén; 1998–2010.
18. Snijders, T.; Bosker, R. *Multilevel analysis: An introduction to basic and advanced multilevel modeling.* Sage; Thousand Oaks, CA: 1999.
19. Raudenbush, SW.; Bryk, AS. *Hierarchical linear models.* Second Edition. Sage; Newbury Park, CA: 2002.
20. Hox, J. *Multilevel analysis: Techniques and applications.* Erlbaum; Hillsdale, NJ: 2002.
21. Mehta PD, Neale MC. People are variables too: multilevel structural equations modeling. *Psychol Methods.* Sep; 2005 10(3):259–84. [PubMed: 16221028]
22. Lenclen R, Ciarlo G, Paupe A, Bussieres L, Ville Y. Neurodevelopmental outcome at 2 years in children born preterm treated by amnioreduction or fetoscopic laser surgery for twin-to-twin transfusion syndrome: comparison with dichorionic twins. *Am J Obstet Gynecol.* Sep; 2009 201(3):291, e1–5. [PubMed: 19608152]
23. Nongena P, Ederies A, Azzopardi DV, Edwards AD. Confidence in the prediction of neurodevelopmental outcome by cranial ultrasound and MRI in preterm infants. *Arch Dis Child Fetal Neonatal Ed.* Nov; 2010 95(6):F388–90. [PubMed: 20870903]
24. Hintz SR, O'Shea M. Neuroimaging and neurodevelopmental outcomes in preterm infants. *Semin Perinatol.* Feb; 2008 32(1):11–9. [PubMed: 18249235]
25. Ong SS, Zamora J, Khan KS, Kilby MD. Prognosis for the co-twin following single-twin death: a systematic review. *BJOG.* Sep; 2006 113(9):992–8. [PubMed: 16903844]
26. Behrman, RE.; Butler, AS. *Preterm Birth: Causes, Consequences, and Prevention.* Board on Health Sciences Policy; The National Academies Press; Washington, DC: 2007.

Figure 1.
Flow diagram of study cohort. TTTS = twin-twin transfusion syndrome; GA = gestational age.

Figure 2.
Prevalence of any cerebral lesion and severe cerebral lesion after laser surgery for TTTS in the “high-risk survivors” according to gestational age at birth. GA=gestational age.

Table 1

Descriptive statistics of donors, recipients, and both in “high-risk survivors” (N=242).

	Donors N (%) or mean (SD)	Recipients N (%) or mean (SD)	Overall N (%) or mean (SD)
<i><u>Individual-level</u></i>			
Donor status	111 (46%)	131 (54%)	242 (100%)
Birth weight (kg)	1.33 (0.53)	1.64 (0.56)	1.50 (0.57)
<i><u>Pregnancy-level</u></i>			
GA diagnosis	20.74 (2.52)	20.57 (2.54)	20.65 (2.52)
GA surgery	20.81 (2.50)	20.65 (2.51)	20.72 (2.51)
GA birth	31.32 (3.09)	31.30 (3.15)	31.31 (3.12)
Prematurity < 32 weeks	61 (55%)	73 (56%)	134 (55%)
Quintero stage			
Stage I	17 (15%)	18 (14%)	35 (14.5%)
Stage II	21 (19%)	24 (18%)	45 (19%)
Stage III	62 (56%)	75 (57%)	137 (57%)
Stage IV	11 (9%)	14 (11%)	25 (10%)
Triplet pregnancy	9 (8%)	12 (9%)	21 (9%)
Co-twin demise	5 (4.5%)	21 (16%)	26 (11%)
Residual anastomoses	3 (3%)	4 (3%)	7 (3%)
<i><u>Outcome</u></i>			
Any lesion	22 (20%)	24 (18%)	46 (19%)
Severe lesion	10 (9%)	8 (6%)	18 (7%)
IVH (any)	16 (14%)	21 (16%)	37 (15%)
IVH (grade 1–2)	12 (11%)	19 (15%)	31 (13%)
IVH (grade 3–4)	4 (4%)	2 (2%)	6 (2.5%)
PVL-cystic	4 (4%)	3 (2%)	7 (3%)
Ventriculomegaly/Hydrocephalus	4 (4%)	2 (2%)	6 (2.5%)
Microcephaly	1 (1%)	0 (0%)	1 (0%)
Single or multiple infarctions	0 (0%)	0 (0%)	0 (0%)
Porencephalic/Dandy-Walker cysts	1 (1%)	0 (0%)	1 (0%)
Bilateral or multiple choroid plexus cyst	0 (0%)	1 (1%)	1 (0%)
Single choroid plexus cyst	5 (5%)	6 (5%)	11 (4.5%)
Subependymal or pseudocyst	0 (0%)	4 (3%)	4 (2%)
Nonspecific echogenicity	1 (1%)	2 (2%)	3 (1%)

Table 2

Unadjusted multilevel regression results describing independently tested individual-level and pregnancy-level characteristics of any cerebral lesion in “high-risk survivors”.

<i>Individual-level</i>	Odds Ratio	95% CI	p-value
Birth weight	0.12	[0.04,0.34]	<0.001
Donor status	1.14	[0.56,2.31]	0.72

<i>Pregnancy-level</i>	Odds Ratio	95% CI	p-value
Quintero stage	1.05	[0.67,1.65]	0.83
GA diagnosis	1.10	[0.95,1.28]	0.21
GA surgery	1.09	[0.94,1.27]	0.24
GA birth	0.73	[0.63,0.85]	<0.001
Prematurity < 32 weeks	4.95	[1.91,12.81]	<0.001
Prematurity < 28 weeks	6.25	[2.16,18.07]	<0.001
Triplet pregnancy	0.37	[0.07,1.88]	0.23
Co-twin demise	0.27	[0.05,1.46]	0.13
Residual anastomoses	1.81	[0.11,29.49]	0.68