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Original article

Preterm twin and triplet pregnancies are at increased risk for the development of cystic periventricular leukomalacia

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ABSTRACT

Background: An increased risk of cerebral palsy in multiples has been reported.
Aims: To determine the risk for the development of periventricular leukomalacia (PVL) of twin and triplet pregnancy.
Study design: Retrospective single-centre study at a tertiary care university hospital.
Subjects: Infants ≤35 weeks gestational age born between 1988 and 2008.
Outcome measures: Risk of twin and triplet compared to singleton pregnancy regarding development of PVL in one offspring.
Results: Of 6195 infants 117 singletons and 39 multiples were diagnosed as having cystic PVL. Perinatal data did not differ as did not ultrasonographic findings and neurologic outcome. The relative risk (RR) of a twin pregnancy resulting in at least one infant with PVL when born prior to 36 weeks was 2.181 (CI 95% 1.474–3.228, $p < .0001$), and 6.793 (CI 95% 2.470–13.108, $p < .0001$) of a triplet pregnancy. In-vitro fertilisation was present in 3% of affected twins compared to 100% in triplets ($p < .001$).
Conclusion: We found an increased risk for PVL in preterm twin and triplet pregnancies.

1. Introduction

Multiple pregnancy is an increasing entity worldwide associated with increasing numbers of preterm birth, intrauterine growth retardation, and higher infant mortality rates with disadvantages reported to be associated with male gender.[1–7] Additionally, an increased risk of cerebral palsy (CP) in multiples has been reported that was higher the higher the number of fetuses was.[8–12] As regards the specific type of CP, data collected from 12 European population-based CP registers on 6613 children revealed that in comparison to singletons, multiples had higher rates of spastic CP (91 vs. 87%, OR 1.59, $p < .006$), and CP was more likely to be bilateral (73 vs. 65%, OR 1.57, $p < .001$).[13] This type of CP correlates with brain MRI findings showing that the most common finding consisted of white matter injury including periventricular leukomalacia (PVL, 42.5%) followed by basal ganglia lesions (12.8%).[14] Several causative mechanisms have been suggested

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to explain the unique characteristics associated with higher rates of CP in multiples, but it is estimated that approximately 80% of the causes of CP in multiples are of antenatal origin.[15]

Multiple pregnancies have been identified as a risk factor for PVL in some studies,[16–19] but data are conflicting. We aimed to determine the risk for the development of cystic PVL in twin and triplet compared to singleton pregnancies in preterm infants of equal or less than 35 weeks of gestational age.

2. Patients and methods

This is a retrospective analysis of all infants ≤35 weeks of gestational age with cystic PVL documented by ultrasound scans (US) admitted to the Division of Neonatology of the Department of Paediatrics of the Medical University of Graz, Austria, a tertiary care centre, between 1988 and 2008. The medical charts, the ultrasound scans and the data from our Outpatient Clinic of Neurodevelopmental Follow-up were reviewed. The number of all preterm infants ≤35 weeks of gestational age from singleton birth having been hospitalized at our two neonatal intensive care units was calculated from a local electronic data base as was the number of all twins and triplets. During the study period no quadruplet and one quintuplet birth was observed; the latter was excluded from analysis. The incidence of PVL in case of twin or triplet pregnancy was either calculated as one per pregnancy or one per infant revealing different prevalence rates. The study was approved by the local ethic committee (21-051 ex 09/10). Perinatal data of the study patients included all relevant epidemiological and clinical parameters as shown in part in Table 1.

Cranial US scans were routinely obtained in all preterm infants on days 1, 3, 5, and thereafter once a week in cases with pathological findings. Real-time US scans were performed with a commercially available unit (Advanced Technology Laboratories Inc., Bothell, WA, USA) using a 7.5 or 8.2 MHz transducer, and multiple images were obtained in the coronal and sagittal planes through the anterior fontanel as described elsewhere.[19,20] Cystic PVL always was confirmed by several neonatologists experienced in cranial US and in case of doubts confirmed by a paediatric radiologist. For *neurodevelopmental outcome* infants were examined at the corrected age of 4, 8, 12, 18, and 24 months, thereafter once yearly. Assessment of outcome was made using the developmental tests as described by Griffith[21] in the first two years, by Kaufman[22] after these years, and neurological examinations as described by Amiel-Tison[23] and Touwen.[24]

Statistical analysis was done with SPSS version 17 (SPSS Inc., 2008, Chicago, USA) and Microsoft Excel 2007 (Microsoft Corporation, 2007, Redmond, USA). Risk factors for presence of PVL were determined using chi-square test and Mann–Whitney test. Binary logistic regression analysis with stepwise forward selection was performed using all significant variables from the univariate analysis as predictor and singleton and multiple pregnancies as outcome variable. A p-value $<.05$ was considered to be significant. Relative risks and 95% confidence intervals were calculated using the software package CIA – Confidence Interval Analysis (Version 2.0.0, Statistics with Confidence, London, BMJ publishing group 2000).

Table 1 – Perinatal and outcome data of 157 infants ≤35 weeks of gestational age with diagnosis of cystic periventricular leukomalacia and selected risk factors comparing singletons and multiples.

	Singletons	Multiples	p-value
Number	117	39	
Gestational age (in weeks)	31 ± 2.5	31 ± 2.4	.255
Birth weight (grams)	1477 ± 422	1501 ± 417	.372
Small for gestational age	11 (9)	2 (5)	.203
Male sex	72 (62)	19 (49)	.081
1 min Apgar score	6.9 ± 1.9	6.5 ± 2.2	.142
5 min Apgar score	8.7 ± 1.2	8.6 ± 1.3	.208
Breech presentation	20 (17)	10 (26)	.115
IVH grade 2	10 (9)	0 (0)	.024
Cerebral palsy	95 (81)	30 (77)	.283
Caesarean section	51(44)	28 (73)	.001
PPROM	68 (58)	13 (33)	.005
Chorioamnionitis	54 (46)	11 (28)	.039
Fetal distress	40 (34)	7 (18)	.001
Hyperbilirubinaemia	62 (53)	9 (23)	.001

Data are presented as n (%) or mean ± SD.
PPROM: preterm premature rupture of the membranes; IVH: intraventricular haemorrhage.

3. Results

During the study period 6200 infants were born ≤35 weeks of gestational age and hospitalized at our two neonatal wards. 4926 births were singleton pregnancies, 579 twins, 37 triplets, and one quintuplet that was excluded from further analysis (see Fig. 1).

A total of 156 infants were diagnosed as having cystic PVL diagnosed by ultrasound scans resulting in an overall PVL rate of 2.5% (156/6195). Calculated per infant 117 out of 4926 singletons (2.4%), 32 out of 1158 twins (2.8%, $p = .221$), and 7 out of 111 triplets (6.3%, $p = .004$ compared to singletons, $p = .019$ compared to twins) were affected by cystic PVL.

Calculated per pregnancy the rate of cystic PVL in singletons was 2.4% (117/4926), 5.2% (30/579) in twins and 13.5% (5/37) in triplets. In two twin pregnancies both infants were diagnosed as having PVL, as were two infants affected in two triplet pregnancies. The relative risk (RR) for twin pregnancy resulting in preterm birth ≤35 weeks and having at least one preterm infant with PVL was 2.181 (CI 95% 1.474–3.228, $p < .0001$), and for triplet pregnancy 6.793 (CI 95% 2.470–13.108, $p < .0001$). The RR increased by 2.608 (1.075–6.329, $p = .017$) from twin to triplet pregnancy.

In twin pregnancy PVL was diagnosed in the first twin in 50% of cases, in the second twin in 38%, and in both twins in 12%. In-vitro fertilisation was present in 3% of affected twin pregnancies compared to 100% in triplet pregnancies ($p < .001$). Twin-to-twin transfusion syndrome was present in 13% of affected twin and 20% of affected triplet pregnancies (differences not significant). Monochorionicity was observed in 27% of affected twin and 20% of affected triplet pregnancies.