Outcome in single and twin pregnancies at 20 to 24 weeks gestation: ten years experience in one perinatal center

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Summary

Objective: The aim of this investigation was to evaluate the outcome at 20 to 24 weeks gestation of twin and singleton extremely low birth weight infants. *Study Design:* The authors conducted a retrospective cohort study of live newborns at 20 to 24 weeks gestation admitted to one neonatal intensive care unit (NICU) from 2000 to 2009. Outcome mortality and predictors of outcome were evaluated. Results were compared for twin and singleton infants. *Results:* The cohort of infants consisted of 60 singleton infants and 17 twins. The results suggest an increased risk of death for twins when compared with singletons. A correlation between neonatal C-reactive protein (CRP) and bacterial culture positive results on admission to NICU might be a predictor of neonatal outcome. *Conclusion*: In extremely low birth weight infants, twin delivery is associated with an independent increased risk of death. Both first- and second-born twins are at increased risk.

Key words: Twins; Extremely low birth weight infants; Mortality; Predictors.

Introduction

Current guidelines are restrictive about life-supporting management at 20 to 24 weeks gestation [1], however this is based on limited data.

In twins, a five-fold higher risk of cerebral palsy has been described compared with singletons [2]. Term twins similarly showed to have a higher morbidity and mortality [3]. Controversy exists regarding more adverse outcomes among second-born twins [4-7]. In the same birth weight category, very low birth weight twins (birth weight < 1,500 g) had similar short-term outcomes compared to singleton infants [8, 9]. Growth-restricted twins and singletons were similar in the two groups, although worse compared with non-growth-restricted infants [10].

At 18 to 22 months, corrected age, extremely low birth weight twins were associated with an independent increased risk of death or neurodevelopmental impairment compared with singleton infants [11]. First- and second-born twins were at increased risk [10].

To the authors' knowledge, there has been no report on the outcome of infants at the border of life (20 to 24 weeks gestation). This retrospective cohort study was designed to compare the short-term neonatal outcomes of twin in comparison with singleton infants for whom life support is controversial.

Materials and Methods

This is a retrospective cohort study of all live newborns at 20 to 24 weeks gestation at the Frankfurt University Hospital from January 1, 2000 to December 31, 2009.

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In total there were 106 infants born from 81 mothers. Of these infants, 60 were singletons and 34 were twins and 12 were triplets (no higher-order multiples).

Infants with a birth weight between 350 and 820 g were included in the study. The cohort consisted of 57 singleton and twin infants admitted to the neonatal intensive care unit (NICU), who were inborn and met the criteria.

Twenty-six singletons (13 intrauterine fetal transfusion (IUFT) and 13 deaths in delivery room) and 11 twins (six IUFT and five deaths in delivery room) had an intra-uterine death or died in the delivery room and were excluded from further evaluation (Figure 1). A total of nine newborns were excluded from the study because of death before 12 hours of life. Of these, six were twins and three were singletons. If one of the sets of twins died before 12 hours of age (n = 2), the second twin was included in further analysis. Higher-order multiple births (triplets = 12 and quadruplets = 0) were excluded from the study.

Newborns were analyzed as singleton and twin cohorts, which were further analyzed as first-born twins (twin A) vs singletons, second-born twins (twin B) vs singleton and first-born twins (twin A) vs second-born twins (twin B). Same-gender twins and unlike-gender twins were not evaluated due to the low-study numbers.

All data (outcome, demographic, and clinical characteristics) were analyzed using medical records. Death was the primary outcome.

Separately, for singleton and multiple newborns, possible predictors for perinatal outcome was evaluated: birth weight, gestational age, mode of delivery (spontaneous vaginal delivery, primary or secondary lower segment cesarean section), birth arterial pH value, length, first temperature at NICU, infant infection markers, intra-uterine steroid ripening, retinopathy, severe intraventicular (intracranial) hemorrhage (IVH, grade 3 or 4), periventricular leukomalacia (PVL), bacterial infection on admission at NICU, and hospital-acquired infection in NICU.

Statistical analysis

For statistical analyses, the Mann-Whitney test and Mantel-

Haenszel test were used. The analyses were carried out using the SPSS Statistics 17.0 software. The means and standard deviation (SD) were processed. A $p < 0.05$ for a two-tailed test was considered statistically significant.

Results

In the study group, there was no difference in gestation age between singleton and twin pregnancies (Table 1). In 33.3% of singletons (n = 60), they were discharged from hospital, however twins were only discharged in 17.6% (n = 17). This difference did not reach statistical significance difference ($p > 0.05$; Table 2). In singletons, 48.3% of newborns' deaths occurred before 12 hours of life, whereas 52.9% of twins died before 12 hours of life (twin A = 35.3%, twin B = 64.7%) ($p > 0.05$).

Between these two groups, there was no difference in age, body mass index (BMI), fetal birth weight, and length, however in the singleton study group, there were more multiparas (p = 0.001; Table 1). There was a trend of higher numbers of in-vitro fertilization (IVF) in the twin cohort, however statistical significance was not reached (p = 0.08). Since both groups had similar clinical and socio-demographic risk factors, no logistic regression adjustment was needed.

Between singleton and twin births, there was no significant difference with regards to: fetal presentation, mode of delivery, meconium staining, amniotic fluid, gender, ventilation, PVL, IVH, severe IVH (grade 3 or 4), necrotizing enterocolitis (NEC), bacterial culture positive on admission to NICU, nocosomial infections, histopathological chorionamnionitis, contractions, premature rupture of membranes, anhydramnion, vaginal bleeding, antepartum betamethasone administration, tocolysis, or no cerclage ($p > 0.05$; Table 2).

With the singletons, there was a correlation of survival with betamethasone (0.55, p = 0.001), birth weight (0.52, $p = 0.002$), mode of delivery (0.37, $p = 0.03$), and nosocomial infection (0.88, $p < 0.001$), as well as the number of nosocomial infections (0.79, $p < 0.001$). Similarly, there was a negative correlation with positive bacterial culture on admission to NICU (- 0.35, p = 0.04), high C-reactive protein (CRP) (- 0.45, $p = 0.02$) and worse grade of IVH (- 0.48, $p = 0.005$). No correlation was demonstrated for gestational age, maternal age, BMI, birth arterial pH value, length, first temperature at NICU, infant leucocytes, retinopathy, intracranial hemorrhage, PVL, histopathological chorionamnionitis, contractions, premature rupture of membranes, amniotic prolapse, IVF, anhydramnion, vaginal bleeding, tocolysis, cerclage, and fetal presentation (cephalic, breech etc.) ($p > 0.05$). There was also a correlation between gestation age and mode of delivery in singletons (0.68, $p < 0.001$).

Only twin A demonstrated a correlation of survival with nosocomial infection (0.75, p = 0.03) and the number of nosocomial infection (0.80, p = 0.02). All other parameters showed no correlation with survival ($p > 0.05$). Similarly, twin B showed no correlation at all ($p > 0.05$). Singletons had an overall discharge rate of 33.3%. Twin A and twin B had a discharge rate of 17.6% and 17.6%, respectively.

Table 1. — *Maternal and fetal demographics (mean ± standard deviation).*

Variable	Singleton (n = 59)	Twin (n = 17)	Mann-Whitney test *p* value
Age (years)	30.5 ± 5.7	31.0 ± 5.2	n. s.
Parity	1.2 ± 1.1	0.3 ± 0.5	0.001
BMI	24.7 ± 5.6	24.7 ± 5.4	n.s.
Gestation age (weeks)	23.5 ± 1.1	23.9 ± 1.0	n.s.
Fetal weight (g)	603.5 ± 126.3	584.4 ± 152.1	n.s.
Fetal length (cm)	30.6 ± 2.3	30.7 ± 1.9	n.s.

Table 2. — *Parameters assessed to predict neonatal outcome (percentage).*

	Singleton (n = 60)	Twin (n = 17)	*p* value
Discharge	33.3%	17.6%	n.s.
Presentation:			
– Cephalic? (1)	17.9%	43.7%	n.s.
– Breech? (2)	53.5%	31.3%	n.s.
– Other? (3)	25.0%	25.0%	n.s.
Mode of delivery			
– vaginal delivery	72.4%	76.%	n.s.
– 1° C-Section	8.6%	5.9%	n.s.
– 2° C-Section	19.0%	17.6%	n.s.
Meconium-stained amniotic fluid	29.8%	11.8%	n. s.
Male Infant	37.1%	44.4%	n. s.
IVF	5.7%	44.4%	n. s.
Ventilation	100.0%	100.0%	n. s.
PVL	11.8%	11.1%	n. s.
IVH	50.0%	55.6%	n.s.
– Grade 3 or 4	27.3%	55.5%	n.s.
NEC	11.8%	28.6%	n.s.
Bacterial culture positive on admission	47.1%	57.1%	n.s.
Nosocomial infection	67.6%	44.4%	n.s.
Histopathological chorionamnionitis	34.2%	18.8%	n.s.
Contractions	46.3%	47.1%	n.s.
Premature rupture of membranes	31.5%	41.2%	n.s.
Amnion prolapse	40.7%	23.5%	n.s.
Anhydramnion	7.4%	0.0%	n.s.
Vaginal bleeding	22.2%	5.9%	n.s.
Betamethasone	57.9%	58.8%	n.s.
Tocolysis	65.5%	76.5%	n.s.
No cerclage	65.5%	47.1%	n.s.

Discussion

In the last decade there has been an increase in multiple births [12], with an increasing concern that twin gestation may be associated with a higher mortality rate [13, 14]. No differences of neonatal birth weight and gestation age were detected in the two study cohorts, although neonatal mortality was higher in the twin cohort.

When adjusted for birth weight, very low birth weight twin and singleton infants controversy still exists whether in twins there is a higher adverse outcome rate [11] or not [9]. In the present study, in agreement with the study of Wadhawan *et al.* [11], the authors did find a higher mortality rate in twins compared with singletons. Similarly, twin B had slightly higher mortality rate, which adds to the con-

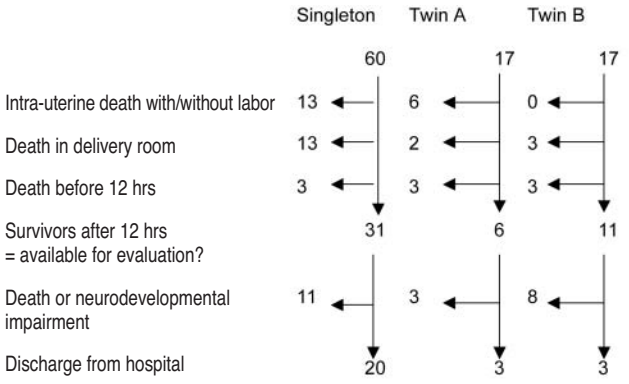

Figure 1. — Number of study infants.

troversy regarding the outcomes of twins with reference to birth order [4-7, 11].

To achieve a more homogenous group of study infants and to exclude the varying resuscitation practices in referring institutions, the authors only evaluated inborn newborns.

In singletons, the mode of delivery was correlated with survival rate, i.e. secondary lower segment Cesarean section had the highest survival rate, however the study numbers were very small. A current larger study described no effect of the mode of delivery on survival, however lower morbidity and better prognosis for neurodevelopment outcome by Cesarean section [15].

Limitations of this study are: retrospective analysis, no long-term follow up data, and important variables that might affect outcomes, such as zygosity and twin-twin transfusion syndrome [16, 17], which were not available.

The present data indicate a higher risk of death in extremely low birth weight infants, independent of the influence of prematurity and birth weight. Further prospective studies, which also examine long-term outcome, are required.

References

[1] Reinhardt D.: "Leitlinie zur Frühgeburt der Grenze der Lebensfähigkeit des Kindes". *Monatsschr Kinderheilkd*, 2008, *156*, 798.
[2] Pharoah P.O.: "Neurological outcome in twins". *Semin. Neonatol.*, 2002, *7*, 223.
[3] Barret J.F.: "Delivery oft he term twin". *Best Pract. Res. Clin. Obstet. Gynaecol.*, 2004, *18*, 625.
[4] El-Jallad M.F., Abu-Heija A.T., Ziadeh S., Obeidat A.: "Is the second-born twin at high risk?". *Clin. Exp. Obstet. Gynecol.*, 1997, *24*, 226.
[5] Sheay W., Ananth C.V., Kinzler W.L.: "Perinatal mortality in first- and second-born twins in the United States". *Obstet. Gynecol.*, 2004, *103*, 63.
[6] Rettwitz-Volk W., Tran T.M., Veldman A.: "Cerebral morbidity in preterm twins". *J. Matern. Fetal. Neonatal. Med.*, 2003, *13*, 218.
[7] Prins R.P.: "The second-born twin: can we improve outcomes?". *Am. J. Obstet., Gynecol.*, 1994, *170*, 1649.
[8] Donovan E.F., Ehrenkranz R.A., Shankaran S., Stevenson D.K., Wright L.L., Younes N., *et al.*: "Outcomes of very low birth weight twins cared for in the National Institute of Child Health and Human Development Neonatal Research Network's intensive care units". *Am. J. Obstet. Gynecol.*, 1998, *179*, 742.
[9] Wolf E.J., Vintzileos A.M., Rosenkrantz T.S., Rodis J.F., Lettieri L., Mallozzi A.: "A comparison of pre-discharge survival and morbidity in singleton and twin very low birth weight infants". *Obstet. Gynecol.*, 1992, *80*, 436.
[10] Baker E.R., Beach M.L., Craigo S.D., Harvey-Wilkes K.B., D'Alton M.E.: "A comparison of neonatal outcomes of age-matched, growth-restricted twins and growth-restricted singletons". *Am. J. Perinatol.*, 1997, *14*, 499.
[11] Wadhawan R., Oh W., Perritt R.L., McDonald S.A., Das A., Poole W.K., *et al.*: "Twin gestation and neurodevelopmental outcome in extremely low birth weight infants". *Pediatrics*, 2009, *123*, 220.
[12] Hartley R.S., Hitti J.: "Increasing rates of preterm twin births coincide with improving twin pari survival". *J. Perinat. Med.*, 2010, *38*, 297.
[13] Doyle P.: "The outcome of multiple pregnancy". *Hum. Reprod.*, 1996, *11*, 110.
[14] Mazhar S.B., Peerzada A., Mahmud G.: "Maternal and perinatal complications in multiple versus singleton pregnancies: a prospective two years study". *J. Pak. Med. Assoc.*, 2002, *52*, 143.
[15] Minguez-Milio J.A., Alcázar J.L., Aubá M., Ruiz-Zambrana A., Minquez J.: "Perinatal outcome and long-term follow-up of extremely low birth weight infants depending on the mode of delivery". *J. Matern. Fetal Neonatal Med.*, 2011, *24*, 1235 [Epub 2011, Mar. 7].
[16] Cordero L., Franco A., Joy S.D.: "Monochorionic monoamniotic twins: neonatal outcome". *J. Perinatol.*, 2006, *26*, 170.
[17] Dickinson J.E., Duncombe G.J., Evans S.F., French N.P., Hagan R.: "The long term neurologic outcome of children from pregnancies complicated by twin-to-twin transfusion syndrome". *BJOG* 2005, *112*, 63.

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