Twin versus singleton pregnancy and preterm prelabour rupture of the membranes

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Summary

Purpose: The primary purpose of this study was to compare the latency period between preterm prelabour rupture of the membranes (PPROM) and delivery in twin versus singleton pregnancies. The secondary purpose was to compare the neonatal outcome of these two groups.

Methods: A retrospective case control study was performed on 33 consecutive bichorionic twin pregnancies with gestational age 20 to 36 weeks admitted to the Antwerp University Hospital with PPROM from 1995 to 2000. These were matched with singletons experiencing PPROM at the same gestational age. Groups were compared for smoking behaviour, whether conception was spontaneous or with artificial reproductive technology, dilation at the moment of PPROM, latency period between PPROM and delivery, the use of tocolytics, antibiotics, corticosteroids, cervicovaginal culture results and neonatal morbidity and mortality.

Results: The latency period was significantly shorter in twins (median 19 versus median 47 hours; p = 0.01) and significantly more twins were born within 48 hours after rupture of the membranes (74.2 % versus 51.5 %; p = 0.01). This is due to a difference in the group with gestational age 30 or less weeks, after gestational age 30 weeks no significant difference exists. No other differences were noted between groups.

Conclusion: No clinically relevant differences for the perinatal outcome after PPROM in twin versus singletons can be noted, but delivery is more likely to result within 48 hours after PPROM in cases of a twin pregnancy.

Key words: Twins; Preterm prelabour rupture of the membranes.

Introduction

Preterm prelabour rupture of the membranes (PPROM) complicates between 3% and 18.5% of pregnancies and is responsible for about 30% of all premature deliveries [1, 2]. Few and contradicting data are available in PPROM in twin gestation [3-5]. The aim of this study was to compare the outcome of twin versus singleton pregnancies after PPROM.

Materials and Methods

A hospital based case-control study was performed matched for gestational age. All twin gestations with PPROM presenting at the Antwerp University Hospital between January 1, 1995 and December 31, 2000 at a gestational age from 20 to 36 weeks were matched with the first two singleton pregnancies hospitalised for PPROM at the same gestational age. If the patient was in labour on admission, she was excluded. Only diamniotic dichorionic (based on first trimester ultrasound) twins were included. During the study period the standard treatment of patients with PPROM before 34 weeks gestational age in our centre consisted of bethamethasone (2 x 12 mg) intramuscularly if no clinical signs of chorioamnionitis were present and tocolysis with ritodrine, indomethacin or nifedipine if labour developped without manifest signs of chorioamnionitis. Steroids and tocolytics were not used after 34 weeks' gestation. From 1995 to 1997 antibiotics were not routinely administered, from 1997 erythromycine (3 x 500 mg orally for 5 days) was given. All fetuses were monitored with daily cardiotocography, weekly biophysical profile score and umbilical artery pulsatility index.

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The following factors were registered on the mother: age, tobacco use, dilatation at the moment of diagnosis of PPROM, latency period, white blood cell count and C-reactive protein on admission, spontaneous pregnancy or pregnancy after artificial reproductive technology (including hormonal stimulation and/or in vitro fertilisation), the results of cervicovaginal cultures, the presence of choioamnionitis or endomyometritis and all drugs administered after PPROM and before delivery.

Tobacco use was registered as smoking or non-smoking, not as the actual number of cigarettes per day. PPROM was diagnosed if clinically amniotic leakage was evident, confirmed by aseptic speculum vaginal examination. In case of doubt, an insulin-like growth factor binding protein-1 test (Actim PROM, Medex, Biochemica, Finland) was performed. The latency period was defined as the time between PPROM and birth of the fetus. Chorioamnionitis was diagnosed on cultures of placenta and membranes and/or histopathologic placental infiltration with leucocytes [7]. Endomyometritis was diagnosed clinically based on fever (≥ 38°C), uterine tenderness and purulent lochia.

For the newborn the following factors were registered: birthweight, artificial ventilation, 1 and 5 minute Apgar score, the presence of transient tachypnea of the neonate (TTN), respiratory distress syndrome (RDS) [6], intraventricular hemorrhage (IVH), necrotising enterocolitis (NEC), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), early and late onset infections, septicaemia, persisting ductus arteriosus (PDA)and neonatal mortality. TTN was defined as a respiratory rate ranging from 60 to 120 breaths/minute with possible hyperinflation with grunting, chest wall retractions and nasal flaring [8]. RDS was defined radiologically and scored according to the classic criteria [9]. IVH was graded according to Papile *et al.* [10], and PVL was diagnosed by transfontanellar ultrasound. NEC was considered to be present based on one or more guanic stools plus radiologic criteria [11]. Sepsis was defined as a pos-

itive blood culture with a recognized pathogen and with the presence of clinical and laboratory signs of infection [12]. Infections were defined as early onset if presenting within the first four days after birth and as late onset after the fifth day. ROP was classified in five distinct stages [13]. Intrauterine growth restriction was considered when neonatal weight was below the tenth percentile for gestational age in our population [14]. The total number of days the infant needed artificial ventilation, including intermittent positive pressure (IPPV) and continuous positive airway pressure (CPAP) were recorded.

Groups were compared using the Chi-square test and 95% confidence intervals for proportions; for continuous variables a Kolmogorov-Smirnov test for normality was performed, Student's t-test and 95% confidence intervals for the difference between the means were used; data that were not normally distributed were analysed using the Mann-Whitney U test. Significance was accepted at $p < 0.05$. Analysis was performed using SPSS 10.0.

Results

No statistically significant difference was present for maternal age, primiparity, maternal smoking behaviour, the presence of pathogenic bacteria in cervicovaginal culture, C-reactive protein and white blood cell count at onset, dilation at first clinical examination or the presence of chorioamnionitis (Table 1), nor for the use of tocolytics, antibiotics and corticosteroids (Table 2). The latency period is significantly shorter in twins and the odds ratio for the mother of a twin to give birth within 48 hours after PPROM is 2.5 with a 95% confidence interval between 1.2 and 5.2.

Further analysis demonstrated that this difference is most outspoken at an earlier gestational age; for gestational age 30 or less weeks (7 pregnancies in each group) the latency period is significantly shorter (median for twins 19 hours, range for twins 7 to 456 hours; median for singletons 132 hours, range for singletons 4 to 1176 hours; $p = 0.01$ in the Mann-Whitney U test) but this is not the case for a gestational age of more than 30 weeks (26 pregnancies in each group; median for twins 17 hours, range for twins 2 to 504 hours; median for singletons 41 hours, range for singletons 2 to 576 hours; $p = 0.25$ in the Mann-Whitney U test).

Multiple regression analysis with the latency period as a dependent variable demonstrated that only gestational

Table 1. — *Pregnancy and maternal characteristics.*

	Twins N. = 33		Singletons N. = 66		p value	OR	95% CI
	Median	Range	Median	Range			
Dilatation at start (cm)	0	0 to 5	0	0 to 6	0.79	–	–
Latency period (hours)	19	2 to 504	47	2 to 1176	0.01	–	–
WBC count at onset	11	4 to 33	12	6 to26	0.25	–	–
	Mean	SD	Mean	SD			
Maternal age (year)	29.8	4.3	29.4	4.9	0.64	–	–1.98 to 1.22 *
	N = 33	%	N = 66	%			
Tobacco use	1	3.0	5	7.5	0.37	0.78	0.53 to 1.16
ART	17	51.5	3	4.5	< 0.001	2.22	5.88 to 8.33
Cervicovaginal culture positive **	14	42.4	20	30.3	0.23	1.69	0.71 to 4.03
Placental abruption	1	3	0	0	0.15	1.03	0.97 to 1.04
Chorio amnionitis	5	15.2	17	25.8	0.23	0.51	0.17 to 1.56
Endomyometritis	1	3	0	0	0.15	1.03	0.97 to 1.09
CRP at onset > 0.5	20	60.6	49	74.2	0.16	0.53	0.21 to 1.30
	N = 66	%	N = 66	%			
Delivery within 48 hours	48	74.2	34	51.5	0.01	2.5	1.21 to 5.18t
Delivery within 7 days	59	89.4	51	77.3	0.06	2.4	0.93 to 6.55
Indicated delivery for clinical infection	5	7.6	17	25.8			
Vaginal delivery	44	66.7	46	69.7	0.71	0.87	0.41 to 1.81

OR: Odds ratio; 95% CI: 95% Confidence Interval; *95% confidence interval on the difference between the means; ** A cervicovaginal culture was considered positive if any other than "normal" vaginal flora was present, including *group B Streptococci, Escherchia coli, Gardnerella vaginalis and Ureaplasme urealyticum;* CRP: C- reactive protein; WBC: White Blood Cell in cells $10^3/mm^3$; ART: pregnancy by artificial reproductive technology including in vitro fertilisation and/or ovulation induction.

Table 2. — *Drugs administered to pregnant women after PPROM and before delivery.*

	Twins N. = 33		Singletons N. = 66		p value	OR	95% CI
	N	%	N	%			
Bethametason	25	75.8	38	57.6	0.07	2.30	0.90 to 5.85
Ritodrine	27	81.8	55	83.3	0.85	0.90	0.30 to 2.69
Indomethacin	8	24.2	7	10.6	0.07	2.69	0.88 to 0.24
Nifedipin	8	24.2	12	18.2	0.47	1.44	0.52 to 3.96
Antibiotics (general)	16	48.4	30	45.45	0.36	1.49	0.62 to 3.58
Erythromycin	11	33.3	16	24.2	0.33	1.56	0.62 to 3.91
Amoxycilline clavulanic acid	4	12.1	9	13.6	0.83	0.87	0.24 to 3.08
Azithromycin	2	6.1	5	7.6	0.78	0.78	0.14 to 4.29

OR = Odds Ratio; 95% CI: 95% Confidence Interval.

age at onset of PPROM was a significant predictor of the interval between PPROM and birth ($p < 0.001$), the inclusion of the twin or singleton pregnancy as a dummy variable did not improve the model, neither did the use of tocolytic agents or antibiotics.

Neonatal outcome was completely comparable for twin and singleton pregnancies (Table 3). Neither were any differences found between the infant from the amniotic cavity with ruptured membranes versus the infant from an intact amniotic sac as demonstrated in Table 4.

Table 3. — *Neonatal outcome.*

	Twins N. = 66		Singletons N. = 66		p value	OR	95% CI
	Mean	SD	Mean	SD			
Birthweight (gram)	1719.1	591.0	1924.3	646.3	0.06	–	-8.10 to 418.5*
	Median	Range	Median	Range			
CPAP (days)	0	0 to 60	0	0 to 29	0.49	–	–
IPPV (days)	0	0 to 15	0	0 to 22	0.91	–	–
Artificial ventilation (days)	0	0 to 73	0	0 to 86	0.74	–	–
NIC (days)	12	0 to 78	10	0 to 90	0.52	–	–
	N	%	N	%			
Apgar one minute < 7	32	48.5	32	48.5	1.00	1.00	0.55 to 1.80
Apgar 5 minutes < 7	14	21.2	16	24.2	0.63	0.84	0.42 to 1.67
IUGR	4	6.1	4	6.1	1.00	1.00	0.23 to 4.17
Transient tachypnae	4	6.1	7	10.6	0.25	0.34	0.15 to 1.95
RDS	19	28.8	19	28.8	1.00	1.00	0.47 to 2.12
IVH	3	4.5	6	9.1	0.30	0.47	0.11 to 1.99
NEC	1	1.5	2	3	0.56	0.49	0.04 to 5.57
PVL	0	0	2	3	0.15	0.97	0.92 to 1.01
ROP	2	3	0	0	0.15	1.03	0.98 to 1.07
Early onset infection	3	4.5	1	1.5	0.31	3.09	0.31 to 30.5
Late onset infection	4	3	1	1.5	0.55	2.03	0.18 to 22.9
Sepsis	0	0	2	3	0.15	0.97	0.92 to 1.01
PDA	7	10.6	14	21.2	0.09	0.44	0.16 to 1.17
Neonatal mortality	6	9.1	5	7.6	0.75	1.22	0.35 to 4.2

*95% Confidence interval on the difference between the means; OR: Odds ratio; 95% CI: 95% Confidence interval; (1) 95% CI on the difference between the means; SD: Standard deviation; CPAP: Continuous positive airway pressure; IPPV: Intermittent positive pressure ventilation; NIC: Neonatal intensive care; IUGR: Intrauterine growth restriction; RDS: Respiratory distress syndrome; IVH: Intraventricular hemorrhage; NEC: Necrotising enterocolitis; PVL: Periventricular leukomalacia; ROP: Retinopathy of prematurity; PDA: Patent ductus arteriosus.

Table 4. — *Twin group: infant from amniotic sac with ruptured membranes versus sibling from intact amniotic sac.*

	Neonate with PPROM		Neonate with intact membranes n = 33		p value	OR	95% CI
	Mean	SD	Mean	SD			
Birthweight (grams)	1646.8	580.2	1791.3	602.6	0.32	–	–435 to 146 *
	Median	Range	Median	Range			
Latency period (hours)	19	2 to 504	19	2 to 504	0.96	–	–
CPAP (days)	0	0 to 60	0	0 to 46	0.88	–	–
IPPV (days)	0	0 to 10	0	0 to 15	0.51	–	–
Artificial ventilation (days)	0	0 to 73	0	0 to 54	0.75	–	–
NIC (days)	16.9	19.4	17.5	17.7	0.90	–	9.72 to 8.57
	N	%	N	%			
Apgar one minute > 7	13	39	19	57	0.40	1.08	0.78 to 8.57
Apgar 5 minutes > 7	6	18	8	24	0.54	1.44	0.43 to 4.73
IUGR	2	6	2	6	1.00	1.00	0.13 to 7.55
Transient tachypnea	1	3	3	9	0.30	0.31	0.03 to 3.23
RDS	10	30	9	27	0.78	1.16	0.4 to –3.45
IVH	2	6	1	3	0.55	2.10	0.18 to 2.58
NEC	1	3	0	0	0.31	1.03	0.97 to 1.09
Early onset infection	2	6	1	3	0.55	2.10	0.17 to 25
Late onset infection	1	3	1	3	1.00	1.00	0.06 to 16.7
PDA	4	12	3	9	0.68	1.38	0.28 to 6.66
Neonatal mortality	3	9	3	9	1.00	1.00	0.18 to 5.35

*95% Confidence interval on the difference between the means; SD: Standard deviation; OR: Odds ratio; 95% CI: 95% Confidence interval; CPAP: Continuous positive airway pressure; IPPV: Intermittent positive pressure ventilation; NIC: Neonatal intensive care; IUGR: Intrauterine growth restiction; RDS: Respiratory distress syndrome; IVH: Intraventricular hemorrhage; NEC: Necrotising enterocolitis; PDA: persisting ductus arterioses.

Discussion

PPROM has been noted to be twice as frequent in twins as compared to singleton pregnancies [3]. The difference in latency period we describe confirms the findings of Bianco *et al.* [4] who concluded that twin pregnancies with PPROM at less than or equal to 36 weeks' gestational age, have a decreased latency period when compared to matched singletons. On the other hand both Hsieh *et al.* and Mercer *et al.* found no difference in latency period but both groups remarked that when PPROM occurred at 30 or more weeks gestational age, latency in twins was shorter than in singleton pregnancies [3, 5]. In our analyses we cannot confirm this, on the contrary the latency period in our study was shorter in younger pregnancies. As more twin fetuses are born within 48 hours after PPROM, this is a strong argument to consider steroid administration without any delay for fetal lung maturation.

A similar perinatal and neonatal outcome for twin pregnancies with PPROM compared to matched singletons has repeatedly been reported [4, 5]. Mercer *et al.* [5] found a lower birth weight in twin versus singletons of matched gestational age. We find a non-significant trend to a higher birthweight in singletons. Differences between studies on this field may be due to differences in the distribution of gestational ages between different studies; the more infants born at a younger gestational age are included the less difference in birthweight between twins and singletons is expected to be noted [15].

It is still unclear whether PPROM induces synchronous accelerated fetal lung maturation in both twins or more rapidly in the PPROM-fetus. Contradictory results have been reported concerning the outcome for infants of ruptured versus non-ruptured amniotic sacs, with some authors mentioning more RDS for the fetus in the non-ruptured sac [3, 16], and others not confirming such differences [17]. The results are disturbed by the use of corticosteroids and by the fact that in most published studies it is not clear whether a first-born twin is actually the one with PPROM.

Conclusion

The latency period is shorter for twins after PPROM especially if PPROM occurs before 30 weeks' gestational age. As more twins will be born within 48 hours immediate administration of corticosteroids is mandatory.

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