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Results of expectant management in singleton and twin pregnancies complicated by preterm premature rupture of membranes

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ABSTRACT

Objectives: This study aimed to examine whether expectant management in twin pregnancies with preterm premature rupture of membranes (pPROM) is as safe as in singleton pregnancies.

Material and methods: It was a retrospective cohort study comparing pregnancy course and outcome in singleton (n = 299) and twin pregnancies (n = 49) complicated by preterm premature rupture of membranes. Analysed factors included maternal diseases, gestational age at premature rupture of membranes (PROM), management during hospitalization, latency periods between PROM and delivery, gestational age at delivery, neonatal management and outcome.

Results: The difference in the proportion of patients with latency up to 72 hours, latency between 72 hours and seven days, and latency exceeding seven days were insignificant. The percentage of patients who received intravenous tocolysis and antenatal corticosteroids were similar; however, patients in twin pregnancies more often received incomplete steroids dose (p = 0.01). The occurrence of the positive non-stress test result and signs of intrauterine infection were similar between the groups. No statistically significant differences in the prevalence of neonatal complications except transient tachypnoea of the newborn were identified (24% in the singleton vs 13% in the twin group, p = 0.03).

Conclusions: Expectant management of pPROM in singleton and twin pregnancies results in similar perinatal and neonatal outcome. Consequently, in case of no evident contraindications, expectant management of twin pregnancies seems to be equally as safe as in singleton pregnancies. Patients in twin pregnancies may be at higher risk of delivery before administration of full antenatal corticosteroids dose, therefore require immediate management initiation and transfer to a tertiary referral centre.

Key words: pregnancy outcome; pregnancy; twin; premature birth; preterm premature rupture of the membranes

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INTRODUCTION

Twin birth rate has been gradually increasing during the recent decades, partly due to pregnancy postponing until more advanced maternal age [1–3]. Availability of infertility treatment methods with ovulation stimulation and assisted reproductive technologies are also associated with more frequent multiple pregnancy occurrences [4, 5]. The incidence of preterm premature rupture of membranes (pPROM) in twin pregnancies is higher than in singleton pregnancies [6]. Intrauterine treatment of previously incurable conditions, including twin-to-twin transfusion syndrome leads to iatrogenic pPROM, which affects up to 50% of treated cases [7–11]. PPROM management strategies in singleton pregnancies include planned early birth and expectant monitoring [12].

Objectives

This study aimed to examine whether expectant management in twin pregnancies with pPROM is as safe as in singleton pregnancies. Neonatal complications incidence

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was compared between twin and singleton pPROM groups managed expectantly.

MATERIAL AND METHODS

Patients

It was a retrospective cohort study comparing pregnancy course and outcome in singleton and twin pregnancies complicated by preterm premature rupture of membranes. We included in our research consecutive patients with rupture of membranes before completed 37th gestational week managed in a tertiary referral centre between October 2016 and December 2018. Exclusion criteria were as follows: patients in multiple pregnancies with more than two foetuses and with congenital foetal anomalies. There were altogether 7198 births during the observation period. Out of them, 299 patients in singleton and 49 in twin pregnancies met the criteria of the study — 4.1% and 0.7% of all births, accordingly. In the twin pregnancy group, there were 40 patients in dichorionic diamniotic pregnancies and nine patients in monochorionic diamniotic pregnancies. Analysed factors included maternal diseases, gestational age at PROM, management during hospitalization, latency periods between PROM and delivery, gestational age at delivery, neonatal management and outcome.

Management

PPROM diagnosis was based on speculum examination, rapid test detecting insulin-like growth factor binding protein (IGFBP-1) and ultrasound scan. Expectant management included empirical antibiotic prophylaxis with intravenous cefuroxime for ten days, non-stress tests, ultrasound examinations, and monitoring of serum inflammatory markers levels. The antibiotic therapy was modified if needed according to the results of each patient's individual cervical culture result and antibiogram collected on admission as soon as it was available. Every two weeks, we repeated the cervical swab and continued personalized antibiotic treatment, if the result was positive. Latency period was identified as the time between pPROM and birth.

Neonatal outcome

Low birth weight was defined as birth weight below 2500 g, very low birth weight — as birth weight under 1500 g, and extremely low birth weight — as birth weight less than 1000 g. We considered the birth weight below 10th percentile as hypotrophy. Early-onset sepsis (EOS) occurred within 72 hours after birth, whereas late-onset sepsis (LOS) developed after 72 hours after delivery. We diagnosed transient tachypnoea of the newborn and respiratory distress syndrome based on clinical presentation and chest X-ray. Respiratory failure was defined as persistent hypoxemia or hypercapnia despite surfactant therapy and 'maximal' conventional ventilation.

Statistical analysis

Statistical analysis was performed using Statistica 13 (StatSoft. Inc.): the T-Student test — for quantitative data comparison between two groups and two-sided Fisher's exact test — for discrete variables.

RESULTS

Group characteristics

Mean maternal age was similar between the groups (Tab. 1). There were no differences regarding primiparity. The history of the previous caesarean section more often occurred in singleton pregnancies ($p = 0.04$).

Differences in the incidence of the following features were insignificant: gestational diabetes, pregestational diabetes, hypertension, hypothyroidism, and intrahepatic cholestasis of pregnancy (Tab. 1). There was no difference in the incidence of cervical insufficiency, the need for cervical cerclage or gestational age at PROM (32.8 vs 32.7 weeks) and delivery (33.5 vs 33.2 weeks). The difference in the proportion of patients with latency up to 72 hours, latency between 72 hours and seven days, and latency exceeding seven days were insignificant (Tab. 2).

Differences in the occurrence of the pathogenic culture of cervical specimen collected in all patients and amniotic fluid obtained during caesarean sections were also non-significant (Tab. 1). The percentage of patients who received intravenous tocolysis and antenatal corticosteroids were similar; however, patients in twin pregnancies more often received incomplete steroids dose ($p = 0.01$) (Tab. 3). The occurrence of the positive non-stress test result and signs of intrauterine infection were similar between the groups (Tab. 3). More patients in the twin group delivered by C-section ($p < 0.001$) but the emergency caesarean section rate was comparable (Tab. 3).

Neonatal outcome

Children born from twin pregnancies had lower mean birth weight ($p < 0.001$) and length ($p = 0.049$). There was no difference regarding the ponderal index between compared groups. No statistically significant differences in the prevalence of neonatal complications except transient tachypnoea of the newborn were identified (24% in the singleton vs 13% in the twin group, $p = 0.03$) (Tab. 4). In the singleton group, there was an association between positive maternal cervical culture and more frequent development of early-onset sepsis in newborns ($p = 0.015$). That was not valid for the twin group. Distribution of early-onset sepsis in children from singleton and twin pregnancies depending on the result of maternal cervical culture is presented in Figures 1 and 2.

Table 1. Group characteristics and pregnancy course

Feature	Singleton pregnancies (n = 299)	Twin pregnancies (n = 49)	p
Mean maternal age [years]	32.6	31.9	0.43
Primiparity (%)	132 (44)	26 (53)	0.28
History of caesarean section (%)	69 (23)	5 (10)	0.04
Cervical insufficiency (%)	47 (16)	12 (24)	0.15
Cervical cerclage (%)	10 (3)	0	0.36
Gestational diabetes mellitus (%)	71 (24)	8 (16)	0.27
Pregestational diabetes mellitus (%)	20 (7)	2 (4)	0.75
Hypertension (%)	24 (8)	3 (6)	1
Intrahepatic cholestasis of pregnancy (%)	9 (3)	4 (8)	0.09
Hypothyroidism (%)	58 (19)	14 (29)	0.18
Pathogenic cervical culture (%)	130 (43)	21 (43)	1
Pathogenic amniotic fluid culture* (%)	19 (14)	3 (8)	0.42
Intrauterine foetal demise (%)	2 (0.7)	0	1

*Amniotic fluid culture was performed only in patients undergoing caesarean section: n = 135 in singleton pregnancies and n = 40 in twin pregnancies

Table 2. Gestational age and latency period

Feature	Singleton pregnancies, n = 299	Twin pregnancies, n = 49	p
Gestational age at PROM [weeks]	32.8	32.7	0.84
Gestational age at delivery [weeks]	33.5	33.2	0.49
Latency period up to 72 h (%)*	202 (68%)	39 (80%)	0.10
Latency period between 72 h and 7 days (%)*	45 (15%)	6 (12%)	1
Latency period over 7 days (%)*	52 (17%)	4 (8%)	0.14

*Latency period between PROM and delivery; PROM — premature rupture of membranes

Table 3. Preterm premature rupture of membranes management

Feature	Singleton pregnancies, n = 299	Twin pregnancies, n = 49	p
Intravenous tocolysis (%)	105 (35)	22 (45)	0.2
Antenatal corticosteroids, any dose (%)	184 (62)	36 (73)	0.11
Antenatal corticosteroids, incomplete dose (%)	35 (12)	13 (27)	0.01
Antenatal corticosteroids, full dose (%)	149 (50)	23 (47)	0.76
Birth within 48 h — 14 days after antenatal corticosteroids full dose administration (%)	61 (20)	5 (10)	0.12
Birth after 14 days since antenatal corticosteroids full dose administration (%)	27 (9%)	3 (6%)	0.59
Positive non-stress test (%)	48 (16)	3 (6)	0.08
Signs of intrauterine infection (%)	24 (8)	2 (4)	0.56
Caesarean section (%)	135 (45)	40 (82)	< 0.001
Non-cephalic presentation, active phase of labor (%)	47 (16)	35 (71)	< 0.001
Emergency caesarean section (%)	41 (14)	5 (10)	0.25

The subgroup analysis concerning neonatal complications rate and duration of the latency period, shown that newborns born from singleton pregnancies within 72 hours after pPROM more frequently developed transient tachypnoea than newborns born from twin pregnancies (23.5 % vs 11.5%, p = 0.02) (Fig. 3 and 4).

Table 4. Comparison of neonatal outcome

Feature	Children born from singleton pregnancies, n = 297	Children born from twin pregnancies, n = 98	p
Birth weight			
Mean birth weight [g]	2416	2027	< 0.001
Mean length [cm]	49.4	46.3	0.049
Median ponderal index [g/cm^3]	19.5	19.7	0.88
Low birth weight (%)	106 (36)	69 (70)	< 0.001
Very low birth weight (%)	19 (6)	13 (13)	0.51
Extremely low birth weight (%)	13 (4)	3 (3)	0.77
Birth weight below 10th percentile (%)	8 (3)	6 (6)	0.12
Respiratory complications			
Pulmonary hypoplasia (%)	2 (0.7)	2 (2)	0.29
Respiratory distress syndrome (%)	38 (13)	12 (12)	1
Pneumothorax (%)	6 (2)	0	0.34
Transient tachypnoea of the newborn (%)	72 (24)	13 (13)	0.03
Broncho-pulmonary dysplasia (%)	20 (7)	7 (7)	0.81
Pulmonary hypertension (%)	12 (4)	1 (1)	0.2
Respiratory failure (%)	77 (26)	25 (25)	1
Infectious complications			
Early-onset sepsis (%)	23 (8)	3 (3)	0.15
Late-onset sepsis (%)	14 (5)	6 (6)	0.6
Pneumonia (%)	13 (4)	6 (6)	0.42
Other complications			
Hyperbilirubinemia (%)	182 (61)	68 (68)	0.08
Anaemia (%)	49 (16)	24 (24)	0.07
Hypoglycaemia (%)	51 (17)	13 (13)	0.43
Intraventricular haemorrhage (%)	20 (7)	3 (3)	0.22
Necrotizing enterocolitis (%)	5 (2)	0	0.34
Retinopathy (%)	7 (2)	3 (3)	0.71
Circulatory failure (%)	20 (7)	2 (2)	0.12
Death (%)	6 (2)	3 (3)	0.7
Management			
NICU admission (%)	76 (26)	21 (21)	0.5
Mechanical ventilation (%)	46 (15)	8 (8)	0.09
nCPAP* (%)	100 (34)	33 (33)	1
Mean hospitalization duration [days]	22.34	20.88	0.55

*Neonatal Continuous Positive Airway Pressure

DISCUSSION

Overall, we identified more similarities than differences between analysed groups. One of the differences regarding the neonatal outcome in singleton and twin pregnancies complicated by pPROM was mean birth weight, mean length and the occurrence of low birth weight. These findings, however, are not directly associated with the course of pPROM. It is known that neonates born from multiple gestations have constitutionally lower birth weight than children from singleton pregnancies [13–15]. The incidence of neonatal birth weight below 10th percentile and difference in the median ponderal index were insignificant. The pregnancy course in singleton and twin pregnancies in this study was characterized by similar mean gestational age at PROM

and delivery. Patients in the twin group more often received incomplete antenatal corticosteroids dose. However, the percentage of patients who delivered between 48 hours and 14 days since the completion of antenatal corticosteroids dose was similar in both groups. We did not observe any differences in the occurrence of the following neonatal complications: pulmonary hypoplasia, respiratory distress syndrome, pneumothorax, broncho-pulmonary dysplasia, pulmonary hypertension, respiratory failure, use of mechanical ventilation, nor use of neonatal continuous positive airway pressure (nCPAP). There was a higher prevalence of transient tachypnoea of the newborn in the singleton group. The reason for it could be a difference in indications for the caesarean section between the groups. Because of more frequent non-cephalic presentation in the twin group, higher percentage of patients underwent caesarean section during the early active phase of labour, which decreases the risk of transient tachypnoea of the newborn [16].

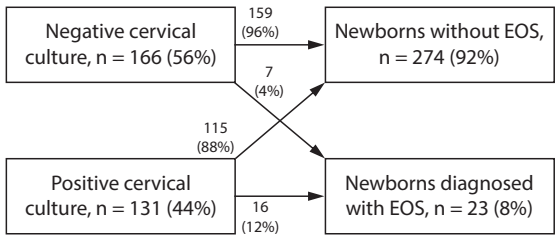

Figure 1. Association between maternal cervical culture results and the occurrence of early-onset sepsis in newborns from singleton pregnancies; p = 0.015; EOS — early-onset sepsis

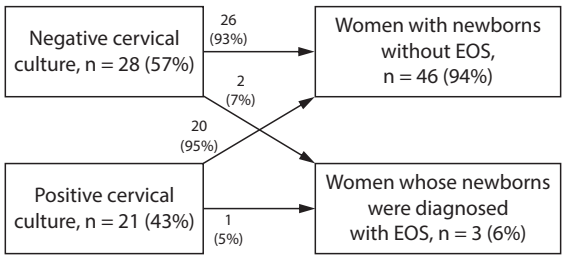

Figure 2. Association between maternal cervical culture results and the occurrence of early-onset sepsis in newborns from twin pregnancies; p = 1; EOS — early-onset sepsis

In a retrospective cohort study by Bianco et al. comparing the outcome of 116 singletons and 116 twin pregnancies complicated by pPROM and managed expectantly, a decreased median latency period in the second group was observed (19.5 hours vs 11.5 hours) [17]. Authors reported no other differences in perinatal nor neonatal outcomes. Twin gestation was also one of the factors influencing latency period in cases of pPROM analysed in a retrospective study (n = 303) by Dagklis et al. [18]. The mean interval between pPROM and delivery was 5.5 and 3.3 days for singleton and twin pregnancies, respectively. In another retrospective case-control study comparing the results of expectant management in pPROM, the median latency period in twin pregnancies was significantly shorter than in singleton gestations, lasting 19 vs 47 hours (p = 0.01) [19]. Ekin et al. [20] obtained similar results in a cohort study from Turkey analysing the outcome of 3257 pregnancies complicated

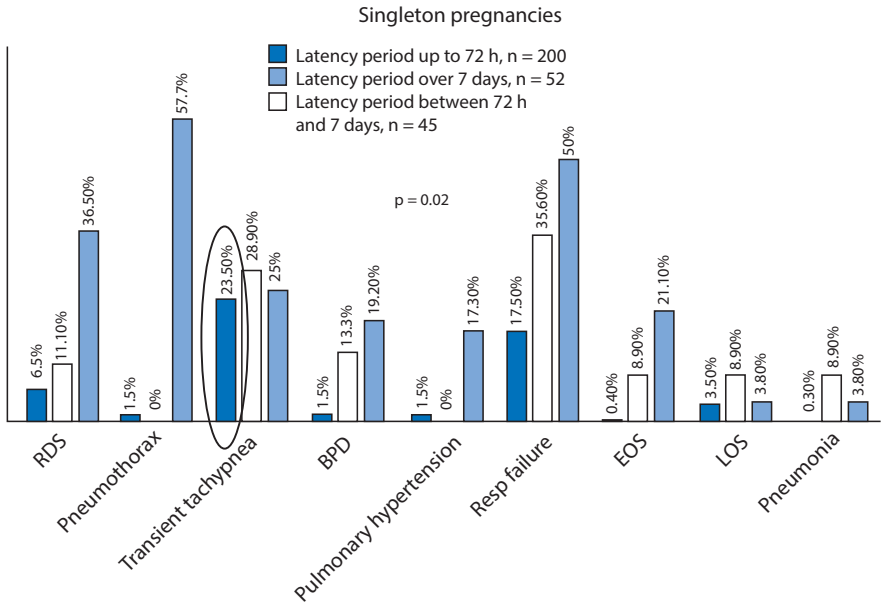

Figure 3. Association between latency periods and the occurrence of neonatal complications in singleton pregnancies; BPD — bronchopulmonary dysplasia; EOS — early-onset sepsis; LOS — late-onset sepsis; RDS — respiratory distress syndrome

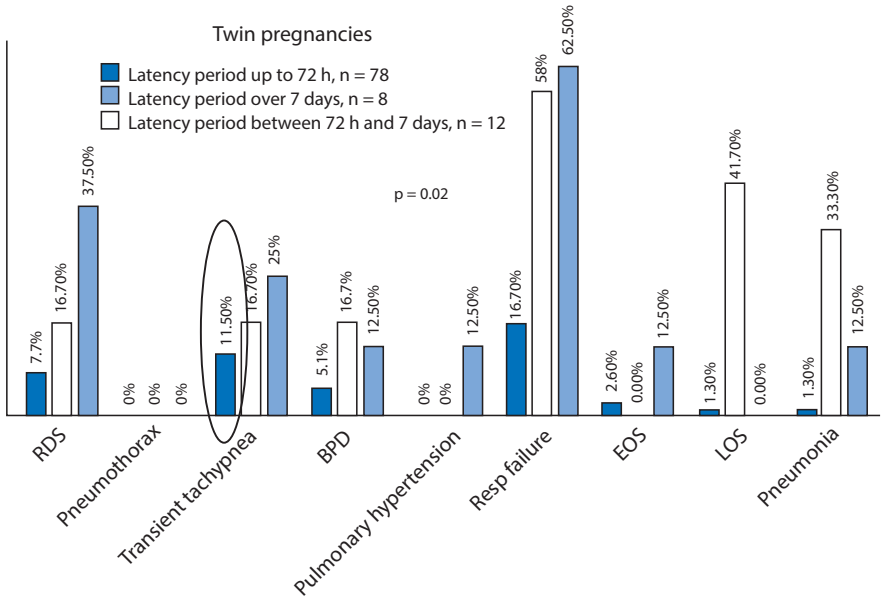

Figure 4. Association between latency periods and the occurrence of neonatal complications in twin pregnancies; BPD —bronchopulmonary dysplasia; EOS — early-onset sepsis; LOS — late-onset sepsis; RDS — respiratory distress syndrome

by pPROM between 24 and 34 gestational weeks. All mentioned studies focused on the comparison of median latency periods between pPROM and delivery. In our research, more emphasis is put on the completion of antenatal corticosteroids dosage, rather than on the median latency period alone. We analyzed the percentage of patients who delivered in less than 72 hours following pPROM after receiving incomplete corticosteroids dose and patients who gave birth between 48 hours and 14 days since the completion of antenatal corticosteroids. No difference in the occurrence of delivery within 72 hours from pPROM was identified (Tab. 2). However, a higher proportion of patients who delivered before receiving the complete corticosteroids dose was observed in the twin group (Tab. 3).

In a study by Ehsanipoor et al. [21], the difference in latency period was not statistically significant (median 3.6 days in twin and median 6.2 days in singleton pregnancies, p = 0.86). The prevalence of infections among newborns from twin pregnancies analysed in this study was lower than in children from singleton pregnancies (9.8% vs 23.2%). Our observations confirmed the higher prevalence of neonatal early-onset sepsis in association with positive maternal cervical culture within the singleton group (Fig. 1), which was insignificant in the twin group (Fig. 2).

Regarding the neonatal complications, our study did not determine any crucial differences between singleton and twin pregnancies. Other authors reported similar findings [17, 19, 22]. In a study by Kibel et al. [23] comparing singleton and twin pregnancies with pPROM, twin pregnancies were complicated by rupture of membranes at more advanced gestational age (29.1 vs 28.5 weeks, p = 0.03), had shorter latency period (5.0 vs 7.0 days, p = 0.01) and a lower rate of chorioamnionitis. In our study, both the gestational age at PROM and the prevalence of intrauterine infection symptoms, early-onset sepsis, late-onset sepsis, and neonatal pneumonia were similar among singleton and twin pregnancies. According to Trentacoste et al. [24], in the case of twin pregnancies, the infection can be the consequence rather than the cause of pPROM. Antibiotics administration in gestations complicated by pPROM is considered beneficial both as prevention of intrauterine infections and as the reduction in prematurity due to pregnancy prolongation [25–27]. However, data on antibiotics use in twin pregnancies complicated by pPROM is limited. In a randomized multicentre trial ORACLE I, Kenyon et al. [25] did not observe any differences in the latency duration nor occurrence of neonatal positive blood culture between antibiotic and placebo arms in multiple pregnancies subgroup.

CONCLUSIONS

To conclude, our observations indicate that expectant management of pPROM in singleton and twin pregnancies results in similar perinatal and neonatal outcome. Consequently, in case of no evident contraindications, expectant management of twin pregnancies seems to be equally safe as in singleton pregnancies.

Patients in twin pregnancies may be at higher risk of delivery before administration of full antenatal corticosteroids dose, therefore require immediate management initiation and transfer to a tertiary referral centre.

Conflict of interest

All authors declare no conflict of interest.

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