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ORIGINAL ARTICLE

The Effect of the Cause of Delivery on Neonatal Outcomes in Early Preterm Deliveries

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Abstract The aim of this study was to evaluate the effect of causes of delivery on short-term neonatal morbidities and mortality in EPD (< 34 gestational weeks). We retrospectively analysed the deliveries occurring between 23 + 0 and 33 + 6th gestational weeks at our tertiary center during 2014–2018. A total of 290 deliveries were evaluated, and 369 newborns [singletons (56.4%), twins (36.6%) and triplets (7.1%)] were included in the study. The causes of deliveries were defined as spontaneously preterm birth (n = 107, 29%), preterm premature rupture of membranes (PPROM) (n = 131, 35.5%) or iatrogenic preterm birth (n = 131, 35.5%). The rate of neonatal respiratory distress syndrome (RDS), patent ductus arteriosus, bronchopulmonary dysplasia (BPD), intraventricular haemorrhagia (IVH), necrotising enterocolitis, retinopathy of prematurity, neonatal resuscitation, sepsis and death were similar between groups. However; neonatal RDS, BPD, IVH and sepsis were found to be higher in cases with chorioamnionitis, which could be considered as subcategory of PPROM. Preterm deliveries have an adverse effect on perinatal outcomes. Also, such causes of labor might be related to varied neonatal morbidities. However, splitting to early preterm deliveries into subgroups, according to cause of delivery, did not provide further information to predict such complications except chorioamnionitis.

Keywords Premature rupture of membranes · Prematurity—risk assessment and prevention · Premature labor

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Introduction

Early preterm delivery (EPD) is one of the most common cause of neonatal morbidity and mortality, which occurs in 12% of all pregnancies [1]. Moreover, recent studies have reported an increasing rate of EPD as a result of multiple pregnancies. Assisted reproductive technologies and maternal factors are the main causes of EPD, which occur before 34 weeks of gestation [2, 3]. The causes of preterm delivery are spontaneous labour and induction of labour with fetal-maternal reasons [4]. However, Goldenberg et al. [5] classified the causes of the preterm delivery into three groups such as iatrogenic preterm birth (IPTB), spontaneous preterm birth (SPTB) and preterm premature rupture of the membranes (PPROM).

Aims and Objectives

The aim of this study was to evaluate the effect of causes of delivery on short-term neonatal morbidities and mortality in EPD (< 34 gestational weeks).

Materials and Methods

We retrospectively evaluated the records of deliveries (included all singleton and multiple pregnancies), occurred at 23 + 0 to 33 + 6th weeks of gestation between 2014 and 2018 at our tertiary center. In utero exitus fetuses, neonates that transferred to different center, cases with unavailable hospital records, labored in < 23 and ≥ 34 week of gestation and major congenital anomalies were the exclusion criteria of the study.

The calculation of gestational week was based on last menstruation date or first trimester ultrasound measurement of the pregnant.

The indications of delivery were classified as SPTB, PPROM, and IPTB. The definitions of SPTB, PPROM and IBTB were accepted as cervical changes in the presence of regular contractions and intact membranes, anamnesis of rupture of membranes prior to labour or inspection of amniotic fluid on the speculum examination and induced vaginal delivery or cesarean section prior to spontaneous labor for maternal or fetal reasons, respectively [6].

We designated the chorioamnionitis and non-chorioamnionitis subgroups of PPROM. We accepted clinical doubt of chorioamnionitis, fever and at least one of the following findings: foul smelling/purulent cervical fluid on a speculum examination, uterine tenderness on abdominal palpation, maternal tachycardia (> 120/min), persistent fetal tachycardia (> 160/min), leucocytosis (> 15,000/mm^3) and C-reactive protein > 5 mg/L [7].

In the presence of clinical suspicion of chorioamnionitis, a pathologist performed further evaluation of placenta. Histological chorioamnionitis was described according to the Blanc classification [8].

Variables that might be related to neonatal outcomes were evaluated accordingly (maternal age, nulliparity, gestational age, birth weight, type of conception, sex, mode of delivery, maternal hypertensive disorders, diabetes, placental pathologies, use of antenatal steroids and magnesium). Also outcomes of neonates (respiratory distress syndrome (RDS), early onset sepsis, haemodynamically significant patent ductus arteriosus (PDA), moderate and severe bronchopulmonary dysplasia (BPD), intraventricular haemorrhagia (IVH) grade 3 or 4, necrotising enterocolitis (NEC) stage 2 or 3, retinopathy of prematurity (ROP), length of stay in the new-born intensive care unit (NICU), small for gestational age and mortality at discharge or at death) were interpreted. We compared neonatal outcomes at each subtypes of EPD and also cases with clinical/histological chorioamnionitis and non-chorioamnionitis subgroups of PPROM.

PPROM was conservatively managed (< 34 gestational weeks) unless chorioamnionitis or fetal distress occurs or active labour began. We administered routinely ampicillin 2 g intravenous (IV) and erythromycin 250 mg per oral (PO) every 6 h for 48 h, then ampicillin 250 mg PO and erythromycin 333 mg PO every 8 h for 5 days. If patient had an history of allergy to penicillin, erythromycin (250 mg PO every 6 h) was administered for 10 days [9]. Antibiotic treatment aims at decreasing the infection-related neonatal mortality [10].

A single course of corticosteroid is recommended for pregnant women between 23 + 0 and 33 + 6 weeks of gestation, who are at risk of preterm delivery within 7 days. Accordingly, we administered corticosteroid therapy with a protocol of two 12-mg doses of betamethasone given intramuscularly 24 h apart for fetal lung maturation [11]. We documented the antenatal steroid (betamethasone) treatment as full course when the two doses given prior to delivery or incomplete treatment when partial or no steroid were applied. We administered magnesium sulphate (4 g intravenously) for neuroprotection over 20 min and continued at 1 g/h for maintenance until 24 h [12].

We defined small for gestational age (SGA) as a birth weight < 10th percentile according to the Fenton growth charts [13].

Fetal distress was diagnosed with cardiotocogram (CTG) and Doppler measurements of umbilical artery (UA) and middle cerebral artery (MCA) evaluation. Serial ultrasounds of fetal growth, CTG, biophysical profile and Doppler were applied at least once a week in SGA and fetal growth restriction (FGR) pregnancies during the follow-up. The timing of delivery was designated according to the follow-up results. If the presence of accompanying oligohydramnios, preeclampsia, severe growth restriction and increasing umbilical artery Doppler index were observed, all the follow-up tests were performed twice a week. In the presence of reverse or absent diastolic flow in the umbilical artery or cerebroplacental Doppler ratio (CPR = MCA/UA) < 1 (brain sparing effect), daily ductus venosus wave was evaluated. When abnormal ductus venosus flow was detected, immediate delivery was planned. Also delivery was planned for patients whose gestation week ≥ 32 with a presence of reverse flow and patients whose gestation week ≥ 34 with an absent flow in umbilical artery Doppler evaluation [14, 15]. The cord blood gases was routinely measures to check the presence of acidosis in the newborn.

The surfactant was used for neonates who required intubation in the delivery room or was used as early selective therapy for neonates who have RDS according to European Consensus Recommendations [16]. The neonates, treated with surfactant were documented as having RDS. Neonates who had haemodynamically significant PDA on two-dimensional echocardiography and treated with indomethacin/ibuprofen or by surgical ligation was documented as PDA [17]. BPD was defined as oxygen use

or the need for ventilator support at 36 weeks postmenstrual age or at discharge [18]. IVH was graded using the Papile classification; grade 3 or 4 IVH was documented as significant [19]. NEC was defined according to the modified Bell's criteria; stage 2 or 3 was documented as significant [20]. Infants with stage $\geq$ 3 ROP, treated with laser photocoagulation based on the International Classification of Retinopathy of Prematurity Update; was documented as ROP [21].

Early (< 72 h) onset of sepsis was defined as the presence of bacteria or fungi in the blood culture or an antibiotic treatment of at least 5 days due to clinical or laboratory findings indicative for sepsis.

Statistical Analysis

SPSS 21.0 was used for the statistical analysis (SPSS Inc., Chicago, IL, USA). Categorical variables were assessed as numbers and percentages, and continuous variables are summarised as means and standard deviations (median and range when needed). The relationship between maternal factors and neonate outcomes were evaluated by the correlation analysis. The Chi square, Fisher's exact or one-way analysis of variance tests (ANOVA) and LSD post hoc test were used for categorical variables. A p value < 0.05 was considered as statistically significant for all analyses.

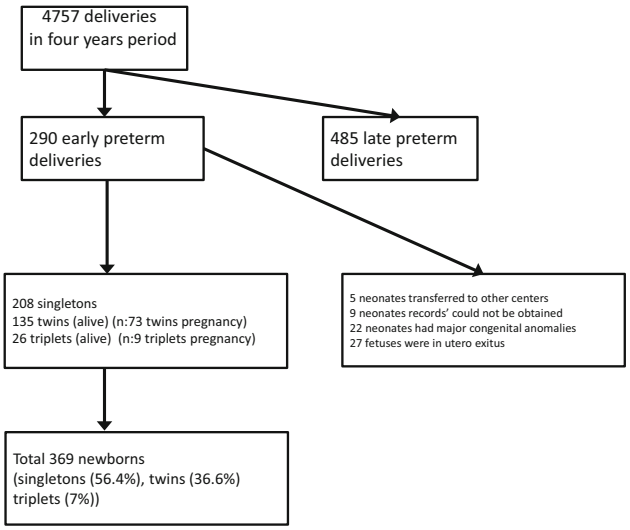

Fig. 1 Workflow of the study

Results

The preterm delivery rate was 16.3% (EPD rate 6.1%). A total of 290 deliveries and 369 newborns, which included singletons (n = 208, 56.4%), twins (n = 135, 36.6%, monochorionic twins n = 12, 3.3%) and triplets (n = 26, 7%) were evaluated in the study. All EPD patients were followed in the NICU. Figure 1 shows the workflow of the study.

The causes of delivery distribution according to defined groups were SPTB (n = 107, 29%), PPROM (n = 131, 35.5%) or IPTB (n = 131, 35.5%). IPTB reasons were hypertension during pregnancy (n = 78), abruption placenta (n = 28), placenta previa/accreta (n = 17) and fetal distress (n = 8). In the SPTB group, 7 patients had a history of preterm delivery with one patient had a cervical cerclage.

The perinatal characteristics according to causes of delivery are presented in Table 1. Average maternal age, gestational week, gestational weight and fetal gender have no difference between subtypes of EPD. Cesarean section was statistically higher in IPTB group ($p < 0.001$).

The maternal, obstetric and perinatal characteristics according to the subtypes of EPD groups are summarised in Table 2. The nulliparity, diabetes mellitus, history of assisted reproductive technologies, antenatal corticosteroid therapy and abruption placenta rates were similar between groups. Hypertensive disorders of pregnancy, magnesium therapy for neuroprotection, previa/accreta placenta, SGA rates were higher in IPTB group. Multiple pregnancies were greater in SPTB and PPROM groups. Monochorionic pregnancies were significantly higher in IPTB group, while dichorionic and trichorionic pregnancies were higher in SPTB and PPROM group (Table 2).

Table 1 The perinatal characteristics according to causes of delivery

	SPTB (n:107)	PPROM (n:131)	IPTB (n:131)	p value
Average maternal age	29.2 ± 7	29.4 ± 3.1	30.2 ± 6.6	0.09
Average gestational age (weeks)	30.0 ± 3	29.4 ± 3.1	30.2 ± 2.2	0.08
Average birth weight (g)	1502 ± 542	1434 ± 519	1368 ± 487	0.141
Type of gender (female/male)	49/58	54/76	68/63	0.24
Vaginal delivery/cesarean section	14/93 (87%)	21/110 (84%)	0/131 (100%)	< 0.001

SPTB spontaneously preterm birth, *PPROM* preterm premature rupture of membranes, *IPTB* iatrogenic preterm birth

Table 2 The maternal, obstetric and perinatal characteristics according to the subtypes of early preterm deliveries

	SPTB N (%)-107	PPROM N (%)-131	IPTB N (%)-131	*p* value
Maternal age < 18, > 35	22 (20.6%)	32 (24.4%)	32 (24.4%)	0.49
Nulliparity	72 (67.3%)	76 (58%)	70 (53.4%)	0.09
Type of conception (ART)	48 (44.9%)	53 (40.5%)	46 (35.1%)	0.31
Diabetes mellitus	15 (14%)	30 (22.9%)	29 (22.1%)	0.24
Hypertensive disorders	8 (7.5%)	12 (9.2%)	103 (63.2%)	**< 0.01**
Multipl pregnancy	65 (60.7%)	57 (43.5%)	39 (29.8%)	**< 0.01**
Monochorionic pregnancy	2 (3%)	3 (5%)	7 (18%)	**0.049**
Di/trichorionic pregnancy	63 (97%)	54 (95%)	32 (82%)	
Antenatal corticosteroids	73 (68.2%)	113 (86.3%)	89 (67.9%)	0.65
Neuroprotection (Mg2+)	29 (27.1%)	25 (19.1%)	73 (55.7%)	**< 0.01**
SGA	5 (4.7%)	0	20 (15.5%)	**< 0.01**
Placental abruption	6 (6.3%)	8 (7.4%)	13 (13.5%)	0.16
Placenta previa/accreta	4 (3.8%)	1 (0.8%)	12 (9.2%)	**< 0.01**
Total chorioamnionitis cases	9 (8.4%)	54 (41.2%)	6 (4.6%)	**< 0.01**
Clinical chorioamnionitis	9 (8.4%)	53 (40.5%)	5 (3.8%)	**< 0.01**
Histological chorioamnionitis	6 (20%)	31 (38.3%)	4 (5.1%)	

SPTB spontaneously preterm birth, *PPROM* preterm premature rupture of membranes, *IPTB* iatrogenic preterm birth, *ART* artificial reproductive technologies, *Mg2+* magnesium sulphate, *SGA* small for gestational age

The bold values in *p* value column shows a statistical significance

Short-term neonatal outcomes (number of cases and *p* values) according to EPD groups are presented in Table 3. The proportion of neonatal sepsis, RDS, PDA, ROP, BPD, IVH, NEC and mortality were not significantly different between groups. Histological and clinical chorioamnionitis had higher rate in PPROM group ($p < 0.001$). The rate of neonatal RDS (65.2 vs. 39.4%, $p < 0.001$), BPD (16.9 vs. 7.1%, $p = 0.02$), IVH (12.1 vs. 5.1%, $p = 0.004$), and sepsis (84.8 vs. 61.6%, $p < 0.001$) were significantly higher in patients with all chorioamnionitis cases. Other neonatal outcomes were not different between groups (neonatal resuscitation, ROP, PDA and death; $p > 0.05$). Neonatal RDS (66.7 vs. 36%, $p = 0.001$), IVH (15.1 vs. 5.3%, $p = 0.03$) NEC (22.6 vs. 8%, $p = 0.03$) and sepsis (87 vs. 64%, $p = 0.004$) significantly higher in the chorioamnionitis subgroup when compared to non-chorioamnionitis subgroup at PPROM cases. Furthermore; PPROM patients were gouped in terms of presence of chorioamnionitis according to gestational weeks, neonatal RDS was higher in 32–33 gestational weeks ($p = 0.039$), but no difference was detected in 23–32 gestational weeks.

Table 3 Neonatal outcomes of the opulation according to the etiology of preterm labor onset

	SPTB n(%)-107	PPROM n(%)-131			IPTB n(%)-131	*p* value
		Non-chorioamnionitis	Chorioamnionitis	Total		
Neonatal resuscitation	10 (9.5%)	4 (5.3%)	7 (13%)	11 (8.5%)	5 (3.9%)	0.19
RDS	48 (45.7%)	27 (36%)	36 (66.7%)	63 (48.8%)	49 (38%)	0.20
ROP	3 (2.9%)	6 (8%)	7 (13.2%)	13 (10.2%)	8 (6.2%)	0.08
BPD	9 (8.7%)	4 (5.3%)	8 (15.1%)	12 (9.4%)	11 (8.5%)	0.97
IVH	6 (5.7%)	3 (4%)	8 (14.8%)	11 (8.5%)	6 (4.7%)	0.42
PDA	20 (19.2%)	8 (10.7%)	9 (16.7%)	17 (13.2%)	11 (8.5%)	0.06
NEC	23 (21.9%)	6 (8%)	12 (22.6%)	18 (14.1%)	20 (15.5%)	0.25
Neonatal sepsis	66 (62.9%)	48 (64%)	47 (87%)	95 (73.6%)	78 (60.5%)	0.06
Neonatal death	12 (11.5%)	8 (10.7%)	10 (18.9%)	18 (14.1%)	17 (13.2%)	0.85

SPTB spontaneously preterm birth, *PPROM* preterm premature rupture of membranes, *IPTB* iatrogenic preterm birth, *RDS* respiratory distress syndrome, *ROP* retinopathy of prematurity, *BPD* bronchopulmonary dysplasia, *IVH* intraventricular haemorrhagia, *PDA* patent ductus arteriosus, *NEC* necrotising enterocolitis

The mean duration of hospitalization was significantly longer for PPROM patients with chorioamnionitis (8.7 days) when compared to non-chorioamnionitis subgroup (5 days) ($p = 0.009$). No significant difference was observed in the neonates among the three groups according to the duration of NICU follow-up or exitus ($p = 0.06$ and 0.85).

Discussion

The cause of the preterm delivery has an impact on neonatal morbidity, however the mortality rates are similar between causes according to literature [22, 23]. In this retrospective study, the results are summarized while the cause of preterm delivery separated into three different groups.

A few studies have classified EPD into the three groups and compared the neonatal outcomes according to causes. Pinto et al. [22] evaluated 266 EPDs, and assessed neonatal mortality/morbidity according to ethology of deliveries. Their results showed higher neonatal RDS and IVH in IPTB. Pinto and Owen's studies [22, 24] also described no difference in PDA and neonatal sepsis in PPROM group. In this study, however, no differences were found between groups for the designated variables except the cases with chorioamnionitis, which could be categorized as a subgroup of PPROM, have higher rate of neonatal RDS, BPD, IVH and sepsis. On the other hand, the study population in the present study consists of triplets comparing the Pinto and Owen's studies. The differences between subgroups of studies were challenging the comparison of our results with similar studies in the literature.

Number of studies showed that the frequency of neonatal RDS in IPTB group varied as a result of heterogeneous mechanisms. Frequent cause of IPTB is preeclampsia in literature likewise in our series. The preeclampsia is one of the causes of the chronic intrauterine stress and stimulates fetal adrenal glucocorticoid production. The stimulation leads to the early production of surface-active phospholipids in the fetal lung and supports fetal lung maturation [25]. Conversely, some studies showed a higher rate of RDS in IPTB cases [2, 22]. The rapid separation of the neonates from the uterine environment as a result of cesarean section may cause a difficulty for the newborn in terms of physiologic adaptation, which may increase the risk for RDS [26].

Of all PPROM cases, 41.9% were associated with chorioamnionitis (40.5% clinical chorioamnionitis and 38.3% histologically proven chorioamnionitis). Bry et al. [27] reported that intra-amniotic interleukin-1 and endotoxin stimulates surfactant protein synthesis and fetal maturation in rabbit fetuses. Shimoya et al. [28] discovered that chorioamnionitis stimulates fetal lung maturation by increasing interleukin-6, hence decreasing the frequency of RDS. On the other hand, chorioamnionitis may cause neonatal pneumonia, and could be a risk factor for RDS due to secondary insufficiency of surfactant [29]. Also, the presence of histological chorioamnionitis is associated with adverse perinatal outcomes in preterm infants such as increasing the risk of neonatal sepsis and PDA [30].

In this study, neonatal RDS, IVH, NEC and sepsis were significantly higher in the chorioamnionitis subgroup when compared to non-chorioamnionitis subgroup at PPROM cases. Similarly, in the study of García-Muñoz Rodrigo et al. [31], neonatal RDS, NEC, IVH, ROP, sepsis and death were more frequent in PPROM cases with chorioamnionitis. On the other hand, Rodríguez-Trujillo et al. [32] found no difference in short-term neonatal outcomes between intra-amniotic inflammation and non-infection/non-inflammation groups when adjusted for gestational age. However, in the study of Tsiartas et al. [33] neonatal ROP and sepsis were observed much more in chorioamnionitis than non-chorioamnionitis cases even after adjustment of gestational age. In the present study, when the PPROM patients were grouped in terms of presence of chorioamnionitis according to gestational weeks, neonatal RDS was higher in 32–33 gestational weeks ($p = 0.039$), but no difference was detected in 23–32 gestational weeks interval. We hypothesize that the different results in the studies may be caused by differences in ethnic and etiological features, and also parameters used to evaluate intra-amniotic infections. Based on the recent literature and this study, we suggest that close monitoring for PPROM cases with signs of chorioamnionitis is necessary to minimize the risk of neonatal complications.

Tita et al. [23] conducted a randomized study, including SPTB (n = 698), IPTB (n = 340) and term nulliparous (n = 8930) deliveries where they did not find difference between the two preterm groups in terms of neonatal RDS. However, the rate of neonatal mortality, IVH, NEC, ROP and sepsis were higher in the SPTB compared with IPTB, though only the neonatal mortality and ROP were significantly higher. These different results related to RDS, NEC, IVH, PDA and BPD in previous studies might be related to differences in study populations and design or heterogeneous mechanisms of the IPTB [4, 22–24].

The cesarean rates were higher in the present study group due to an unfavorable cervix, concern for fetal intolerance of labor, or fear of prolonged induction. Cesarean rate was 100% in iatrogenic preterm delivery group. This might be a usual tendency when there was a medical indication for pregnancy termination. Also different studies showed that the maternal and neonatal outcomes did not differ based on mode of delivery, induction of labor should be considered in

appropriate patients when early preterm birth is indicated [34, 35].

A significant proportion of early preterm births are multiple pregnancies (43.6% in this study group). While different pathophysiologic pathways may consist in the distinctive types of multiple pregnancy (e.g. monochorionic, dichorionic), which could alter the results, the monochorionic group had very low rate (3.3%) in present cohort. In present study, multiple pregnancies are frequently observed in SPTB and PPROM groups. It is known that uterine overdistention causes contraction and rupture of the membranes; hence, preterm deliveries increase [36]. Multiple pregnancies may have better prognosis unless chorioamnionitis develops. Some studies in the literature have shown that, preterm twins have similar prognosis with singleton preterm infants when the gestational age was similar [37, 38]. However, it may not be appropriate to generalize singleton and multiple pregnancies. Further studies with larger cohort are needed to identify the effect of the cause of delivery on neonatal outcomes of singletons and multipl pregnancies.

The limitations of this study are; retrospective nature, heterogeneous mechanisms of induced deliveries and inadequate cases for subtype analysis of IPTB, potential overlap between groups, the inclusion of multiple pregnancies, high rate of cesarean section and evaluating too many parameters in a multifactorial process. On the other hand, the present study has comparable larger cohort and evaluated the early preterm deliveries in three different groups.

EPD neonates with maternal PPROM, especially when associated with chorioamnionitis, warrant close monitoring and utmost care in view of higher complications rate. Gestational age was a strong predictor of neonatal death in preterm neonates. Hence, the other risk factors for preterm delivery which includes maternal characteristics, birth weight distribution, medical care and preventive policies vary over time and by country [39]. Assessment of the factors related to EPD would provide knowledge to better care of these patients. Improved understanding of these mechanisms should allow clinicians to design appropriate interventions that the incidence of preterm delivery and related fetal and neonatal morbidity and mortality will decrease. However, large randomized studies related to neonatal mortality and morbidity are needed.

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Compliance with ethical standards

Conflict of interest We declare no competing financial interests in relation to this study.

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