ECRONICON OPEN ACCESS

EC PAEDIATRICS
Research Article

Impact of Delivery Type and Prenatal Steroids in a Cohort of Premature Infants in Bosnia and Herzegovina

Suada Heljic[1], Sabina Terzic[1], Sebija Izetbegovic[1], Emina Vukas[1], Hajrija Maksic[1], Nedim Strukar[1], Ana Zovko[1], Mia Martinovic[1] and Mark A Underwood[2]*

[1]*Clinical University Center Sarajevo, Bosnia and Herzegovina*

[2]*University of California Davis Children's Hospital, Sacramento California, USA*

***Corresponding Author:** Mark A Underwood, Division of Neonatology, University of California Davis, Sacramento CA, USA.

Received: December 30, 2019; **Published:** January 18, 2020

Abstract

Background: Cohort studies are useful in determining how risk factors and outcomes differ among regions, populations and available resources. The aim of this five-year cohort study of premature infants from Bosnia and Herzegovina was to examine the impact of mode of delivery and administration of prenatal corticosteroids on key neonatal outcomes.

Methods: This cohort study included 734 infants with gestational age 24 - 32 weeks, admitted to the neonatal intensive care unit of the Pediatric Hospital in Sarajevo from 1 Jan 2012 to 31 Dec 2016, including both inborn infants and infants transported from the smaller hospitals throughout the country. We also examined the subgroup of 225 infants with gestational age 24 - 28 weeks for the same outcomes.

Results: In the full cohort, cesarean delivery was associated with a lower incidence of severe intraventricular hemorrhage (IVH) [6.5% (cesarean section, CS) vs. 13% (vaginal delivery) OR 0.45, 95% CI: 0.26 - 0.78 ($p < 0.01$)], but not with increased survival to discharge. Administration of prenatal corticosteroids was associated with decreased mortality [13% (yes) vs 21% (no) OR 0.53, 95% CI: 0.33 - 0.84 ($p < 0.01$)]. In the subgroup of extremely premature infants, CS was associated with a higher incidence of respiratory distress syndrome and surfactant administration, and prenatal steroid administration was associated with a lower mortality rate. Multiple regression analysis showed birth weight to be a significant predictor of survival to discharge and both birth weight and delivery type to be significant predictors of severe IVH. In this model, antenatal steroid administration was not a significant predictor of survival or severe IVH.

Conclusion: In this cohort of premature infants born in Bosnia and Herzegovina, survival was not influenced by delivery type. In the full cohort, CS was associated with decreased risk of severe IVH but this association was not seen in the subgroup of more premature infants. We found an association between prenatal corticosteroids and decreased mortality, but this did not remain significant with multiple regression analysis.

Keywords: *Cesarean Section; Antenatal Corticosteroids; Intraventricular Hemorrhage; Mortality*

Abbreviations

BPD: Bronchopulmonary Dysplasia; CI: Confidence Intervals; CS: Cesarean Section; EOS: Early Onset Sepsis; IUGR: Intrauterine Growth Restriction; IVH: Intraventricular Hemorrhage; LOS: Late Onset Sepsis; NEC: Necrotizing Enterocolitis; NICU: Neonatal Intensive Care Unit; OR: Odds Ratio; RDS: Respiratory Distress Syndrome; ROP: Retinopathy of Prematurity

Introduction

Preterm birth is the delivery of a baby before 37 completed weeks gestation. Most mortality and morbidity affects infants born before 33 weeks gestation, and especially those born before 29 weeks of gestation [1]. A systematic review of data from 107 countries estimated a global preterm birth rate of 10.6% for the year 2014 (equating to an estimated 15 million preterm births) [2]. Regional preterm rates ranged from 13.4% in North Africa to 8.7% in Europe with consistently higher rates in low and middle income countries. In Bosnia and Herzegovina such data are not routinely collected, but one report showed the incidence is about 7%, with 12.5% occurring before 32 gestational weeks [3].

In spite of multiple studies, the impact of mode of delivery on key outcomes for preterm infants remains uncertain. The most recent Cochrane review of this question found only 4 high quality randomized studies (including only 116 women) and concluded that there was insufficient data to make a conclusion [4]. Given the challenges of randomizing women to cesarean or vaginal delivery, much of the literature is focused on observational studies. A recent review of 11 observational studies found no evidence for improved survival of premature infants in vertex position delivered by cesarean section [5]. A separate systematic review of seven studies demonstrated decreased mortality with cesarean section in premature infants in breech presentation [6]. The benefit of prenatal administration of corticosteroids when preterm delivery seems likely has been well established in developed countries [7], however significant regional variation in outcomes has been demonstrated with some studies in low and middle income countries showing increased neonatal mortality and stillbirths related to antenatal corticosteroids, likely due to increased maternal and neonatal infections [8].

We sought to determine the impact of both delivery type and administration of antenatal dexamethasone on mortality and other key outcomes in a cohort of premature infants in Bosnia and Herzegovina.

Methods

This is a retrospective observational cohort study of preterm infants born at < 33 weeks gestation. This study included 734 infants with gestational age 24 - 32 weeks, admitted to the neonatal intensive care unit (NICU) of Pediatric Hospital in Sarajevo, Bosnia and Herzegovina during 5 years, from 1 January 2012 to 31 December 2016, including infants transported from the smaller hospitals throughout the country. Infants with gestational age 22 and 23 weeks were excluded from the study. All infants were categorized by the mode of delivery and by receipt of at least one maternal dose of dexamethasone prior to delivery to determine differences between groups for the following key outcomes: survival to discharge, early onset sepsis (EOS, defined as clinical signs of infection with a positive blood culture obtained in the first 72 hours of life), late onset sepsis (LOS, defined as clinical signs of infection with a positive blood culture obtained after the first 72 hours of life), respiratory distress syndrome (RDS, based on the need for oxygen in the first days of life plus radiographic findings), surfactant administration, days of mechanical ventilation, severe intraventricular hemorrhage (IVH grade 3 or 4, as classified by Volpe [9]), necrotizing enterocolitis (NEC stage 2 or 3 based on the modified Bell criteria [10]), severe retinopathy of prematurity (ROP, defined as stage 3 or 4 requiring surgical intervention), pneumothorax, pulmonary hemorrhage, and bronchopulmonary dysplasia (BPD, defined as oxygen requirement at 28 days of life [11]). Note that betamethasone was not available in Bosnia and Herzegovina during the study period, so dexamethasone was the only corticosteroid administered.

We also compared the following independent variables between groups: gestational age and birth weight at delivery, delivery type, sex, Apgar scores at one and five minutes, intrauterine growth restriction (defined as birth weight below the 10th centile for sex and gestational age based on the revised Fenton growth curves [12]) and outborn with postnatal transport. All analyses were repeated in the subgroup of infants born at 24 - 28 weeks gestation.

Statistical analysis was performed using Stata (College Station, Texas, version 12.1). Logistic regression was used to calculate adjusted odds ratios (ORs) with 95% confidence intervals (CI). Maximum likelihood estimation using an iterative approach where various solutions are estimated to find the best solution was followed with a likelihood ratio chi squared test to determine final multiple regression models for death and severe IVH.

Results

753 infants with gestational age less than 33 weeks were either born at our hospital or transported to the NICU from other hospitals during the study time period. Ten of the infants were excluded due to incomplete data for all major outcomes and an additional nine infants were excluded for gestational age at birth less than 24 weeks for a total cohort of 734 premature infants. Figure 1 presents the CS rate, administration of antenatal steroids, and mortality over the 5 year period. The comparison of independent variables and key outcomes based on delivery type is presented in table 1. Infants born vaginally were larger and more likely to be female or outborn than those born by CS. Intrauterine growth restriction (IUGR) was more common among infants born by CS. CS was associated with a lower incidence of severe IVH. Table 2 presents the same data for the subgroup of infants born at < 29 weeks gestation. Among the subgroup of extremely preterm infants, gestational age at birth was lower among infants born vaginally. Infants in this subgroup born by CS had a higher incidence of RDS and surfactant administration and a trend towards a lower incidence of severe IVH.

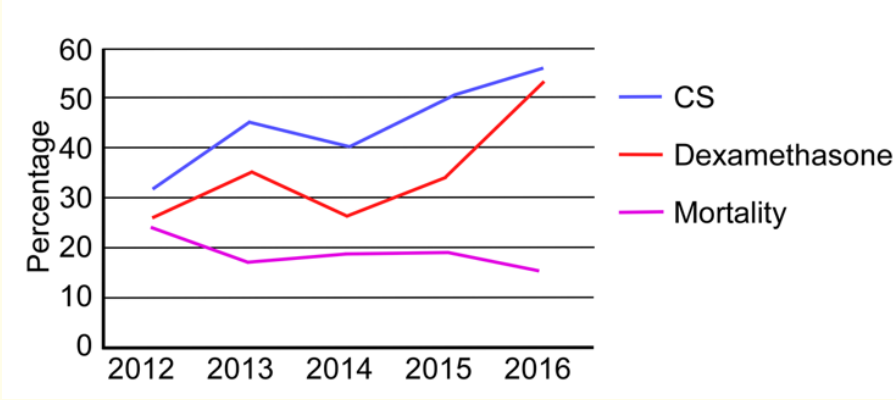

Figure 1: *Cesarean sections, administration of antenatal steroids, and mortality over the five-year period.*

	Cesarean delivery N = 331	Vaginal delivery N = 403	Statistical test	P value
Gestational age (weeks)[1]	29.7 (1.7)	29.5 (2.2)	T test	0.18
Birth weight (grams)[1]	1386 (376)	1465 (409)	T test	< 0.01
Males[2]	171 (52)	174 (43)	Chi Square	0.03
Multiples (%, sets of twins, sets of triplets)	25, 37, 3	22, 43, 1	Chi Square	0.39
Neonatal transport[2]	35 (11)	92 (23)	Chi Square	< 0.01
Apgar score at 1 minute[3,4]	6 (4, 7) [327]	6 (5, 7) [313]	Mann-Whitney	0.25
Apgar score at 5 minutes[3,4]	7 (6, 8) [325]	7 (6, 8) [306]	Mann-Whitney	0.66
IUGR[2]	22 (6.6)	8 (2.0)	Chi square	< 0.01
Antenatal dexamethasone[2]	116/311 (37)	106/306 (35)	Chi square	0.55
			Odds ratio (95% CI)	**P value**
Survived to discharge[2]	274 (83)	326 (81)	0.88 (0.60-1.3)	0.50
RDS[2]	265/323 (82)	259/327 (79)	1.2 (0.81-1.8)	0.37
Surfactant administration[2]	130/323 (40)	114/327 (35)	1.3 (0.92-1.7)	0.16

Mechanical ventilation (days)[1,4]	2.6 (5.9) [314]	2.6 (5.9) [323]	1.3 (0.92-1.7)	0.15
NEC[2]	28/317 (8.9)	20/322 (6.2)	1.5 (0.81-2.7)	0.21
Severe IVH[2]	20/310 (6.5)	42/314 (13)	0.45 (0.26-0.78)	< 0.01
EOS[2]	13/309 (4.2)	18/317 (5.7)	0.73 (0.35-1.5)	0.40
LOS[2]	58/310 (19)	57/312 (18)	1.0 (0.69-1.5)	0.89
BPD[2]	27/316 (8.5)	31/323 (9.6)	0.88 (0.51-1.5)	0.64
Pneumothorax[2]	8/325 (2.5)	12/328 (3.7)	0.66 (0.27-1.6)	0.37
Pulmonary hemorrhage[2]	16/315 (5.1)	15/321 (4.7)	1.1 (0.53-2.2)	0.81
Severe ROP[2]	2/320 (0.63)	4/338 (1.2)	0.53 (0.096-2.89)	0.45

Table 1: *Delivery type for the entire cohort.*

[1]: Mean (SD), [2]: N (%), [3]: Median (25th and 75th centiles), [4]: [N analyzed].

	Cesarean delivery N = 92	**Vaginal delivery N = 133**	**Statistical test**	**P value**
Gestational age (weeks)[1]	27.1 (1.2)	26.8 (1.2)	T test	0.02
Birth weight (grams)[1]	1048 (233)	1071 (256)	T test	0.50
Males[2]	48 (52)	77 (58)	Chi Square	0.48
Multiples (%, sets of twins, sets of triplets)	20, 9, 0	18, 12, 0	Chi Square	0.91
Neonatal transport[2]	14 (15)	92 (25)	Chi Square	0.12
Apgar score at 1 minute[3,4]	5 (3, 6) [89]	5 (4, 7) [114]	Mann-Whitney	0.73
Apgar score at 5 minutes[3,4]	6 (5, 7) [88]	6 (5, 7) [111]	Mann-Whitney	0.22
IUGR[2]	4 (4.3)	1 (0.75)	Chi square	0.18
Antenatal dexamethasone[2]	30/90 (33)	32/114 (28)	Chi square	0.51
			Odds ratio (95% CI)	**P value**
Survived to discharge[2]	61 (66)	326 (61)	0.79 (0.45-1.4)	0.41
RDS[2]	89/92 (97)	104/121 (86)	4.8 (1.4-17)	0.014
Surfactant administration[2]	64/90 (71)	63/122 (52)	2.3 (1.3-4.1)	<0.01
Mechanical ventilation(days)[1,4]	6.1 (9.9) [89]	4.6 (8.2) [120]	1.7 (0.94-3.1)	0.08
NEC[2]	13/89 (15)	12/120 (10)	1.5 (0.67-3.6)	0.31
Severe IVH[2]	11/85 (13)	28/116 (24)	0.47 (0.22-1.0)	0.051
EOS[2]	4/86 (4.7)	10/120 (8.3)	0.54 (0.16-1.8)	0.31
LOS[2]	21/87 (24)	35/116 (30)	0.74 (0.39-1.4)	0.34
BPD[2]	19/88 (22)	24/120 (20)	1.1 (0.56-2.2)	0.78
Pneumothorax[2]	4/91 (4.4)	3/121 (2.5)	1.8 (0.39-8.3)	0.44
Pulmonary hemorrhage[2]	10/87 (11)	8/120 (6.7)	1.8 (0.69-4.8)	0.23
Severe ROP[2]	0/92 (0)	3/126 (2.4)	1	

Table 2: *Delivery type for infants born at 24 - 28 weeks gestation.*

[1]: Mean (SD), [2]: N (%), [3]: Median (25th and 75th centiles), [4]: [N analyzed].

Table 3 presents the comparison between infants receiving at least one dose of antenatal dexamethasone and infants that did not (note that this information was only available for 617 infants). Infants receiving antenatal steroids had greater gestational age, higher birth weight, and higher Apgar scores at 1 and 5 minutes and had lower mortality and lower incidence of treatment with surfactant and severe IVH. Table 4 presents the same data for the subgroup of infants born at 24 - 28 weeks gestation. This subgroup of extremely preterm infants demonstrated improved mortality with antenatal corticosteroid administration but more of these infants had BPD with a trend towards more RDS.

	Prenatal dexamethasone N = 222	No N=395	Statistical test	P value
Gestational age (weeks)[1]	29.6 (2.0)	29.2 (2.1)	T test	0.046
Birth weight (grams)[1]	1471 (376)	1385 (404)	T test	0.01
Males[2]	121 (54)	201 (51)	Chi Square	0.44
Multiples[2]	57 (26)	84 (21)	Chi Square	0.25
Neonatal transport[2]	18 (8.1)	82 (21)	Chi Square	<0.01
Apgar score at 1 minute[3,4]	7 (5, 7) [217]	6 (4, 7) [381]	Mann-Whitney	0.02
Apgar score at 5 minutes[3,4]	7 (6, 8) [214]	7 (6, 8) [376]	Mann-Whitney	0.02
IUGR[2]	9 (4.1)	17 (4.3)	Chi square	0.95
Cesarean section[2]	116 (52)	195 (49)	Chi square	0.55
			Odds ratio (95% CI)	**P value**
Survived to discharge[2]	194 (87)	311 (79)	0.53 (0.33-0.84)	<0.01
RDS[2]	180/217 (83)	311/391 (80)	1.2 (0.77-1.8)	0.45
Surfactant administration[2]	68/218 (31)	156/390 (40)	0.67 (0.47-0.95)	0.02
Mechanical ventilation(days)[1,4]	2.5 (6.5) [211]	3.0 (6.6) [384]	0.77 (0.55-1.1)	0.14
NEC[2]	19/212 (9.0)	26/386 (6.7)	1.3 (0.73-2.5)	0.35
Severe IVH[2]	14/207 (6.8)	43/379 (11)	0.53 (0.34-0.85)	<0.01
EOS[2]	12/207 (5.8)	16/381 (4.2)	1.4 (0.64-2.9)	0.41
LOS[2]	46/203 (23)	67/381 (18)	1.3 (0.89-2.0)	0.16
BPD[2]	22/213 (10)	31/386 (8.0)	1.3 (0.73-2.3)	0.37
Pneumothorax[2]	9/220 (4.1)	9/392 (2.3)	1.8 (0.71-4.6)	0.22
Pulmonary hemorrhage[2]	9/210 (4.3)	20/385 (5.2)	0.82 (0.37-1.8)	0.62
ROP[2]	1/215 (0.47)	5/386 (1.3)	0.36 (0.041-3.1)	0.30

Table 3: *Prenatal corticosteroid administration for the entire cohort.*

[1]: Mean (SD), [2]: N (%), [3]: Median (25th and 75th centiles), [4]: [N analyzed].

Multiple logistic regression was performed for two outcomes of interest: severe IVH and death. The primary independent variables (delivery type and prenatal corticosteroids) plus all independent variables that differed between groups were included in the analysis. Because birth weight and gestational age at birth are collinear only birth weight was included. The models are summarized in table 5. In the full cohort, birth weight and delivery type were significant predictors for severe IVH, and birth weight was the only significant predictor for death. In the subgroup of extremely preterm infants, birth weight was the only significant predictor of death or severe IVH. Antenatal steroid administration was not significant in either model.

	Prenatal dexamethasone N=62	No N=142	Statistical test	P value
Gestational age (weeks)[1]	27.1 (1.1)	26.9 (1.2)	T test	0.35
Birth weight (grams)[1]	1108 (200)	1055 (265)	T test	0.16
Males[2]	33 (53)	79 (56)	Chi Square	0.87
Multiples[2]	16 (26)	24 (17)	Chi Square	0.20
Neonatal transport[2]	8 (13)	34 (24)	Chi Square	0.11
Apgar score at 1 minute[3,4]	5 (4, 7) [60]	5 (3, 7) [134]	Mann-Whitney	0.53
Apgar score at 5 minutes[3,4]	6 (5, 7) [58]	6 (5, 7) [133]	Mann-Whitney	0.87
IUGR[2]	0 (0)	4 (2.8)	Chi square	0.43
Cesarean section[2]	30 (48)	60 (42)	Chi square	0.51
			Odds ratio (95% CI)	**P value**
Survived to discharge[2]	48 (77)	86 (61)	0.45 (0.23 - 0.89)	0.02
RDS[2]	60/62 (97)	122/140 (87)	4.4 (0.99 - 20)	0.051
Surfactant administration[2]	37/62 (60)	82/139 (59)	1.0 (0.56 - 1.9)	0.93
Mechanical ventilation(days)[1,4]	5.9 (10) [61]	4.8 (8.4) [137]	1.0 (0.53 - 1.9)	0.99
NEC[2]	9/61 (15)	15/138 (11)	1.4 (0.58 - 3.4)	0.44
Severe IVH[2]	9/59 (15)	28/132 (21)	0.67 (0.29 - 1.5)	0.34
EOS[2]	7/59 (12)	7/137 (5.1)	2.5 (0.84 - 7.5)	0.10
LOS[2]	16/58 (28)	38/135 (28)	0.97 (0.49 - 1.9)	0.94
BPD[2]	18/61 (30)	23/137 (17)	2.1 (1.02 - 4.2)	0.044
Pneumothorax[2]	2/62 (3.2)	4/140 (2.9)	1.1 (0.2-6.4)	0.89
Pulmonary hemorrhage[2]	4/60 (6.7)	12/137 (7.3)	0.74 (0.23-2.4)	0.62
ROP[2]	0/62 (0)	3/141 (2.1)	1	

Table 4: *Prenatal corticosteroid administration for infants born at 24 - 28 weeks gestation.*

[1]: Mean (SD), [2]: N (%), [3]: Median (25th and 75th centiles), [4]: [N analyzed].

Model 1	**Severe IVH, full cohort (N = 593, LR² = 49, p = 0.0000)**		**Severe IVH, subgroup[1] (N = 187, LR² = 13, p = 0.02)**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Birth weight	0.998 (0.997, 0.999)	0.000	0.997 (0.996, 0.999)	0.007
Sex (female)	0.79 (0.45, 1.37)	0.40	0.75 (0.35, 1.60)	0.45
Neonatal transport	1.76 (0.93, 3.33)	0.08	1.41 (0.59, 3.33)	0.44
IUGR[3]	0.36 (0.077, 1.68)	0.19		
Cesarean section	0.42 (0.23, 0.75)	0.003	0.52 (0.24, 1.16)	0.11
Antenatal dexamethasone	0.75 (0.40, 1.39)	0.36	0.81 (0.34, 1.92)	0.63
Model 2	**Death, full cohort (N = 617, LR² 101, p = 0.0000)**		**Death, subgroup[1] (N = 204, LR² 47, p = 0.0000)**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Birth weight	0.997 (0.996, 0.998)	0.000	0.995 (0.993, 0.997)	0.000

Sex (female)	0.65 (0.41, 1.03)	0.067	0.65 (0.33, 1.27)	0.21
Neonatal transport	0.78 (0.42, 1.45)	0.44	0.72 (0.32, 1.64)	0.44
IUGR	0.47 (0.12, 1.28)	0.14	0.22 (0.024, 1.89)	0.17
Cesarean section	0.76 (0.48, 1.20)	0.23	0.86 (0.44, 1.68)	0.66
Antenatal dexamethasone	0.64 (0.39, 1.06)	0.08	0.53 (0.25, 1.12)	0.10

***Table 5**: Multiple logistic regression models for severe IVH and death.*

[1]: Gestational age 24 - 28 weeks, [2]: Likelihood ratio chi square test statistic,

[3]: IUGR was dropped from the model for the subgroup due to too few observations.

Location and number	Population	C/S %	Neonatal outcomes
Uganda N = 1455 mothers (14)	Premature rupture of membranes after 28 weeks	31	No difference in mortality. C/S: Increased admission to the special care unit
Canada N = 6636 infants (15)	Twins at 24-33 weeks	6 (one twin) 65 (both twins)	No difference in mortality. C/S: decreased severe neurological injury and increased RDS
United Kingdom N = 1722 singleton pregnancies (16)	Gestational age 22-26 weeks	21	Prenatal steroids associated with heart rate > 100 at 5 minutes in infants born vaginally but not C/S. In women without preterm labor, C/S at < 26 weeks associated with lower mortality and heart rate > 100 at 5 minutes.
Hungary N = 66 infants (17)	Birth weight < 500 grams	89	C/S: Increased survival
Chile N = 4386 infants (18)	24-30 weeks gestation	54	Prenatal steroids improved survival regardless of delivery type. At < 26 weeks combining prenatal steroids and C/S improved survival
Southeast Asia N = 765 infants (19)	Gestational age < 36 weeks	38	No difference in mortality, RDS or low 5 minute Apgar score
France N = 1518 infants (20)	27-32 weeks gestation	59	No difference in neonatal mortality based on breech vs vertex presentation
Brazil N = 830 infants (21)	Birth weight 800-2000 grams	63	Higher rates of RDS and IVH in vaginally delivered
Australia and New Zealand N = 625 infants (22)	Gestational age 23-26 weeks	52	No difference in survival
United States (Texas) N = 591 infants (23)	23-36 weeks gestation	38	No difference in survival. Increased RDS in infants born by C/S at 1500-1999 g
United States (New York) N = 937 infants (24)	Birth weight < 1500 g	43	No difference in survival, NEC, IVH, or sepsis

United States (California) N = 652 infants (25)	Gestational age < 30 weeks	70	No difference in survival or severe IVH, higher incidence of RDS with C/S
Austria N = 132 infants (26)	23-33 weeks gestation	74	Better 5 minute Apgar score with C/S in some subgroups
Germany N = 2203 infants(27)	22-36 weeks gestation	71	Less IVH with planned CS compared to vaginal or emergent CS

Table 6: *Recent observational studies of delivery type in premature infants.*

Discussion

Over the past decades, the percentage of cesarean deliveries has risen in many high-income countries. The rate of CS in the subgroup of very preterm infants varies widely from country to country. According to recent data, CS for very preterm infants in European countries varies from 37% in Lithuania to 83% in Germany [13]. Of the 734 infants that met inclusion criteria in our study, 331 (45%) underwent CS. The CS rate in very preterm infants appears to have increased across the 5 years, ranging from 32% in 2012 to 56% in 2016.

Table 6 summarizes several recent observational studies that include delivery type [14-27]. Most demonstrated no difference in mortality rates, however three studies of very small premature infants found improved mortality with cesarean delivery [16-18]. We found no difference in mortality based on mode of delivery in this cohort or in the subgroup of extremely preterm infants, but were not able to analyze key outcomes based on breech vs vertex presentation.

We detected a higher incidence of RDS following CS among the subgroup of extremely premature infants as reported by others [6,15,25,28,29]. Labor facilitates displacement of lung fluid through complex mechanisms including sodium transport through epithelial sodium channels [28]. Incomplete lung development, reduced surfactant production and difficulty clearing lung fluid increase the need for mechanical ventilation which can cause ventilation-induced lung injury, believed to be a major contributor to the development of BPD [30]. We found no difference in BPD based on the delivery type in either the full cohort or the subgroup of extremely premature infants.

Our study showed that preterm infants delivered by CS had a lower risk for severe IVH compared to infants delivered vaginally. A similar trend was noted in the subgroup of the more premature infants. Several reports suggest that early IVH is associated with a longer duration of labor and that CS may be protective against IVH occurring within the first hours of life rather than later. In one systematic review, three studies concluded that CS was independently associated with a lower risk of early IVH, but two small studies found no association between mode of delivery and early IVH [31]. Another review found that CS in premature infants does not reduce neurodisability [32].

The Antenatal Corticosteroids Trial, a multi-country, cluster-randomized trial to improve appropriate use of antenatal corticosteroids in low-middle income countries, increased antenatal steroid administration, but the intervention failed to show benefit in the targeted < 5th percentile birth weight infants and was associated with increased neonatal mortality and stillbirth in the overall population [8]. In our cohort, administration of at least one dose of antenatal dexamethasone was associated with improved survival to discharge and decreased severe IVH in the full cohort. In the subgroup of extremely premature infants, antenatal steroids improved survival, did not impact severe IVH and paradoxically demonstrated an increase in BPD with a trend towards increased RDS. It is likely that the higher rates of lung disease are due to a higher number of survivors in the steroid treated group. In the multiple regression models antenatal steroid administration was not significant for either death or the composite outcome of death or BPD.

This study has several limitations. Cohort studies are valuable for establishing associations but do not demonstrate causality. The limitations inherent in the way the data were recorded include the inability to establish the exact number of days of oxygen therapy (as utilized in more recent definitions of BPD) and the inability to determine the exact number of doses of dexamethasone administered.

Conclusion

In this cohort of premature infants, the rate of CS was in the mid-range for Europe. Delivery type did not influence survival, but CS was associated with less severe IVH. The increased maternal risk very early in pregnancy due to the need for classical CS must be taken into consideration when counseling parents. Antenatal steroid administration was associated with improved survival by logistic regression, but this did not remain significant in the multiple regression model.

Ethics Approval/Consent to Participate

The Institute for Science and Development at the Clinical University Center in Sarajevo determined that informed consent and oversight were not necessary for this retrospective observational study.

Competing Interests

MAU has received honoraria from Abbott for educational presentations (not related to the current study). The authors have no ethical conflicts or conflicts of interests to declare.

Funding

MAU receives funding from the National Institutes of Health. None of the authors received any funding for this research.

Author Contributions

SH study design, data collection, wrote first draft, approved final draft; ST, SI, EV, HM, NS, AZ, MM study design, data collection, approved final draft; MAU data analysis, edited and wrote final draft.

Bibliography

1. Tucker J and McGuire W. "Epidemiology of preterm birth". *British Medical Journal* 329.7467 (2004): 675-678.
2. Chawanpaiboon S., *et al*. "Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis". *Lancet Global Health* 7.1 (2019): e37-e48.
3. Hudic I., *et al*. "Low Preterm Birth Rate with Decreasing Early Neonatal Mortality in Bosnia and Herzegovina during 2007-2014". *Materia Socio-Medica* 28.1 (2016): 32-35.
4. Alfirevic Z., *et al*. "Caesarean section versus vaginal delivery for preterm birth in singletons". *Cochrane Database of Systematic Review* 9 (2013): CD000078.
5. Simoes R., *et al*. "Cesarean delivery and prematurity". *Revista da Associação Médica Brasileira* 61.6 (2015): 489-94.
6. Bergenhenegouwen LA., *et al*. "Vaginal delivery versus caesarean section in preterm breech delivery: a systematic review". *European Journal of Obstetrics and Gynecology and Reproductive Biology* 172 (2014): 1-6.
7. Roberts D., *et al*. "Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth". *Cochrane Database of Systematic Reviews* 3 (2017): CD004454.

8. McClure EM., *et al*. "Reducing neonatal mortality associated with preterm birth: gaps in knowledge of the impact of antenatal corticosteroids on preterm birth outcomes in low-middle income countries". *Reproductive Health* 13.1 (2016): 61.

9. Volpe JJ. "Neurology of the Newborn". Philadelphia: W. B. Saunders Company (2000).

10. Walsh MC and Kliegman RM. "Necrotizing enterocolitis: treatment based on staging criteria". *Pediatric Clinics of North America* 33.1 (1986): 179-201.

11. Tooley WH. "Epidemilology of bronchopulmonary dysplasia". *The Journal of Pediatrics* 95(5 part 2) (1979): 851-858.

12. Fenton TR and Kim JH. "A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants". *BMC Pediatrics* 13 (2013): 59.

13. Delnord M., *et al*. "Varying gestational age patterns in cesarean delivery: an international comparison". *BMC Pregnancy Childbirth* 14 (2014): 321.

14. Kayiga H., *et al*. "Impact of mode of delivery on pregnancy outcomes in women with premature rupture of membranes after 28 weeks of gestation in a low-resource setting: A prospective cohort study". *PloS one* 13.1 (2018): e0190388.

15. Hunter T., *et al*. "Neonatal outcomes of preterm twins according to mode of birth and presentation". *Journal of Maternal-Fetal and Neonatal Medicine* 31.5 (2018): 682-688.

16. Morgan AS., *et al*. "Impact of obstetric interventions on condition at birth in extremely preterm babies: evidence from a national cohort study". *BMC Pregnancy Childbirth* 16.1 (2016): 390.

17. Varga P., *et al*. "Morbidity and mortality trends in very-very low birth weight premature infants in light of recent changes in obstetric care". *European Journal of Obstetrics and Gynecology and Reproductive Biology* 211 (2017): 134-139.

18. Hubner ME., *et al*. "Mode of delivery and antenatal steroids and their association with survival and severe intraventricular hemorrhage in very low birth weight infants". *Journal of Perinatology* 36.10 (2016): 832-836.

19. Sangkomkamhang U., *et al*. "Mode of delivery and outcomes in preterm births". *Journal of the National Medical Association* 94.4 (2011): 415-420.

20. Azria E., *et al*. "Neonatal Mortality and Long-Term Outcome of Infants Born between 27 and 32 Weeks of Gestational Age in Breech Presentation: The EPIPAGE Cohort Study". *PloS one* 11.1 (2016): e0145768.

21. Negrini R., *et al*. "Delivery modes and the neonatal outcomes of low birth-weight neonates in a Brazilian reference health center". *Ceska Gynekologie* 80.5 (2015): 366-371.

22. Thomas PE., *et al*. "The influence of mode of birth on neonatal survival and maternal outcomes at extreme prematurity: A retrospective cohort study". *Australian and New Zealand Journal of Obstetrics* 56.1 (2016): 60-68.

23. Racusin DA., *et al*. "Mode of Delivery in Premature Neonates: Does It Matter?". *American Journal of Perinatology Reports* 6.3 (2016): e251-259.

24. Durie DE., *et al*. "Mode of delivery and outcomes in very low-birth-weight infants in the vertex presentation". *American Journal of Perinatology* 28.3 (2011): 195-200.

25. Blue NR., *et al*. "Neonatal Outcomes by Mode of Delivery in Preterm Birth". *American Journal of Perinatology* 32.14 (2015): 1292-1297.

26. Holzer I., *et al*. "Effect of delivery mode on neonatal outcome among preterm infants: an observational study". *Wiener klinische Wochenschrift* 129.17-18 (2017): 612-617.

27. Humberg A., *et al*. "Delivery mode and intraventricular hemorrhage risk in very-low-birth-weight infants: Observational data of the German Neonatal Network". *European Journal of Obstetrics and Gynecology and Reproductive Biology* 212 (2017): 144-149.

28. Ramachandrappa A and Jain L. "Elective cesarean section: its impact on neonatal respiratory outcome". *Clinics in Perinatology* 35.2 (2008): 373-393.

29. Gerten KA., *et al*. "Cesarean delivery and respiratory distress syndrome: does labor make a difference?". *American Journal of Obstetrics and Gynecology* 193 (2005): 1061-1064.

30. Brown MK and DiBlasi RM. "Mechanical ventilation of the premature neonate". *Respiratory Care* 56.9 (2011): 1298-1231.

31. Al-Abdi SY and Al-Aamri MA. "A Systematic Review and Meta-analysis of the Timing of Early Intraventricular Hemorrhage in Preterm Neonates: Clinical and Research Implications". *Journal of Clinical Neonatology* 3.2 (2014): 76-88.

32. Ray Chaudhuri Bhatta S and Keriakos R. "Review of the recent literature on the mode of delivery for singleton vertex preterm babies". *Journal of Pregnancy* 2011 (2011): 186560.

Volume 9 Issue 2 February 2020