Neonatal Outcome of Inborn and Outborn Extremely Low Birth Weight Infants: Relevance of Perinatal Factors

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Abstract

Background: A substantial number of premature deliveries occur in hospitals lacking neonatal intensive care facilities. We previously demonstrated a comparable outcome of very low birth weight infants delivered in a level II nursery to that of inborn infants delivered in our tertiary care center, but a similar comparison of extremely low birth weight infants has not been done.

Objectives: To compare the neonatal outcome (mortality, severe intraventricular hemorrhage/periventricular leukomalacia, bronchopulmonary dysplasia and intact survival) of inborn and outborn ELBW infants, accounting for sociodemographic, obstetric and perinatal variables.

Methods: We compared 97 ELBW infants (birth weight ≤ 1000 g) delivered between the years 2000 and 2004 in a hospital providing neonatal intensive care to 53 ELBW babies delivered in a referring hospital. A univariate model was first applied to examine the associations of the individual independent variables with the outcome variable, followed by a logistic stepwise regression analysis for each of the outcome variables. The odds ratios for each predictor were reported as well as their *P* values and 95% confidence intervals.

Results: In the stepwise logistic regression analysis, accounting for a possible confounding effect of the independent variables, 'hospital of birth' remained a statistically significant predictor in the final step only for mortality, with odds ratio (inborns relative to outborns) of 3.32 (95%CI 1.19–9.28, *P* = 0.022). No statistically significant associations with the other outcome variables were found (severe IVH/PVL odds ratio = 1.99, 95%CI = 0.77–5.14, *P* = 0.155; BPD odds ratio = 0.60, 95%CI = 0.19–1.91, *P* = 0.384; intact survival OR = 0.56, 95%CI = 0.23–1.35, *P* = 0.195).

Conclusions: ELBW outborn infants may share an outcome comparable with that of inborn babies, if adequate perinatal care is provided.

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Most previous studies reported higher survival rates and improved outcome of preterm and very low birth weight infants born in tertiary perinatal centers (inborn) than of outborn infants who were delivered in primary and secondary care facilities and later transferred to intensive care units [1-3]. In a recent study however, Palmer and co-authors [4] found no significant difference between mortality and morbidity of 746 inborn and 148 outborn ventilated preterm infants (23 to 32 weeks gestation), following adjustment for maternal treatment with antenatal steroids.

Factors that accounted for the higher incidence of adverse outcomes of outborn premature infants included lack of adequate laboratory, radiological and specialist medical support, insufficient staffing and equipment in the delivery room and nursery, inadequate stabilization, and delays in commencing assisted ventilation or administration of surfactant [3]. In addition, transport to a tertiary center itself could adversely affect infants [5], the adverse association being greater for the least mature babies [6]. While much focus was directed at optimizing the quality and availability of neonatal transfer, it has been emphasized that the key factor in the outcome of a sick preterm infant is the level of initial care provided at the hospital of birth [7,8]. Accordingly, Cifuentes et al. [9] found that subsequent neonatal transfer to a regional intensive care unit only marginally decreased the disadvantage of birth in less advanced facilities.

In our system, one neonatal intensive care unit serves two hospitals and physicians of the neonatal team rotate in the two facilities. Almost all extremely low birth weight infants delivered in the referring hospital are transported to the neonatal intensive care unit in the tertiary center following stabilization and surfactant administration as needed. In a previous study of very low birth weight infants delivered in our facilities between 1996 and 2000, a higher survival among outborn infants was demonstrated but the intact survival was comparable between inborn and outborn infants [10]. We decided to study and compare the neonatal outcome of our inborn and outborn extremely low birth weight infants (≤ 1000 g) delivered and treated in both facilities during 2000–2004. We hypothesized that since the level of obstetric and initial neonatal medical care is similar in the two facilities, the neonatal outcome will not be significantly different following adjustment for perinatal variables.

Patients and Methods

The Hadassah Medical Organization operates two university hospitals in Jerusalem, Israel, located at Mt. Scopus and Ein Kerem. Both hospitals provide high risk obstetric services, each with 4000–5000 annual deliveries. The NICU is located at Mt. Scopus while Ein Kerem has a Level II nursery with the capability of neonatal resuscitation and provision of mechanical ventilation until transportation to the NICU at Mt. Scopus. The distance

tELBW = extremely low birth weigh
CI = confidence interval
IVH = intraventricular hemorrhage
PVL = periventricular leukomalacia
BPD = bronchopulmonary dysplasia
OR = odds ratio

NICU = neonatal intensive care unit

between the two hospitals is 15 km and the transportation time 30–40 minutes, depending on traffic conditions. Babies delivered in Ein Kerem and requiring intensive care are transported by a neonatologist to the NICU at Mt. Scopus. Maternal transport is only infrequently practiced in our system.

All premature infants with birth weights of ≤ 1000 g delivered in our hospitals and admitted to our nurseries between 1 January 2000 and 31 December 2004 were candidates for participation in the study. The time frame for evaluation was limited to 5 years to minimize the impact of changing treatment policies. Excluded were infants referred for treatment in other institutions and those with severe chromosomal abnormalities or life-threatening major anomalies that might affect treatment decisions. During this period 162 ELBW infants were delivered alive in our hospitals. Ten of them (4 from Ein Kerem, and 6 from Mt. Scopus) were transferred to other hospitals on the first day of life because of full occupancy in the NICU and hence were excluded from the study, as were 2 infants with major congenital anomalies. Thus, mortality and morbidity during hospitalization were compared between 97 inborn infants delivered at Mt Scopus and 53 babies delivered at Ein Kerem, comprising 51 transferred infants and 2 stable infants who remained in Ein Kerem until discharge. No cases of death occurred during transportation.

Socioeconomic, obstetric, perinatal and neonatal data were extracted from the hospitalization files. Most data were already routinely collected at discharge or death of infants for submission to the Israeli Neonatal Network. We evaluated the effect of delivery in the tertiary center (Mt. Scopus) on mortality during hospitalization and selected morbidity – including severe intraventricular hemorrhage/periventricular leukomalacia, bronchopulmonary dysplasia, and intact survival (without severe IVH/PVL) – as compared with the outborn population (Ein Kerem). The factors considered were:

- *sociodemographic variables*: maternal age, origin and education (complete years of schooling)
- *obstetric variables*: number of pregnancies and live births, type of present conception (natural, hormonal or in vitro fertilization), type of delivery (vaginal or cesarean section), single or multiple gestation, pregnancy complications (placental abruption, toxemia, premature rupture of membranes and premature contractions), steroid treatment received prior to delivery (partial or complete course)
- *neonatal variables*: gestational age by weeks calculated from the last menstrual period and confirmed by physical examination, birth weight in grams, Apgar scores at 1 and 5 minutes, weight appropriate or small for gestational age, presence of any bruising (hematoma/ecchymosis) at birth, presence of respiratory distress syndrome, patent ductus arteriosus (confirmed by echocardiography), bronchopulmonary dysplasia (defined by the requirement of oxygen or mechanical ventilation at corrected gestational age of 36 weeks), necrotizing enterocolitis (grades 2 or 3), sepsis (not including coagulase-negative staphylococci), intraventricular hemorrhage (mild: grades I and II; severe: grades III and IV), retinopathy of prematurity (grades 2 or 3), surfactant treatment and laser therapy.

In both hospitals, a neonatologist was almost always present, in addition to a pediatric resident, at the resuscitation of ELBW infants, and transportation to the NICU was arranged within 4 hours of birth. Cranial ultrasounds were first done within 72 hours of birth and then repeated routinely between 7 and 10 days and at age one month. Intraventricular hemorrhage was defined and graded by the criteria of Papille [11]. Periventricular leukomalacia was defined by the presence of echo-lucent areas around the lateral ventricles. Respiratory distress syndrome was defined by the need for mechanical ventilation by 12 hours of age in an infant with pulmonary radiological appearance of diffuse granularity. The study was approved by the head of the institutional committee responsible for human experimentation. Patient anonymity was assured.

Statistical analysis

The numerical data were expressed as mean ± SD and the categorical data as proportions. The baseline characteristics of the two hospital groups, Mt. Scopus vs. Ein Kerem, were compared using Student's *t*-test and the Mann-Whitney test for the numerical variables and chi-square test or Fisher's exact test for the categorical variables. *P* values for the comparison between the two groups were reported.

To begin with, we examined the possible effects of the predictors, the independent variables, on the outcome variables, the dependent variables (mortality, severe IVH/PVL, BPD and intact survival) using a univariate approach. The effect of each of the predictors on the outcome was examined separately using chi-square or Fisher's exact test for the categorical predictors and *t*-test and Mann-Whitney test for the numerical predictors. Later on we used a multivariate approach to examine the overall multivariate effect of the predictors on the outcome variables. The logistic regression model was performed for each of the outcome variables. The model was performed using the stepwise regression method. The logistic regression model allows us to estimate the odds ratio of each of the predictors, which is the magnitude of the effect of the predictor variable on the outcome. The odds ratios for each predictor were reported as well as their *P* values and 95% confidence intervals. All analyses were performed with SPSS version 13.0.1 software (SPSS Inc, Chicago, IL, USA) and Splus version 6.1 software (Copyright 1988, 2002 Insightful Corp.).

Results

The distribution of the variables of the two hospital populations is listed in Table 1. For most variables the distributions in the two populations were similar. Of the independent variables – non-Jewish origin (mostly Moslem Arab) and bruising present at birth – were more prevalent in the Mt. Scopus population than among Ein Kerem infants, as were the outcome-dependent variables of mortality and severe IVH. Forty-four percent of Mt.

Table 1. Distribution of sociodemographic, obstetric, perinatal and neonatal variables by hospital

	Ein Kerem n=53	Mt. Scopus n=97	*P*
Sociodemographic variables			
Maternal age (yrs)	31.3 ± 6.7	30.2 ± 5.4	0.270
Maternal education (yrs).	14.0 ± 2.3	13.1 ± 4.0	0.159
Origin*			0.000
Jewish	96.2%	64.6%	
Non-Jewish	3.8%	35.4%	
Obstetric variables			
No. of pregnancies	3.2 ± 2.7	3.6 ± 2.9	0.399
Live births	2.3 ± 1.9	2.8 ± 2.7	0.251
Type of conception			0.388
Natural	64.7%	61.9%	
IVF	21.6%	29.9%	
Hormonal treatment	13.7%	8.2%	
Type of delivery			0.843
Vaginal	22.6%	24.7%	
Cesarean section	77.4%	75.3%	
Pregnancy duration (wks)	26.8 ± 2.2	26.4 ± 2.1	0.214
Pregnancy complications			
Placental abruption	22.0%	17.0%	0.309
Toxemia	24.5%	21.6%	0.688
Premature rupture of membranes	18.9%	21.6%	0.833
Premature contractions	50.9%	44.3%	0.495
Treatment during pregnancy			
Antenatal steroids			0.343
Partial treatment	15.4%	17.5%	
Complete treatment	65.4%	53.6%	
Perinatal/neonatal variables			
Multiple birth	35.8%	39.2%	0.728
Female gender	45.3%	50.5%	0.609
Birth weight (g).	794 ± 138	761 ± 163	0.218
Birth weight/gestation			0.854
Appropriate for age	67.9%	70.1%	
Small for age	32.1%	29.9%	
Apgar score at 1 min	6.4 ± 2.2	6.0 ± 2.4	0.260
Apgar score at 5 min	8.5 ± 1.5	8.2 ± 1.9	0.288
Diseases of the newborn			
Bruising at birth*	13.2%	27.8%	0.044
Respiratory distress syndrome	66.0%	68.0%	0.856
Surfactant	62.3%	62.9%	0.999
Patent ductus arteriosus	34.0%	36.1%	0.428
Sepsis	32.1%	20.8%	0.142
Necrotizing enterocolitits	3.8%	5.1%	0.563
Severe IVH *	9.4%	27.4%	0.032
PVL	7.5%	3.2%	0.250
Severe IVH/PVL	17.0%	27.4%	0.165
Bronchopulmonary dysplasia **	29.6%	30.0%	0.999
Retinopathy of prematurity **			
Not treated	45.4%	33.3%	0.407
Laser therapy	15.9%	23.3%	
Mortality *	17.0%	39.2%	0.006

Numeric variables are presented as percentages and continuous variables as mean ± SD

* $P < 0.05$

** Among 104 infants surviving at 36 weeks corrected gestational age.

Table 2. Stepwise logistic regression analyses of mortality, severe IVH/PVL, BPD and intact survival (final steps)*

	OR	95% CI	*P*
Mortality			
Gestational age (wks)	0.70	0.53–0.93	0.015
Apgar score at 1 minute	0.79	0.66–0.96	0.019
Hospital (Mt. Scopus vs. Ein Kerem).	3.32	1.19–9.28	0.022
Delivery (cesarean vs. vaginal).	3.52	1.15–10.78	0.027
Toxemia	0.22	0.06–0.80	0.021
Bruising at birth	2.95	1.12–7.80	0.029
Severe IVH/PVL			
No. of pregnancies	1.18	1.02–1.36	0.021
Toxemia	0.21	0.05–0.80	0.022
Respiratory distress syndrome	4.11	1.38–12.19	0.011
Bronchopulmonary dysplasia			
Birth weight	0.99	0.98–0.99	0.000
Gender (female vs. male).	0.15	0.04–0.50	0.002
Premature rupture of membranes	11.30	2.19–58.39	0.004
Antenatal steroids	0.21	0.05–0.91	0.037
Intact survival			
Gestational age (wks)	1.30	1.03–1.65	0.027
Apgar score at 1 minute	1.22	1.02–1.45	0.027
Delivery (cesarean vs. vaginal).	0.36	0.13–0.97	0.043
Toxemia	5.29	1.71–16.33	0.004
Bruising at birth	0.35	0.14–0.91	0.032

* Of postnatal variables, only Apgar scores, bruising at birth and RDS included.

Scopus patients and 36% of Ein Kerem patients had a birth weight ≤ 750 g.

All antenatal and natal variables were included in the analyses. Some postnatal variables can be sequelae rather than antecedents of IVH. Since IVH and death may occur soon after birth, we confined the postnatal risk interval to the first 12 hours of life including only Apgar scores, bruising present at birth and respiratory distress syndrome in the logistic regression analyses on mortality, severe IVH/PVL and intact survival. In the case of bronchopulmonary dysplasia, where the diagnosis is established only at a corrected gestational age of 36 weeks, other postnatal variables were also included in an additional analysis (PDA sepsis, IVH).

Mortality

In a stepwise logistic regression analysis, gestational age, Apgar score at 1 minute and toxemia had a significant protective association with mortality, while delivery at Mt. Scopus, cesarean delivery versus vaginal delivery, and bruising at birth were associated with increased mortality [Table 2]. Birth weight, Apgar score at 5 minutes, small for gestational age and respiratory distress syndrome were significantly associated with mortality only in the univariate analysis.

PDA = patent ductus arteriosus

Severe IVH/PVL

In the stepwise logistic regression analysis only toxemia had a protective association with the outcome while RDS[3] and the number of pregnancies were significantly associated with increased occurrence of IVH/PVL [Table 2]. Gestational age was significantly associated with the outcome only in the univariate analysis.

It is noteworthy that among patients with severe IVH/PVL, 60% of the outborn babies survived versus only 28% in the inborn group. Also, 34.3% of infants with severe IVH/PVL were bruised (34.3%) versus 19.5% of infants without the lesions ($P = 0.105$).

Bronchopulmonary dysplasia

In a stepwise logistic regression analysis of BPD, birth weight, female gender and the administration of antenatal steroids were significantly protective, while premature rupture of membranes was associated with increased incidence of BPD [Table 2]. Gestational age, Apgar score at 5 minutes and RDS were associated with the outcome only in the univariate analysis.

We performed an additional stepwise logistic regression analysis, including also postnatal variables (sepsis, PDA, IVH). The same independent variables maintained their significant association with the outcome variable (data not shown).

Intact survival (survival without severe IVH/PVL)

In the stepwise logistic regression analysis, gestational age, Apgar score at 1 minute and toxemia were significantly associated with intact outcome while cesarean section and bruising at birth were associated with worse outcome [Table 2] Gestational age, birth weight, small for gestational age and RDS were significantly associated with the outcome only in the univariate analysis.

As our primary aim was to compare the neonatal outcome of inborn (Mt. Scopus) and outborn (Ein Kerem) infants, we repeated analyses introducing 'hospital of birth' as an obligatory variable. No statistically significant associations with the relevant outcome variables were found (data not shown)

Discussion

The results of our study show no advantage of inborn over outborn deliveries of extremely low birth weight infants. In fact, the survival rate of outborn infants was higher than that of inborn babies but there was no significant difference between the two hospital populations in intact survival. The above discrepancy of results was due to a higher percentage of surviving infants with brain damage among the outborn babies (60%) than among the inborn ones (28%). We speculate that this difference is, at least in part, due to parental insistence on continuation of aggressive treatment. This attitude is more typical of ultra-Orthodox families who constitute a higher proportion of the outborn than the inborn population. However, this issue has not been methodologically analyzed in the current study.

Other measured factors that could contribute to the difference in mortality between the two hospital populations were the origin of the patients and the incidence of 'bruising at birth', which differed in the two study groups. Those variables, however, were controlled for in the logistic regression analyses.

Infants of toxemic mothers had a better outcome than infants exposed to other complications at the time of delivery (i.e., premature rupture of membranes, premature contractions, or placental abruption). Similar protective associations of maternal toxemia with neonatal outcome were observed by others [12,14].

Severe bruising and pulmonary hemorrhages were previously associated with the evolution of intraventricular hemorrhage [15,16]. Suggested explanations for this association included hemodynamic instability or consumption of clotting factors caused by the primary event [16]. Bruising at birth, in our study, was associated with reduced survival and reduced intact survival. Early hemorrhagic phenomena may represent already existing hematological disturbances or can be the result of complicated delivery and serve as antecedents of consequent complications. In view of the paucity of literature on this subject, further study and preventive measures are needed.

Antenatal steroid administration has been shown to reduce mortality and morbidity of preterm infants [17,18]. Smrcek et al. [19], however, found that the protective effect was significant only after 28 weeks of gestation. In our study, partial and complete courses were analyzed together versus no treatment, as graded effect was not demonstrable. A statistically significant protective association was found only with BPD. Premature rupture of membranes, on the other hand, was associated with a higher incidence of BPD. This finding is in line with the notion that premature rupture of membranes is often associated with the fetal inflammatory response syndrome [20], which, in turn, is associated with the evolvement of chronic lung disease in preterm infants [21,22].

Cesarean delivery in our cohort was associated negatively with survival and intact survival but was not associated with severe IVH/PVL. We speculate that cases of fetal distress necessitating emergency section could explain this unexpected finding, but no significant correlation between the mode of delivery and Apgar scores was found to support this assumption.

In many studies comparing inborn and referred populations, outborn infants with a relatively mild course could have remained in the referring hospital and others could be transported following prolonged periods of suboptimal care [23]. The inclusion of almost all infants born alive in our hospitals in the analyses, surfactant administration and the early transportation following stabilization, and no case of death during transport minimized the possibility of such biases in our study.

In conclusion, despite the utilization of maternal transport, a substantial number of premature deliveries occur in hospitals lacking neonatal intensive care facilities [24,25]. Our data, though of a relatively small number of patients, suggest that even tiny premature outborn infants may share an outcome comparable with that of inborn babies, if adequate obstetric, perinatal and immediate neonatal care is provided.

RDS = respiratory distress syndrome

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