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Extreme preterm survival and short term outcomes study

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Abstract

Background: Advances in perinatal care have aided in the steady rise in survival rate among extreme preterm babies. Babies in periviable age often pose a serious challenge to medical practitioners and parents alike.

Aim: To examine the trend of survival and short term morbidities among the extreme preterm babies over the study period

Methods: A retrospective study in which data was collected for a period of last five years. Detailed evaluation of medical records of babies admitted to the Neonatal Intensive Care Unit was done.

Results: There were 107 infants included in the study. Survival rates of preterm term during the study period was stable. Infants with a higher gestation had higher survival rates ($p = 0.009$). More number of survivors were noted among preterm with higher birth weight categories ($p = 0.001$). BPD and sepsis were most prevalent morbidity seen among the preterm babies. More cases of BPD were noted among infants less than 26 weeks of age (0.001).

Conclusion: A systematic approach by a multidisciplinary team with active participation of the parents will help in making judicious decisions pertaining to ideal medical management of extreme preterm babies.

Keywords: Extreme preterm, morbidity, periviable, survival

Introduction

Extreme preterm babies are those born before 28 weeks of gestation. According to the American College of Obstetricians and Gynecologists (ACOG), peri-viable birth is defined as delivery occurring from 20 0/7 weeks to 25 6/7 weeks of gestation [1].

Extreme preterm babies especially those in the periviable age pose several challenges to the medical fraternity.

There are multiple factors like antenatal complications, antenatal steroids, chorioamnionitis, congenital malformations which play a role in successful resuscitation, initial stabilization as well as prognosis of these conditions.

The high mortality and probability of long term adverse neurological outcome and other detrimental health effects in extreme preterm babies in periviable age often presents an ethical dilemma with regards to active resuscitation at birth.

A systematic approach by a multidisciplinary team with active participation of the parents is essential in making judicious decisions pertaining to ideal medical management of these babies.

Due to the rapid advancements in research and treatment modalities in the care of extreme preterm babies, their survival rate has shown an encouraging trend over the past few decades. The EPI Cure study from UK and Ireland in 1995, showed survival rates of 20% for infants born before 24 weeks of gestation and greater than 60% for births at 25 weeks of gestation [2].

The National Institute of Child Health and Human Development - Neonatal Research Network (NICHD NRN) data collected between 2003 to 2007 showed no increases in extreme preterm survival rates over the period [3]. However, latest reports from the NICHD NRN and other centers in the US [4, 5], as well as from several other developed nations around the world [6, 7, 8] showed increasing trends in survival rates the extreme preterm babies particularly those belonging to the periviable gestational age.

Our study was designed to identify the overall incidence, survival trends and short term morbidities of extreme preterm babies born at a tertiary health care center in Bahrain.

Methodology

This was a retrospective study in which data was collected for a period of five years from January, 2017 to December, 2021.

Detailed evaluation of medical records was performed using a standardized questionnaire for data collection.

All extreme preterm babies born at gestational age between 22+0 and 27+6 weeks were included in the study.

Exclusion criteria was those babies in periviable gestational age between 20+0 and 21+6 weeks, still births in the delivery room and preterm babies transferred from other hospitals.

Terms and definitions

Extreme preterm babies were defined as those born at less than 28 weeks of gestation.

Broncho pulmonary dysplasia (BPD) was considered in preterm babies who were dependent on oxygen for at least 28 days^[9].

Intra ventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) were diagnosed by cranial ultrasonography or magnetic resonance imaging (MRI) and IVH was graded according to Papile criteria^[10].

Retinopathy of prematurity (ROP) was defined and classified by the International classification of retinopathy of prematurity (ICROP)^[11].

Sepsis was defined by clinical symptoms and positive culture from blood or cerebrospinal fluid samples. The modified Bell's criteria were used for the diagnosis and grading of Necrotizing enterocolitis (NEC)^[12].

Maternal complications during pregnancy included, gestational diabetes, Pregnancy induced hypertension, placental abruption or placenta Previa, chorioamnionitis and premature rupture of membranes (PROM).

Chorioamnionitis was diagnosed clinically or histopathologically.

Antenatal steroid was referred to as any corticosteroid used to promote fetal lung maturity, regardless of doses and timing of administration.

Statistical analysis

Data analysis was done using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp). Descriptive statistics was used to compute the frequencies, percentages, mean and standard deviations. Chi-square tests and Mann-Whitney tests were used for categorical and continuous variables respectively to compute the statistical difference. Bivariate correlations were computed using Pearson correlation coefficient. Binary logistic regression was used to find out the factors related to preterm survival. Multivariate regression model was computed to evaluate the perinatal factors associated with survival. All the p values were 2 tailed and a p value <0.05 was considered statistically significant.

Results

A total of 107 preterm infants were born during the study period (2017- 2021) born at 22 weeks and 1 day to 27 weeks and 6 days' gestation. 9.3% infants were below 500 gms.

17.8% infants were born in 900-999 gm weight category, 16.8% infants were 700-799 gms, followed by 15.9% infants each of 500-599gm and 600-699 gms. There were more infants in the lower GA categories, with 64 (60%) infants with GA less than 26 weeks (Table S1).

There was no major difference in survival rates among the preterm babies from 2017 to 2021. A relatively lower survival rate in 2021 could be attributed the more number of babies born at 22 weeks of gestation (Table 1). Gestational age has a significant impact on survival of the infant. Infants with higher gestation age had higher survival rates ($p=0.009$). More number of survivors were noted among preterms with higher birth weight categories ($p = 0.001$) (Table 2).

Table S1 describes the maternal and infant characteristics of the preterm babies by the gestational age. More numbers of preterm babies were born to mothers who had more than 2 doses of antenatal dexamethasone (61.7%, $p= 0.000$). 1 min and 5 min for APGAR score was 62.6% and 61.7% respectively. Almost 32% (34 of 107) of the infants were born via *In-vitro* fertilization with 55.9% (19 of 34) infants born at gestational age <26 weeks.

BPD was the most prevalent morbidity seen among the preterm babies, followed by sepsis (Fig. 1). More cases of BPD were noted among infants less than 26 weeks of age ($p < 0.001$). Trend of ROP cases increased from 2017 to 2021 with more cases among infants below 25 weeks ($p=0.03$). IVH cases were comparatively low as compared to BPD and ROP. Incidences of PVL and NEC were low among the preterm during the study period with no differences in occurrence across the week distribution of preterm. Prevalence of positive blood culture was low during the study period; however, a slight increase was noted in 2021.

Survival to discharge increased with increasing GA: 1 of 9 at 22 weeks (11.1%), 9 of 17 (52.9%) at 23 weeks, 11 of 20 (55.0%) at 24 weeks, 12 of 18 (66.7%) at 25 weeks, 15 of 21 (71.4%) at 26 weeks and 18 of 22 (81.8%) at 27 weeks. One infant born at 22 weeks of gestation survived. Majority of the infants (62.5%) born at 22 weeks of gestation survived only for <24 hours of their life (Fig. 2).

Univariate analysis showed that gender of the infant, IVF, PROM, APH, gestational diabetes, cesarean delivery does not have an impact on the survival of the infant. Infants with gestational age ≥ 26 weeks had a higher odds of survival as compared to that of infants <26 weeks of gestation (OR 4.09, 95% CI: 1.74- 9.57, $p= 0.01$). Higher the birth weight of the infant, higher was the odds of survival (OR 1.58, 95% CI: 1.24-2.02, $p= 0.00$). Infants born to mother who were not primigravida had a better survival rate (OR 2.77, 95% CI: 1.23- 6.22, $p= 0.013$). Infants who were given at least one antenatal dexamethasone had a higher odds of survival (OR 11.5, 95% CI: 2.40- 55.41, $p= 0.002$). Infants born to mother with no chorioamnionitis had a higher survival rates (OR 3.87, 95% CI: 1.21- 12.3, $p= 0.02$). Infants with 5 min APGAR score ≥ 7 had better survival outcomes (OR 6.17, 95% CI: 2.14-17.7, $p < 0.001$). Infants not born as multiple pregnancies had a higher survival rates ($p= 0.006$) (Table S2). The factors with significant impact on survival outcomes in Univariate analysis were considered for multivariate analysis. Multivariate analysis showed that the infants been provided with antenatal dexamethasone (aOR 6.96, 95% CI: 1.22-39.77, $p= 0.03$) and those with 5 min APGAR score ≥ 7 (aOR 0.26, 95% CI: 0.07-0.88, $p=0.03$) had better survival outcomes (Table S2).

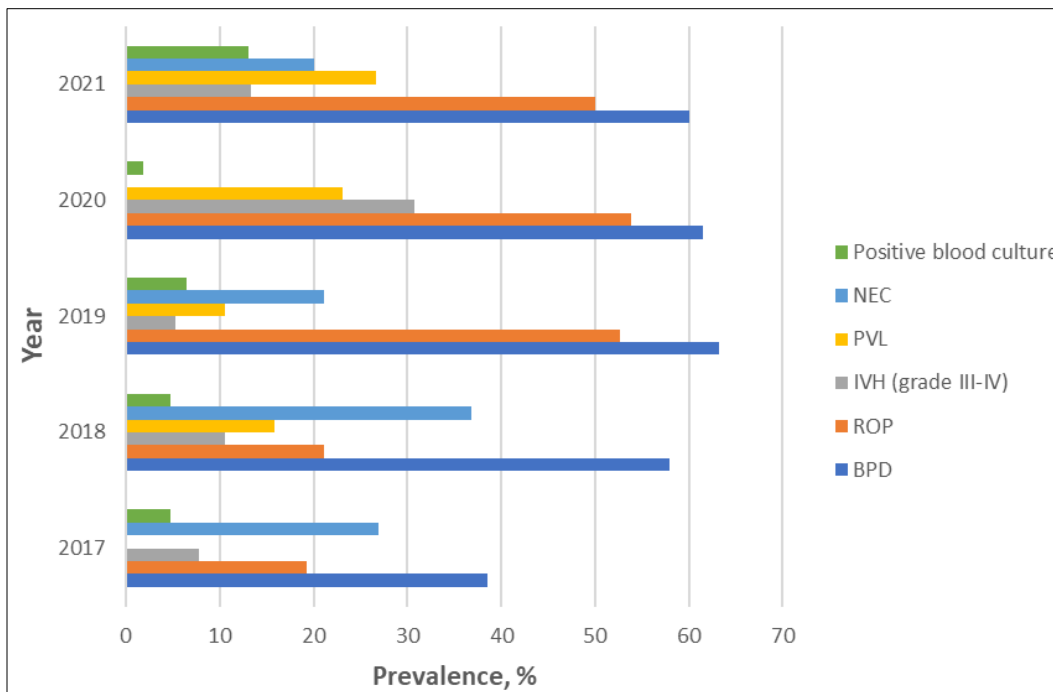


Fig 1: Major morbidity prevalence

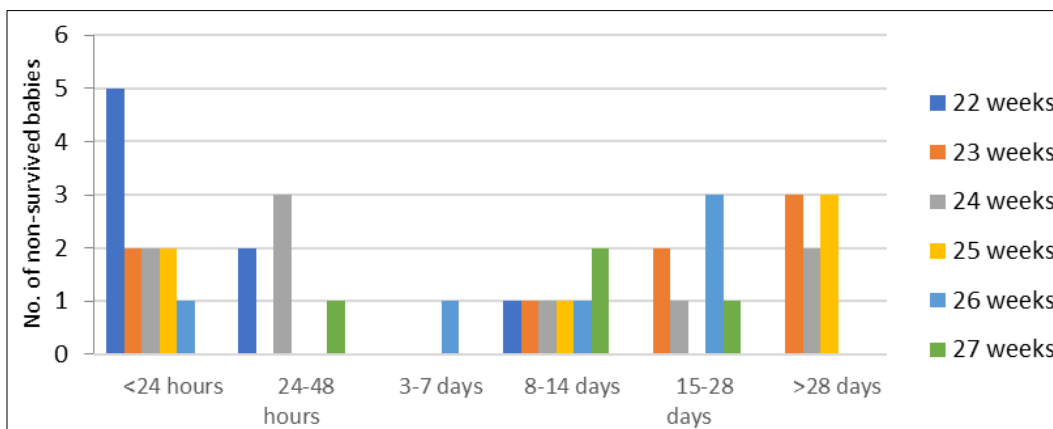


Fig 2: Survival hours/days for non-survived babies as per gestational age

Table 1: Frequency distribution of survived and non-survived during the study period

	2017	2018	2019	2020	2021
All extreme preterm babies (< 28 weeks)	26 (24.3%)	19 (17.8%)	19 (17.8%)	13 (12.1%)	30 (28.0%)
Survived	15	11	15	9	16
Died	11	8	4	4	14
Total babies	2980	2944	2788	2745	2339
Survival rate [Among extreme preterm (overall)]	57.7% (0.50%)	57.8% (0.37%)	78.9% (0.53%)	69.2% (0.32%)	53.3% (0.68%)

Chi-square p value= 0.380

Table 2: Frequency distribution of preterm survivals across gestational age and birth weight categories

Gestational age in weeks	22	23	24	25	26	27	Total
All extreme preterm babies (< 28 weeks)	9	17	20	18	21	22	107
Survived	1 (11.1%)	9 (52.9%)	11 (55.0%)	12 (66.7%)	15 (71.4%)	18 (81.8%)	66 (61.7%)
Died	8 (88.8%)	8 (47.05%)	9 (45.0%)	6 (33.3%)	6 (28.6%)	4 (18.2%)	41 (38.3%)
Chi-square p value: 0.009							
Weight in grams	<500	500-599	600-699	700-799	800-899	900-999	≥1000
All extreme preterm babies (< 28 weeks)	10	17	17	18	12	19	14
Survived	2 (10.0%)	6 (35.3%)	12 (70.6%)	9 (50.0%)	11 (91.7%)	14 (73.7%)	12 (85.7%)
Died	8 (80.0%)	11 (64.7%)	5 (29.4%)	9 (50.0%)	1 (8.3%)	5 (26.3%)	2 (14.3%)
Chi-square p-value: 0.001							

Supplementary

Table S1: Maternal and Infant characteristics by Gestational Age

Maternal and Infant characteristics by Gestational Age								
Characteristic	Births, No./Total No. (%)							P value
	22 week (n=9)	23 week (n=17)	24 week (n= 20)	25 week (n=18)	26 week (n=21)	27 week (n=22)	Total (n=107)	
Maternal characteristic								
Age, Mean (SD), y								
18-35	8 (88.8%)	15 (88.2%)	14 (70.0%)	14 (77.8%)	15 (71.4%)	19 (86.4%)	86 (80.4%)	0.327
>35	0 (11.2%)	2 (11.7%)	6 (30.0%)	4 (22.2%)	6 (28.6%)	3 (13.6%)	21 (19.6%)	
Multiple pregnancy	7 (77.7%)	8 (44.4%)	11 (55.0%)	10 (55.6%)	6 (28.6%)	8 (36.4%)	49 (45.8%)	0.190
Antenatal Dexa								
0	6 (66.6%)	2 (11.7%)	1 (5.0%)	1 (5.6%)	2 (9.5%)	1 (4.5%)	13 (12.1%)	0.000
1	1 (11.1%)	2 (11.7%)	8 (40.0%)	3 (16.7%)	5 (23.8%)	9 (40.9%)	28 (26.2%)	
≥ 2	2 (22.2%)	13 (76.4%)	11 (55.0%)	14 (77.8%)	14 (66.7%)	12 (54.5%)	66 (61.7%)	
Gestational Diabetes	0 (0.0%)	0 (0.0%)	6 (30.0%)	4 (22.2%)	3 (14.3%)	1 (4.5%)	14 (13.1%)	0.039
IVF	2 (22.2%)	8 (47.05%)	5 (25.0%)	6 (33.3%)	5 (23.8%)	8 (36.4%)	34 (31.8%)	0.369
Primigravida	8 (88.8%)	7 (38.9%)	9 (45.0%)	10 (55.6%)	10 (47.6%)	7 (31.8%)	51 (47.7%)	0.034
PROM*	2 (12.5%)	10 (58.8%)	9 (45.0%)	10 (55.6%)	7 (33.3%)	8 (36.4%)	46 (43.0%)	0.166
Chorioamnionitis	4 (50.0%)	3 (16.7%)	4 (20.0%)	1 (5.6%)	1 (4.8%)	2 (9.1%)	15 (14.0%)	0.031
Thyroid dysfunction	0 (0.0%)	4 (22.2%)	2 (10.0%)	3 (16.7%)	2 (9.5%)	2 (9.1%)	13 (12.1%)	0.612
Infant characteristic								
Birth weight, Mean (SD), g								
<500	5 (55.5%)	3 (17.6%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	10 (9.3%)	0.000
500-599	4 (44.4%)	7 (41.1%)	5 (25.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	17 (15.9%)	
600-699	0 (0.0%)	6 (35.2%)	6 (30.0%)	4 (22.2%)	1 (4.8%)	0 (0.0%)	17 (15.9%)	
700-799	0 (0.0%)	1 (5.8%)	6 (30.05)	5 (27.8%)	6 (28.6%)	0 (0.0%)	18 (16.8%)	
800-899	0 (0.0%)	0 (0.0%)	3 (15.0%)	4 (22.2%)	3 (14.3%)	2 (9.1%)	12 (11.2%)	
900-999	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (16.7%)	9 (42.9%)	7 (31.8%)	19 (17.8%)	
≥1000	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	13 (59.1%)	14 (13.1%)	
Sex								
Male	6 (66.6%)	10 (58.8%)	7 (35.0%)	12 (66.7%)	12 (57.1%)	12 (54.5%)	59 (55.1%)	0.351
Female	3 (33.3%)	7 (41.1%)	13 (65.0%)	6 (33.3%)	9 (42.9%)	10 (45.5%)	48 (44.9%)	
Mode of delivery								
LSCS**	0 (0.0%)	0 (0.0%)	5 (25.0%)	10 (55.6%)	12 (57.1%)	10 (45.5%)	37 (34.6%)	0.000
SVD‡	9 (100.0%)	17 (100.0%)	15 (75.0%)	8 (44.4%)	9 (42.9%)	12 (54.5%)	70 (65.4%)	
1 min APGAR								
≤3	6 (66.6%)	11 (64.7%)	6 (30.0%)	6 (33.3%)	7 (33.3%)	3 (13.6%)	39 (36.4%)	0.026
4-7	3 (33.3%)	6 (35.2%)	14 (70.0%)	11 (61.1%)	14 (66.7%)	19 (86.4%)	67 (62.6%)	
>7	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	
5 min APGAR								
≤3	0 (0.0%)	4 (23.5%)	1 (5.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	6 (5.6%)	0.003
4-7	9 (100.0%)	12 (70.5%)	13 (65.0%)	12 (66.7%)	10 (47.6%)	10 (45.5%)	66 (61.7%)	
>7	0 (0.0%)	1 (5.8%)	6 (30.0%)	6 (33.3%)	10 (47.6%)	12 (54.5%)	35 (32.7%)	

* Premature rupture of membrane, ** Lower segmental caesarean section, ‡ Spontaneous vaginal delivery

Table S2: Regression analysis of perinatal factors associated with survival among infants

Variable	Crude model		Adjusted model (R ² = 0.410)	
	OR (95% CI)	P value	aOR (95% CI)	p-value
GA ≥26 weeks	4.09 (1.74- 9.57)	0.01	1.09 (0.27- 4.38)	0.89
Birth weight	1.58 (1.24- 2.02)	0.00	1.34 (0.91-1.97)	0.13
Female gender	1.51 (0.68- 3.35)	0.30		
Primigravida				
Yes (Ref)				
No	2.77 (1.23- 6.22)	0.013	1.30 (0.47-3.55)	0.60
Multiple pregnancy	0.31 (0.14-0.71)	0.006	0.32 (0.13- 0.95)	0.04
Elderly pregnancy (>35)	1.03 (0.38-2.75)	0.95		
IVF	0.85 (0.37-1.97)	0.71		
Antenatal dexa	11.5 (2.40-55.41)	0.002	6.96 (1.22- 39.77)	0.03
PROM				
Yes (Ref)				
No	1.21 (0.55-2.67)	0.62		
Chorioamnionitis				
Yes (Ref)				
No	3.87 (1.21-12.3)	0.02	2.15 (0.52-8.79)	0.28
APH				
Yes (Ref)	1.46 (0.48-4.40)	0.49		

No				
Gestational Diabetes				
Yes (Ref)	0.86 (0.26- 2.78)	0.80		
No				
Cesarean delivery	2.20 (0.92-5.24)	0.07		
5-min APGAR score ≥ 7	6.17 (2.14-17.7)	0.001	0.26 (0.07-0.884)	0.03

Discussion

Extreme preterm births often pose several challenges to the clinician in ensuring their survival and reduction in associated morbidities. The paucity of data from the Middle East countries regarding extreme preterm infants, whose numbers are steadily increasing owing to the availability of advanced neonatal care has led to the conceptualization of this study.

Extreme preterm survival has been showing a positive trend over the years owing to the advances in the field of neonatal medicine and the advent of newer modalities of treatment.

In our study, overall survival rate of extreme preterm babies was 61.6%. Survival to discharge increased with increasing gestational age. Survival at 22 weeks was low at 12.5% but increased to 55.6% at 23 weeks. Survival rate of 50.0% at 24 weeks and 66.7% at 25 weeks of gestation was noted, which showed a significant rise to 71.4% and 81.8% at 26 weeks and 27 weeks of gestation respectively. Majority of the infants (62.5%) born at 22 weeks of gestation survived only for <24 hours of their life.

According to recent NICHD data [3], which studied extreme preterm born between 2013 and 2018, overall survival rate was 78%. At 22 weeks of gestation, 10.9% (60/549) survived and at 23 weeks, survival increased to 49.4% (535/1083) while the survival at 28 weeks was 94.0% (2267/2412).

In comparison to a similar study by Stoll *et al.* [5] analyzing the NICHD data from 2008 to 2012, although the overall survival rate of extreme preterm babies was slightly less at 76% there was significant difference between the survival to discharge at 22 weeks and 23 weeks which was 6.6% and 32.3% respectively.

In Epicure study [6] from UK, survival of babies in 2006 was 2%,19%,40%,66%,77% at 22, 23,24,25 and 26 weeks of gestation respectively. In comparison to the data from 1995, survival increased from 40% to 53% overall and at each week of gestation by 9.5% (at 23 weeks, 12% at 24 weeks, and 16% at 25 weeks).

Survival improved with advancing gestational age in several other studies from Canada [7] France [8], Japan [13] which was similar to the trend seen in our study.

Perinatal factors play an important role in the survival and outcomes of extreme preterm babies [21]. Our study found that infants who were given at least one dose of antenatal steroid had a higher odds of survival.

Several studies showed lower mortality in extreme preterm babies who received antenatal corticosteroid therapy [6, 14, 15, 16, 17], while a few of them found no association between survival and antenatal steroid administration [18, 19].

In our study, *in-vitro* fertilization (IVF), premature rupture of membrane (PROM), antepartum hemorrhage (APH), gestational diabetes, cesarean delivery did not have an impact on survival of these extreme preterm infants. It was also noted that higher the birth weight and more the APGAR score (5 min ≥ 7), better was the chance of survival. Similarly, a recent study by Norman *et al.* [20] concluded that APGAR scores, gestational age and birth weight show stronger associations with mortality in extreme preterm.

Tyson *et al.* [21] found that higher birth weight, female sex, and antenatal steroid therapy were all associated with improved survival, while multiple pregnancies were linked to lower survival.

Few studies found higher survival rate of infants born by cesarean delivery [18, 19, 22], while one study found a lower rate [6].

Another study demonstrated lower mortality in infants at 22-24 weeks born by cesarean delivery and in infants at 25-28 weeks born by vaginal delivery [23]. However, there are reports which did not find a difference in mortality among preterm infants based on mode of delivery [6, 15, 24].

Several studies showed increasing birth weight was associated with better survival [18, 23], whereas some did not find a link between these two factors [5, 22, 24]. In our study multiple births were associated lower survival rates similar to some studies [21, 25]. Other research showed no difference [26], or even interestingly a reduced risk for multiple births was reported as well [27].

Prevalence of major morbidities were higher in our study compared to several others [NICHD bell *et al.*, Epicure] [3, 6] with no significant variations among them over the years. Some studies [28] showed an increasing trend of morbidities in comparison to earlier reports. This can be attributed to the increasing number extreme preterm babies who are successfully resuscitated at birth and surviving for longer periods.

In contrast, a study from France [8] found an increasing proportion of infants surviving without severe morbidities like NEC, BPD, periventricular Leukomalacia, and severe ROP. It underlies the importance of institution of more advanced and comprehensive evidenced based approaches in managing extreme preterm babies

Owing to the higher morbidities in extreme preterm babies in periviable age as seen in many studies, further detailed discussions and consensus regarding the threshold of resuscitation is essential. Currently, as per the recent British Association of Perinatal Medicine (BAPM) guidelines, it is not appropriate to attempt to resuscitate babies born before 22 weeks of gestation.

Several other factors like availability of advanced facilities and well trained personnel, play an important role in taking decision regarding the threshold of gestational age at which resuscitation should be attempted and often presents an ethical dilemma to the clinicians.

There were some limitations of the study. This was a retrospective analysis from the hospital records, accuracy of the information may not be uniformly reliable. As it was a single centered study, data may not be generalized for the country as a whole. Sample size was relatively smaller in comparison to other similar studies, which may interfere with the interpretation of the study when viewed in a general perspective.

Conclusions

Extreme preterm infants are a vulnerable section of the population who are prone to severe morbidities and mortality. Dealing with extreme prematurity is an ever-

growing challenge in the neonatal care worldwide. Increasing survival rate with provision of improved care is the current trend in this group of population. Further research with a large sample involving multiple centers will help to explore the real situation of these extreme preterm babies and suggest areas of improvement.

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Conflict of Interest

Not available

Financial Support

Not available

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