

## OUTCOMES OF PREMATURE AND VERY-LOW-BIRTH-WEIGHT INFANTS FROM 1991 TO 2002

Nada SBEITI<sup>1</sup>, Fouad ZIEDEH<sup>2</sup>, Mohammad RAMADAN<sup>3</sup>, Hani LABABIDI<sup>4</sup>, Mariam RAJAB<sup>1</sup>

Sbeiti N, Ziedeh F, Ramadan M, Lababidi H, Rajab M. Outcomes of premature and very-low-birth-weight infants from 1991 to 2002. *Leb Med J* 2005 ; 53 (3) : 162-167.

**ABSTRACT • BACKGROUND :** Intensive care nursery (ICN) survival rates reflect the efficacy of the perinatal management achieved in each institution. It became of great importance to compare outcome data of individual hospitals to international numbers, taking into consideration the dramatic changes in medical care for very-low-birth-weight (VLBW) infants and their mothers that occurred during the past decade worldwide.

**OBJECTIVE :** Evaluate the neonatal outcome (mortality and morbidity) of VLBW and premature infants born at Makassed General Hospital (MGH) and admitted to ICN and compare it to the international rates.

**METHODS :** Detailed data were collected for all VLBW (< 1500 g) and/or premature infants (< 30 weeks) born at MGH and admitted to ICN from Jan 1, 1991, through May 31, 2002, retrospectively. Three study periods were defined according to the emergence of new treatment modalities, namely antenatal steroid use and surfactant treatment. Outcome measures were the survival rates at day 28 and on discharge. Secondary outcomes were morbidity rates for patent ductus arteriosus, necrotizing enterocolitis, intraventricular hemorrhage, bronchopulmonary dysplasia, and nosocomial and maternofetal infections. We studied the effect of antenatal steroids, surfactant, and new respiratory support modes as well as the effect of birth weight, etiology of pre-term labor, mode of delivery, Apgar score, gender, multiple gestation, and intrauterine growth retardation on both survival and morbidity.

**RESULTS :** There were 207 VLBW ( $\leq 1500$  g) and/or premature ( $\leq 30$  W) infants. Four infants were excluded because of major congenital anomalies. A total 203 were enrolled in the study. The mean birth weight was  $1195 \pm 274$  grams. There were 99 males and 104 females. The overall survival rate was 69.5%. There was significant improvement in survival over the study periods. Mortality decreased from 50.0% to 26.4% at the end of the study ( $p < 0.001$ ). Antenatal steroids had a significant positive effect on survival. The antenatal steroid use increased during the study period from 11% to 83%. Surfactant had a positive effect on those who experienced early respiratory distress with survival rate of 69% for those not prepared with antenatal steroids compared to universal rate of 75%. Birth weight, gestational age and Apgar score were positively related to survival rate ( $p < 0.001$ ). There was no proven relation between delivery mode, multiple gestation, gender, intrauterine growth retardation and survival. Infection was the major cause of morbidity and mortality.

**CONCLUSION :** A considerable reduction in mortality was observed at our institution over the 12 years study period. Changes in survival appear to reflect newer therapies namely antenatal steroid use and surfactant treatment.

Sbeiti N, Ziedeh F, Ramadan M, Lababidi H, Rajab M. Devenir des prématurés et des nouveau-nés de faible poids de naissance de 1991 jusqu'à 2002. *J Méd Lib* 2005 ; 53 (3) : 162-167.

**RÉSUMÉ • INTRODUCTION :** Le taux de survie dans les soins intensifs pour nouveau-nés (NN) reflète l'efficacité de la prise en charge périnatale de chaque institution. Il est primordial d'évaluer le réseau de chaque institution en le comparant aux résultats internationaux et de prendre en considération les changements effectués ces dix dernières années dans les soins médicaux pour NN de très faible poids de naissance ainsi que de leurs mères. Les progrès réalisés dans le domaine de réanimation néonatale ont permis l'amélioration du taux de survie de la prématurité.

**OBJECTIFS :** Etudier le devenir (mortalité et morbidité) des NN de faible poids de naissance (PN) et celui des prématurés de très faible PN, nés à l'Hôpital Général Makassed de janvier 1991 à mai 2002.

**MÉTHODES :** C'est une étude rétrospective. Les données ont été collectées pour tous les NN de très faible PN ( $\leq 1500$  g) et ou prématurés (< 30 semaines d'âge gestationnel). Paramètres évalués : le taux de survie au 7<sup>e</sup> jour, au 28<sup>e</sup> jour et à la sortie de l'hôpital. La morbidité évaluée concerne le canal artériel, l'entérocolite nécrosante, l'hémorragie intraventriculaire, la dysplasie bronchopulmonaire, les infections nosocomiales et materno-fœtales. Les effets de la corticothérapie anténatale, du surfactant, des nouveaux mode de ventilation ont été étudiés de même que le poids de naissance, le mode d'accouchement, le score d'Apgar, le sexe, la multiparité, le retard de croissance intra-utérine, et leur impact sur la morbidité.

**RÉSULTATS :** Il s'agit de 207 NN de très faible PN ( $\leq 1500$  g) et/ou prématurés (< 30 semaines) dont 4 ont été exclus pour malformations congénitales majeures. 203 NN ont été inclus dans l'étude, 99 garçons et 104 filles. Le PN moyen est  $1195 \pm 274$  grammes et le taux global de survie 69,5%. Le taux de survie a augmenté de façon significative au cours de la période de l'étude. La mortalité a diminué de 50% à 26,4% en fin d'étude, alors que l'administration de la corticothérapie anténatale a augmenté de 11% à 83%. La corticothérapie anténatale améliore significativement le taux de survie ( $p < 0,001$ ). L'administration de surfactant(s) a un effet positivement significatif sur la détresse respiratoire idiopathique avec un taux de survie de 69% chez le NN n'ayant pas reçu de corticothérapie anténatale en comparaison avec un taux universel de 75%. Le PN, l'âge gestationnel, et le score d'Apgar ont un effet positivement significatif sur le taux de survie ( $p < 0,001$ ). Aucune corrélation n'a été retrouvée entre le mode d'accouchement, la multiparité, le sexe, le retard de croissance intra-utérine et le taux de survie. L'infection est la cause majeure de morbidité et de mortalité.

**CONCLUSION :** La mortalité des NN a considérablement diminué au cours de notre étude. Ceci paraît être le reflet d'une nouvelle stratégie thérapeutique, à savoir l'administration de la corticothérapie anténatale et de surfactant(s).

<sup>1</sup>Division of Neonatology, <sup>2</sup>Department of Biostatistics, <sup>3</sup>Department of Obstetrics and Gynecology, <sup>4</sup>Division of Critical Care Medicine, Makassed General Hospital, Beirut, Lebanon.

Correspondance : *Mariam Rajab, MD, Makassed General Hospital. POBox 11-6301. Riad El Solh. 110702210 Beirut. Lebanon.*  
Tel. : (961) 3 3010846 Fax : (961) 1 646 589

#### ABBREVIATIONS

MGH	• Makassed General Hospital
ICN	• Intensive care nursery
VLBW	• Very-low-birth-weight infant
IUGR	• Intrauterine growth restriction
HFO	• High frequency oscillation
IVH	• Intraventricular hemorrhage
PDA	• Patent ductus arteriosus
NEC	• Necrotizing enterocolitis
CLD	• Chronic lung disease
AS	• Apgar score

#### INTRODUCTION

Prematurity and low birth weight are major problems still to face and overcome in neonatology [1-3]. They are the most important determinants of neonatal survivability and morbidity. Perinatal management decisions are highly affected by our knowledge of fetal prognosis in terms of survivability and morbidity [4-5].

In the 1990's, new approaches emerged for both the obstetric management of pre-term births and the neonatal care of prematurely born infants [6-9]. These included : advanced prenatal care, consideration of transport condition, prenatal and postnatal steroid therapy [10-11], introduction of surfactant as prophylaxis and treatment of neonatal respiratory distress syndrome [12-13], and new modes of respiratory support. The emerging changes were associated with decreases in mortality and morbidity for very-low-birth-weight infants during the first half of the decade [4, 7-10]. Many changes, in accordance with the new advances in the field of neonatology, took place at our institution as well. It is uncertain how these developments have affected the outcome measures at our hospital.

The aim of this study is to evaluate and report the results of our neonatal practice and to determine the survivability and morbidity rates in comparison to the international ones.

#### MATERIALS AND METHODS

Makassed General Hospital is one of the main tertiary medical centers in Lebanon, which covers Beirut, and is a referral center for the periphery, particular for neonatal care. We retrospectively reviewed the charts of all infants born at MGH and admitted to ICN from January 1<sup>st</sup> 1991 through May 31<sup>st</sup> 2002. Inclusion criteria were VLBW (< 1500 grams) or premature (< 30 weeks) infants. All infants born with major congenital anomalies that might have affected the outcome were excluded. The medical records of the infants' mothers were reviewed thoroughly as well.

Collected data included maternal demographic factors, medical and obstetrical history, prenatal cares including antenatal steroid intake, etiology of pre-term delivery, events during delivery, and interventions done. Neonatal

factors collected consisted of demographic details, interventions done : surfactant use (doses number and timing), oxygen requirement and detailed hospital course.

Two major developments occurred in the management of premature infants during the study period. First, antenatal steroids were started as regular treatment for pregnant women < 34 weeks at risk for pre-term delivery in 1994. Second, surfactant treatment began regularly for infants with early respiratory distress syndrome or those in need for oxygen treatment with consistent radiological findings in 1999. Accordingly we divided our study into 3 periods:

- Period I from 1991 through 1994 before the use of antenatal steroid treatment
- Period II from 1995 through 1998 before the emergence of regular surfactant rescue treatment
- Period III from 1999 through the end of the study, i.e. 2002.

It is worth mentioning that high frequency ventilation was introduced in 1999, and nitric oxide therapy was introduced in 2000.

The study population was divided into three groups according to gestational ages ; Group 1 : 23-28 weeks, Group 2 : 29-34 weeks, and Group 3 : > 34 weeks, to stratify infants according to the severity of prematurity. The primary outcome measure was the survival rate at day 28 and on discharge. Secondary outcomes were the incidence of different morbidities including intraventricular hemorrhage, necrotizing enterocolitis, chronic lung disease, patent ductus arteriosus and nosocomial and maternofetal infections.

#### RESULTS

A total of 207 neonates were born at MGH during the study period. Four patients with congenital anomalies including severe hydrocephalus, anencephaly, meningo-myelocoele and biliary atresia were excluded. The study population comprised of 203 neonates. The number of infants in each of the three-study group was 77, 112 and 14 respectively.

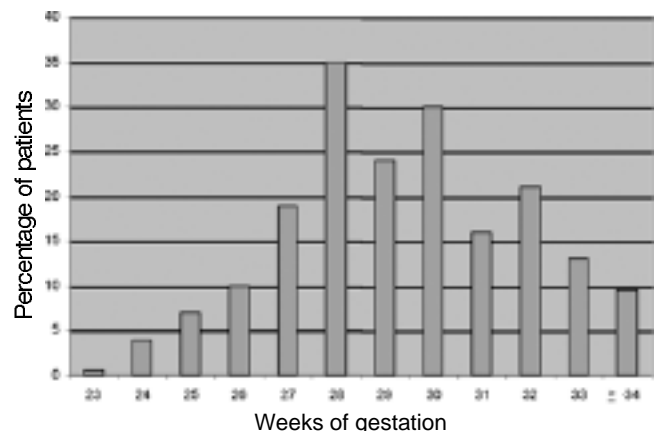


FIGURE 1  
Distribution of the 203 infants according to gestational age

**TABLE I**  
FETAL AND MATERNAL FACTORS  
AND EFFECT ON SURVIVAL

FACTOR	Died	Survived	<i>p</i> -value
DELIVERY MODE			
Vaginal	34.5%	65.5%	0.72
Cesarean	32.6%	67.4%	
MULTIPLE GESTATIONS			
Yes	27.5%	72.5%	0.11
No	39.2%	60.8%	
GENDER			
Male	30.4%	69.6%	0.07
Female	41.5%	58.5%	
IUGR			
Yes	28.9%	71.1%	0.06
No	34.9%	65.1%	
APGAR SCORE	5.6	7.6	< 0.001

The distribution of study population according to the gestational age is shown in Figure 1. Most of the studied infants (53.2%) were between 27-30 weeks. Demographic analysis results are shown in Table I. The birth weight ranged from 450 to 1920 grams with a mean of  $1195 \pm 274$  grams. There were 99 males (48.8%) and 104 females (51.2%). Intrauterine growth retardation defined as birth weight less than 10% of expected weight, was observed in 20.3%. A total of 70 neonates (34.5%) were a product of multiple gestations. There were no statistical significant differences in the distribution of gestational age along the three study periods (Figure 2).

The overall survival rate of the 203 neonates was 69.5%.

There was significant improvements in survival over the three study periods : Period I = 50%, Period II = 67.6%, and Period III = 73.6 % (Figure 3).

The maternal causes of pre-term delivery elicited did not have any statistical significant effect on survival of neonates. The etiologies considered were hypertensive disease of pregnancy, pre-term prolonged rupture of membranes, chorioamionitis, antepartum hemorrhages (placenta previa and abruption), medical illnesses, IUGR, oligohydramnios, cervical anomalies, idiopathic pre-term labor and multiple gestations. Neither the delivery mode nor time of delivery had any effect on survival

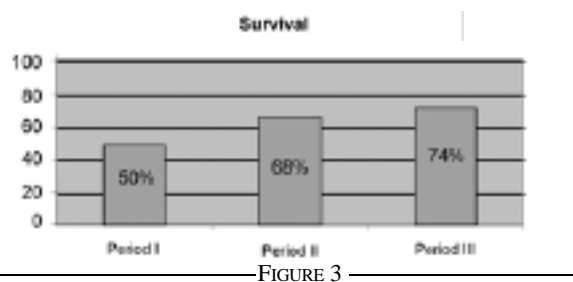


FIGURE 3  
Increasing survival rate from period I through period III

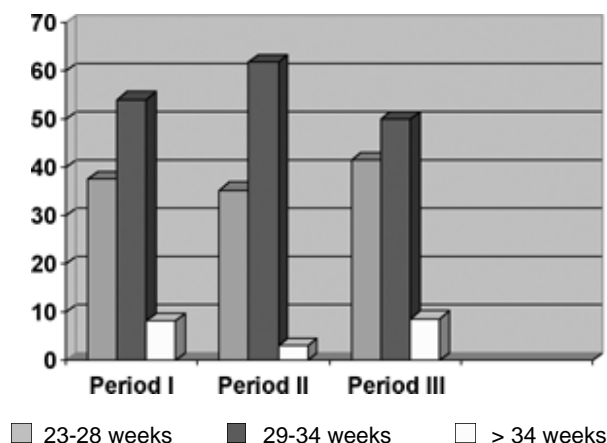


FIGURE 2. Study population distribution according to gestational age across study periods

of neonates. Fetal factors including multiple gestations, gender and IUGR had no effect on survival (Table I).

The survival rate increased with the gestational age as shown in Figure 4. These rates ranged from 42.9% at 25 weeks of age to 83.3% at 34 weeks. The mean birth weight for those who survived at discharge ( $1269 \pm 249$  grams) was significantly higher than the weight of those who didn't ( $996 \pm 241$  grams) ( $p < 0.001$ ). The survival rate was 20% at birth weight of < 700 grams and more than 90% at birth weight of > 1500 grams (Figure 5). The Apgar score at minute 5 was significantly higher in neonates who survived ( $7.6 \pm 1.6$ ) compared to those who died ( $5.6 \pm 2.0$ ) with  $p < 0.001$  (Table I).

There was an increase in the use of antenatal steroids from 1991 to 2002. While only 11% of pregnant women with pre-term labor received steroids, this rate increased to a peak of 83% in year 2000. The effect of antenatal steroid on survival rate of pre-term infants at day 7 is shown in Table I . The overall survival rate of neonates whom their mothers' received steroid treatment was 55.8% compared to 15.0% in neonates with no antenatal steroids ( $p < 0.001$ ). There was a positive effect of complete course (2 shots) versus a single shot versus no steroids, 88%, 75%, and 58% respectively ( $p < 0.001$ ). The earlier use of steroids the higher the survival of pre-term neonates. The mean period for steroid dose was 40.2 hours before delivery for those who survived versus 20.8 hours for those who didn't ( $p < 0.028$ ). There was no difference between the two steroid brands used,

**TABLE II**  
EFFECT OF ANTENATAL STEROID ON SURVIVAL  
AT DAY 7

ANTENATAL STEROID	Died	Survived
NIL	42%	58%
1 DOSE	25%	75%
2 DOSES	12%	88%

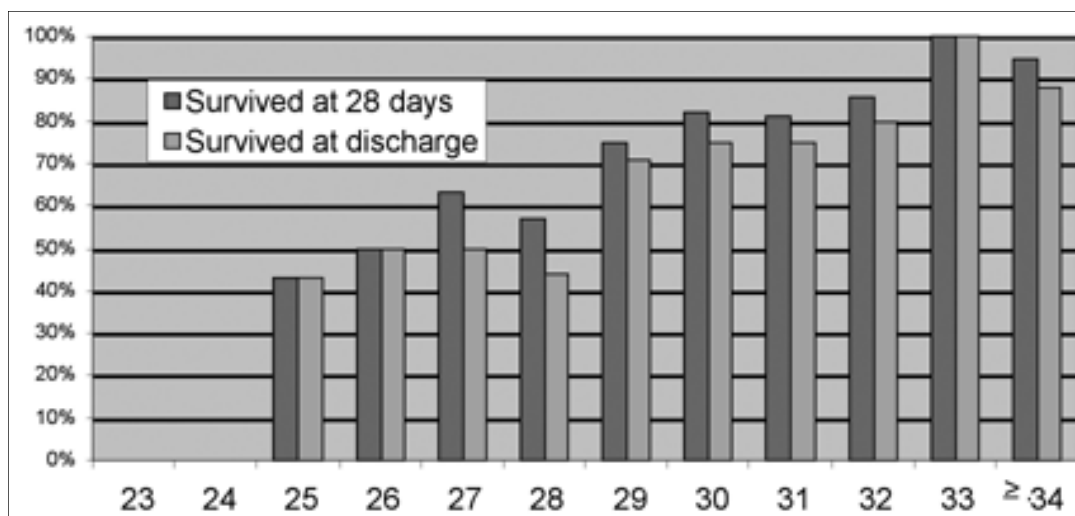


FIGURE 4  
Survival rates according to weeks of gestational age

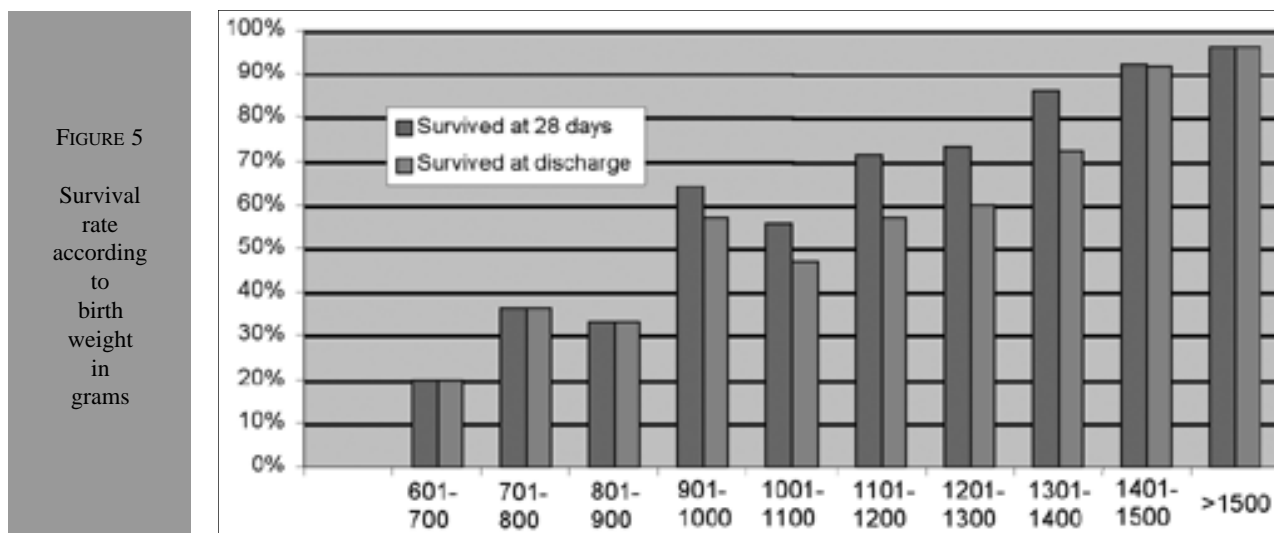


FIGURE 5  
Survival rate according to birth weight in grams

$\beta$ -methasone or dexamethasone, on survival rates ( $p = 0.8$ ).

Surfactant was given as rescue treatment to two categories of patients. Group A included neonates who received antenatal steroid but did have early respiratory distress. Group B included those who didn't receive antenatal steroid and developed early respiratory distress. The survival rate in Group A was comparable to the control group i.e. the neonates who received antenatal steroids and didn't develop respiratory distress, 84.6% vs. 85.2%,  $p = 0.83$ . However, the survival rate in Group B was significantly lower than the control group, 85.2% vs. 69.0%,  $p = 0.04$ .

Infection was defined either as positive blood culture or positive parameters (CBC, CRP) with consistent clinical presentation. Maternofetal infection rate was 30%. The most common pathogens, in order of frequency, were:  $\beta$ -hemolytic *Streptococcus* group B, *E. coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Streptococcus Enterobacter* and *Corynebacter* species.

Nosocomial infection rate was 41.8%. The most common pathogens, in order of frequency, were: *Klebsiella*

*pneumoniae*, *Pseudomonas aerogenosa*, *E. coli* and species of *Acintobacter*, *Streptococcus*, and *Staphylococcus*, *Candida albicans*, and *Enterobacter* and *Citrobacter* species.

Infection was the leading cause of death followed by immaturity defined as newborn of weight  $\leq 750$  g or GA  $\leq 28$  weeks that died of no other known cause, 46% vs. 35% respectively. The causes of mortality among the study population are shown in Figure 6.

The morbidities observed were PDA, CLD, NEC and IVH (Table III). In addition cases of convulsions, blood sugar instability, pneumothorax, electrolyte disturbances and acidosis were reported.

We studied factors that are known to have or in query relation with major morbidities.

No relation was found between maternal antibiotic of amoxicillin/clavulonic acid intake and development of NEC. The only significant positive relation was between development of NEC and antenatal steroid therapy ( $p < 0.02$ ). No relation was found between IVH and antenatal steroid.

The hospital stay for those who survived ranged

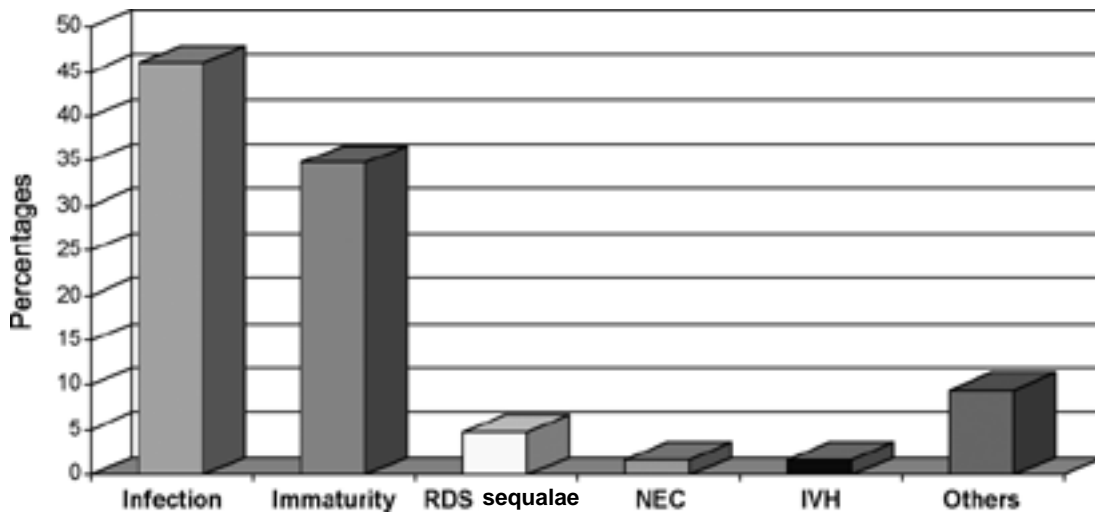


FIGURE 6  
Causes of mortality among study population

between 5 and 118, with a mean of  $52.7 \pm 22.5$  days. For non-survivors the hospital stay before death ranged from 0.5 to 65 days, with a mean of  $14.1 \pm 17$  days.

A follow-up till the age of one year was available for 23.2% patients only. Around 15.8% of the babies were completely healthy, 5.4% had related morbidities and 2% had unrelated morbidities.

#### DISCUSSION

The survival rate of VLBW and premature infants increased significantly from 1991 to 2002 at our institution. The largest improvement was observed for 1991 to 1998, i.e. from study period I to II. Thus changes in survival appear to reflect newer therapies, namely antenatal steroid use and surfactant treatment. At very low gestational age, our rates fell behind international means. Allen et al. reported a 79% survival rate for neonates 25 weeks of age at Johns Hopkins University [6]. Whereas the annual average rate from 1996 to 2000 for 24, 26 and 29 weeks of gestational age were 50.8%, 81.6% and 97.6% respectively according to the British Columbia annual neonatal outcome report [1]. Our survival rates were 43%, 50%, and 70% for 25, 26 and 29 weeks of gestation respectively. There exist limitations in comparing these rates. Our data represents pooled survival rates from 1991 to 2002 for a relatively small number of neo-nates when compared to those of larger surveys. We

expect better rates for this category of neonates after 1999. A sub-analysis for the study period III could be of value ; however, numbers are too small for such analysis.

In accordance with other studies [1, 8, 10], giving steroids to all pregnant women < 34 weeks at risk for preterm delivery improved the survival of neonates significantly. There was an increasing trend for the use of antenatal steroids over the study period comparable to the results reported by Horbar [14] in 1993 (25%), and in 2000 it reached 83% at our institution. Moreover, two doses of steroids were superior to one shot indicating that the longer the steroid to delivery duration the better the maturity of the lung hence the better the outcome. Our studies, in consensus with others [1], did not reveal any difference between betamethasone and dexamethasone.

A positive effect between antenatal steroids and IVH has been reported [10]. However, we did not observe similar effect in our study. This could be due to the small number of infants who developed IVH (10%). On the other hand, a positive relation was observed between antenatal steroids and development of NEC.

The positive effect of surfactant therapy on survival of premature infants with respiratory distress syndrome has been well documented in the literature [7, 11-13, 15-16]. Our study demonstrated lower survival rates in neonates who received surfactant therapy without preceding antenatal steroids. However, the survival rates were comparable in neonates who received antenatal steroids and developed respiratory distress syndrome and those who received the steroids but did not develop the respiratory distress syndrome. These figures are in accordance to those reported by Ferrara and Hoekstra [15-16].

Our data emphasizes the role of Apgar score as an important assessment tool for neonatal asphyxia and as a predictor of outcome [17]. In contrast to previously published reports, we did not find an increase in mortality in neonates product of multiple gestation, or infants with IUGR [18]. As for the controversial issue of NEC and antibiotic use, we did not find a relation between them in our study.

**TABLE III**  
MORBIDITIES AMONG STUDY POPULATION

MORBIDITY	(N)	% of study population	Survival rate
PDA	29	15	52%
CLD	27	14	59%
NEC	21	11	67%
IVH	20	10	45%

## CONCLUSION

A considerable reduction in mortality was observed at our institution over the 12 years study period. Changes in survival appear to reflect newer therapies namely antenatal steroid use and surfactant treatment.

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## مستقبل الخُدج والمولودين حديثاً قليلي الوزن حين الولادة من ١٩٩١ لغاية ٢٠٠٢

**موجز:** مدخل - تعكس نسبة الحياة في وحدة العناية الفائقة للمولودين حديثاً، فعالية الاهتمام الموطد بعد الولادة في كل مؤسسة، وقد أصبح كثير الأهمية تقييم دوائر كل مؤسسة ومقارنة نتائجها مع النتائج الدولية والأخذ بالاعتبار التغيرات التي تمت في السنوات العشر الأخيرة في ما يتعلق بالاعتناءات الطبية بالمولودين حديثاً قليلي الوزن حين الولادة أو بأمهاتهم. التطور الذي تحقق في ميدان إنعاش المولودين حديثاً سمح بتحسين نسبة الحياة عند الخُدج.

**الموضوع -** موضوع الدراسة هو معرفة مستقبل (وفاة وامراضية) المولودين حديثاً ذوي الوزن القليل حين الولادة والخُدج ذوي الوزن القليل حين الولادة في المستشفى العام للمقاصد بين كانون الثاني (يناير) ١٩٩١ إلى أيار (مايو) ٢٠٠٢.

**الطرق -** دراسة استرجاعية، وقد جمعت المعطيات لكل المولودين حديثاً قليلي الوزن (أقل أو مساوي ١٥٠٠ غراماً) والخُدج (أقل من ٢٠ أسبوعاً للحمل).

**المعالم التقييمية:** نسبة الحياة في اليوم السابع واليوم الثامن والعشرين وحين مغادرة المستشفى. تشمل تقييم المراضة على: القناة الشريانية، التهاب الامعاء والقولون المنخر (موات النسج)، النزف داخل البطينات، سوء تنسج رئوي قصبي، الانتانات الاستشفائية للأم والجنين ودرست تأثيرات المعالجة بالقشريات الستيروئيدية قبل الولادة وكذلك «الفعال بالسطح» وطرق التهوية الحديثة وكذلك الوزن حين الولادة وطريقة الولادة وحرز أبعاد الجنس وعديدات الولادة وتأخر النمو داخل الرحم وتأثير كل ذلك على المراضة.

**النتائج -** يشمل بحثنا ٢٠٧ مولوداً حديثاً قليلي الوزن أقل من ١٥٠٠ غراماً أو الخُدج أقل من ٢٠ أسبوعاً للحمل. ولا يدخل في بحثنا ٤ مولودين حديثاً بسبب تشوهات ولادية مهمة فاشتمل البحث على ٢٠٢ مولوداً حديثاً. الوزن الوسطي حين الولادة ١١٩٥ غراماً  $\pm$  ٢٧٤ غراماً، ٩٩ ذكراً و ١٠٤ أنثى والنسبة الإجمالية للحياة ٦٩,٥٪. ازدادت نسبة الحياة بصورة واضحة أثناء مرحلة الدراسة وتناقصت نسبة الوفيات من ٥٠٪ إلى ٢٦٪ بنهاية الدراسة بينما حين إعطاء القشريات الستيروئيدية قبل الولادة، ازدادت من ١١٪ إلى ٨٢٪. كان تأثير القشريات الستيروئيدية قبل الولادة بليغاً ويشكل إيجابياً لنسبة الحياة (احتمال أقل من ٠,٠٠١). ان إعطاء «الفعال بالسطح» له تأثير بالغ الإيجابية على الكرب التنفسي الذاتي مع حياة ٦٩٪ للمولودين حديثاً دون تناول القشريات الستيروئيدية قبل الولادة مقارنة مع النسبة العالمية ٧٥٪. الوزن حين الولادة، مدة الحمل وحرز أبعاد لهم تأثير بليغ واضح على الحياة (احتمال أقل من ٠,٠٠١). لم نجد صلة بين طريقة الولادة وعديدات الولادة والجنس وتأخر النمو داخل الرحم وبين نسبة الحياة. والانتان هو السبب الهام للوفاة أو الامراضية.

**الخلاصة -** لوحظ نقص للوفيات في مؤسستنا خلال الدراسة وهذا التغير هو انعكاس للاستراتيجية الحديثة للمعالجة بالقشريات الستيروئيدية و«الفعال بالسطح».