

# Preterm Infants' Follow-Up Program at a Public Hospital in Buenos Aires: Two-Decade Study

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**Abstract:** *Objectives:* To analyze temporal trends of mortality, morbidity, growth and neurodevelopment until 2 years of corrected age (CA) of very low birth weight infants (VLBWI) born between 1986- 2005 in Ramon Sardá Maternal Infant Hospital (RSMIH).

*Methods:* Descriptive temporal trend study divided in 5 quinquenniums. 1255 VLBWI were born at RSMIH between 1986-2005; 46 were excluded (genetic syndromes, major congenital malformations, confirmed intrauterine infections), 84 were referred out and 1125 were studied. Birth weight (BW), gestational age (GA); morbidity; growth; neurodevelopment at 1 and 2 years of CA; neurological and sensorial disorders, antenatal steroids use, breastfeeding; rehospitalizations; mothers' age and years of schooling and Unsatisfied Basic Needs Index (UBNI) were recorded.

*Results:* Survival rates increased during the last two periods, especially in <1000g BW infants despite the decrease in GA and BW. Children receiving surfactant (Sf), parenteral nutrition (PN) and antenatal steroids (AS) in the last quinquennium obtained better results in growth (40 weeks GA and 1 CA). The use of these therapies increased greatly in the last decade. Also breastfeeding at 40 weeks GA and 4 months tended to be better. Bronchopulmonary dysplasia (BPD) increased. Rehospitalizations (majorly attributable to lower tract infections) and UBNI stayed equal all along. Mothers' years of schooling increased a little in the last two quinquenniums.

*Conclusion:* In the last quinquennium children tended to be smaller in GA and BW due to an increase in the survival rate as a result of higher technology and appropriate interventions such as AS, PN, Sf, etc.

**Keywords:** Preterm, growth, morbidity, mortality, neurodevelopment.

## INTRODUCTION

Preterm birth (PB) is a major burden and there are approximately 15 million of them worldwide. Very low weight infants (VLWI <1500g) represent approximately 1% of still births, and extremely low birth weight infants (ELBWI<1,000g) between 0.3% and 0.5% [1-3].

PB is associated with many specific acute complications of immaturity including bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), periventricular leukomalacia (PVL) and retinopathy of prematurity (ROP) [1, 2].

There is good evidence that advances in perinatal care including sophisticated ventilator techniques, antenatal steroids (AS), pulmonary surfactant (Sf), parenteral nutrition (PN), skin-to-skin mother-infant contact (kangaroo mother care), early breastfeeding, mothers' residency, and professional development, have resulted in improved survival rates of VLBWI and ELBWI over the last three decades [2, 4-11].

Although improvements in the care of newborn babies (neonatal care) mean that preterm babies are more likely to survive than in the past with smaller gestational age (GA), PB remains the single biggest cause of infant death and the second most common cause of death in children under-five after pneumonia [1, 12]. PB also increases the risk of death due to neonatal infections. Moreover, hypothermia and malnutrition increase vulnerability. PB is a direct cause of 36% of all infant deaths, but two-thirds of all infant deaths are among babies who were born preterm [1, 2, 12]. In Argentina 65% of neonatal and 34% of under-one infants' deaths are associated to VLBW, determined by the type and quality of the institution [6, 13]. As regards of rehospitalizations in VLBWI, the percentage reaches around 20-40% and doubles that of term infants under 1 year old [14].

In addition to its contribution to mortality, PB may lead to long-term health problems and disabilities by reason of a higher vulnerability in a wide spectrum of developmental domains. There are lifelong effects on neurodevelopment, increased risks of cerebral palsy (CP), impaired learning, mental /behavioral and sensorial disorders, and cognitive and language delays, hyperkinetic disorders, emotional problems, and learning disabilities, which contribute to the

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prematurity-related burden of chronic disease in adulthood particularly for those born before 32 weeks of gestation [1, 2, 12, 15].

This is due to biological factors associated to perinatal clinical antecedents (GA, birth weight -BW, multiple birth, fetal malnutrition, chronic diseases, brain lesions, hospitalizations) as well as environmental factors independently of the socioeconomic status, since these babies have stayed for long periods in the NICU's. Despite advanced technology and better policies, these units cause the babies to be stressed out by the noises and lights, the interventions, the parents stress, the lack of bonding, etc. Therefore, this perinatal/environmental or mixed risk influences both short- and long-term outcomes and quality of life [1, 2, 16].

In order to understand and intervene on these outcomes follow-up programs are vital. Our program for preterm children has been evolving since 1986 as well as the database that has been modified according to changes and needs, and its data registered since the beginning [17, 18]. The aim of this study is to determine the temporal trends in: survival, mortality (according to BW), morbidity (BPD, NEC, PVL, IVH, ROP) growth and neurodevelopment (at 40 weeks of GA, 12 and 24 months of corrected age – CA) of VLWI born at Ramon Sardá Maternal Infant hospital (RSMIH) from 1986 to 2005. The percentage of lost-to follow up patients, deaths, rehospitalizations, neurological and sensorial disorders in the first 2 years of CA and breastfeeding in the 1<sup>st</sup> year of CA, as well as the socioeconomic status (SES) are described.

## MATERIALS AND METHODS

### Subjects

VLBWI (BW<1,500 g) born at RSMIH from 1986 to 2005. Infants with major genetic disorders and malformations, intrauterine infections (toxoplasmosis, rubella, HIV, CMV) and those referred out were excluded.

### Instruments

Medical records were used for:

- Perinatal variables: AS, surfactant use (Sf), sex, BW, GA and neonatal morbidity (ROP, BPD, ICH, PVL, NEC); and
- Follow-up variables:

1. Growth: Argentinean' growth charts were used. Height (H), weight (W) and head circumference (HC) at 40 weeks of GA, 12 and 24 months of CA were recorded. CA was used for HC in the 1<sup>st</sup> year and for W and H up to 2 years [19].
2. Neurodevelopment assessment: the test used was EEDP (Escala de Evaluación del Desarrollo Psicomotor). Neurodevelopment coefficient (NDC) at 12 and 24 months of CA were recorded. This test divides children in three categories: normal, at risk and delayed. The first one includes NDC values around average or within 1 standard deviation (SD). The second one includes NDC values around 1 and 2 SD. The infants below 2 SD belong to the delayed category [20].
3. Neurological disorders: Bobath classification of cerebral palsy (CP) was used [21]. Only those with quadriplegia were accounted for.
4. Sensorial disorders:
  - Eye test: ROP, strabismus and myopia were diagnosed through repeated dilated eye exams.
  - Ear test: during the early years of the follow-up program the usual exam was response to sound stimulus through transducers and the observation of behavior. Afterwards oto-acoustic emissions (OAE) and brain stem evoked potentials (BSEP) were introduced through a policy.
5. Breastfeeding, number of rehospitalizations and its cause (lower tract infection-LTI, surgical or other), lost to follow-up patients, and number of deaths were recorded.
6. Socioeconomic status (SES): The Unsatisfied Basic Needs Index (UBNI), mothers' age and years of schooling were considered for SES. The UBNI comprises type of household, number of schooled children, persons per square meter, presence of overcrowding, unavailability of a toilet, and parents years of schooling (<2 years) [22].

### Statistical Analysis

Univariate and bivariate analysis were performed using Statistic 7.0 software program. The results were expressed as the means  $\pm$  SD. The 20-year period was divided in quinquenniums for the analysis and to

**Table 1: Survival of VLBWI According to Birth Weight, 1986-2005**

Survival	500- 749 g	750- 999 g	1000- 1249 g	1250- 1499 g
1986-1990 n (%)	3 (4.1)	35 (31.5)	108 (63.1)	147 (75.4)
1991-1995 n (%)	5 (6.7)	34 (33.4)	80 (59.2)	155 (81.1)
1996-2000 n (%)	15 (18.3)	61 (56)	110 (79.1)	140 (84.3)
2001-2005 n (%)	17 (15.9)	70 (55.2)	107 (77.5)	168 (91.8)

examine temporal changes: 1Q (1986-1990), 2Q (1991-1995), 3Q (1996-2000), 4Q(2001-2005). Kruskal-Wallis test was used for numerical data and Chi<sup>2</sup> test for categorical data. Statistical significance was set at p < 0.05.

**RESULTS**

In the two decades studied (January 1986-December 2005) 1,255 children were born at RSMIH, 46 were excluded (35 major malformations and 11 genetic syndromes), 84 were referred out, therefore 1,125 children were studied (1Q n=275, 2Q n=237, 3Q n=284, 4Q n=329).

**Survival**

The average number of total deliveries was 32,383.75 ± 2,409.73. The average number of VLBWI was 526 ± 30,80. The prevalence of VLBWI remained practically the same along the decades: 1.58% ± 0.17. The survival rate changed from 53.27% in 1Q to 65.23% in 4Q. However, the change for infants <1000g of BW went from 6.91% to 15.68% (Table 1).

There was an important rise of survival along the years especially after the 2Q for the ELBWI, a twofold

rise for infants with a BW of 975-999g and a threefold for those with BW<750g (Figure 1). The survival between 1Q and 4Q also increased 14% for those with BW of 1000-1249g and 16% for those in the 1250-1499 g group.

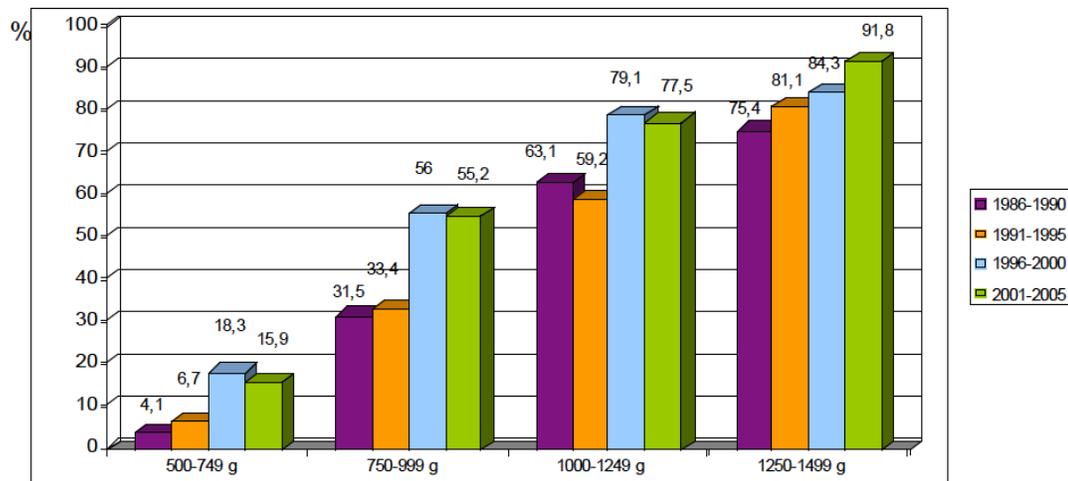
GA, BW, Sf, AS and PN were very different between the 2 decades (Table 2). AS use increased almost 50%. The Sf use and PN augmented majorly in 4Q.

**Morbidity**

There was a rise in BPD in 4Q. NEC was lowest in 1Q. ROP percentage remained constant. Despite this, there is a paramount difference between the percentage of intervened infants between 1Q and 4Q. Regarding IVH and PVL, there is an important increase in 2Q (Table 3).

**SES**

There were not any significant differences along the years regarding UBNI percentage, mothers' years of schooling and age. The percentages of UBNI were: 1Q=34% (59), 2Q=35% (n=57), 3Q=36% (n=72) and 4Q= 32% (n=96). The mothers' years of schooling



**Figure 1:** Survival at discharge of VLBWI according to BW between 1986-2005.

**Table 2: Perinatal Characteristics of Very Low Birth Weight Infants 1986-2005**

	1986-1990	1991-1995	1996-2000	2001-2005
N° of infants	275	237	284	329
GA <sup>a</sup> (weeks)	31,0 ±2,64	30,6 ±2,68	30,0 ±,60	29,6 ±2,39
BW <sup>a</sup> (g) Range	1225 ±185 (600-1490)	1238 ±178 (790-1490)	1164±225 (600-1490)	1100 ±231 (540-1490)
Weight Z- score	-1,08	-0.73	-0,75	-0,44
BW <1,000 g n (%)	35 (13)	26 (11)	68 (24)	75 (23)
Sex M (%)	41,6	45,8	47,	49,1
AS <sup>a</sup> (n, %)	11/42 (26)	34/132 (26)	204/284 (71)	235/329 (71)
Sf <sup>a</sup> (n, %)	0 (0)	10/237 (4)	77/284 (27)	158/329 (48)
PN <sup>a</sup> (n, %)	3/275 (1)	15/237 (6)	84/284 (29)	323/329 (98)

<sup>a</sup>GA= gestational age, BW= birth weight, AS= antenatal steroids, Sf= plmonary surfactant, PN= parenteral nutrition.

**Table 3: Morbidity of Very Low Birth Weight Infants, 1986-2005**

Morbidity	1986- 1990	1991- 1995	1996- 2000	2001- 2005
N° of infants	275	237	284	329
BPD <sup>a</sup> (n, %)	17 (6)	27 (11)	45 (16)	102 (31)
ROP <sup>a</sup> (n, %)	18 (7)	23 (10)	23 (8)	32 (10)
N° treated	3	5	12	26
IVH <sup>a</sup> (n, %)	14/ 193 (7)	21/ 176 (12)	17/ 272 (6)	18/ 329 (5)
PVL <sup>a</sup> (n, %)	7/ 193 (4)	16/ 176 (9)	17/ 272 (6)	13/ 329 (4)
NEC <sup>a</sup> (n, %)	0	9/ 171 (5)	17/ 284 (6)	7/ 329 (2)

<sup>a</sup>BPD: Bronchopulmonary dysplasia, ROP: Retinopathy of prematurity (grade2+, 3, 3+ and 4 treated with laser or cryotherapy), IVH: Intraventricular hemorrhage (grade ≥III), PVL: Periventricular leukomalacia, necrotizing enterocolitis.

were: 1Q=8.5 ± 3.23, 2Q=8.1 ± 3.14, 3Q=9.1 ± 2.63 and 4Q=9.7 ± 2.89, and the average mothers' ages were: 1Q=27.5 ± 7, 2Q=27.3 ± 6.87, 3Q=26.8 ± 7.07, 4Q=26.8 ± 7.20. The range was between 14 and 46 years old.

### Lost to Follow-Up

During the 1st year of life (YOL) there were 8.7% of patients lost in 1Q, however it remained around 20% in the following periods (2Q=21.8%, 3Q=22.5%, 4Q=17.6%). As regards the 2<sup>nd</sup> YOL there were around a 15% lost in 1Q and 4Q, and around 25% in 2Q and 3Q (1Q=14.7%, 2Q=29%, 3Q=22.5%, 4Q=15.2%).

### DEATHS

The number of infants that died in the 1<sup>st</sup> YOL were as follows: 1Q n=13, 2Q n=5, 3Q n=9, 4Q n=8. There were no deaths during the 2<sup>nd</sup> YOL in 1Q and 2Q, and 2 deaths in 3Q and 4Q.

### Rehospitalizations

The average percentage of rehospitalizations during the 1<sup>st</sup> YOL were 33% ±7.53 (1Q n=60, 24%, 2Q n=55, 31%, 3Q n=93, 42%, 4Q n=94, 35%). However, they were much lower for the 2<sup>nd</sup> YOL: 5.5% ±1.25 (1Q n=7, 4.3%, 2Q n=6, 4.9%, 3Q n=9, 5.6%, 4Q n=15, 7.2%). The most common cause were lower tract infections (LTI: 64.55%, surgical: 10.9%, others: 5.2%) especially in the last three periods. The quinquennium with lowest surgical rehospitalizations was 4Q (Table 4).

### Breastfeeding

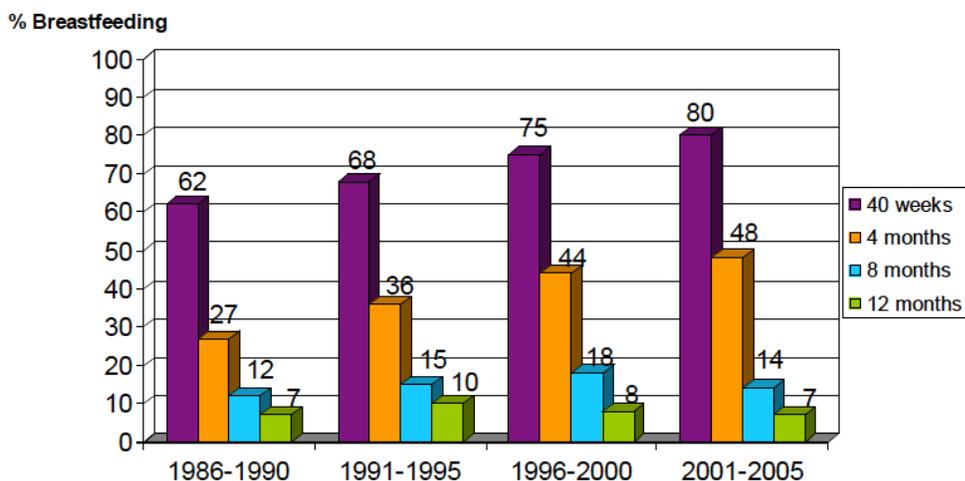
Breastfeeding increased along the quinquenniums when compared at 40 weeks of GA (62% to 80%) and at 4 months (27% to 48%) (Figure 2).

### Growth

The growth improved along the decades. The Z-score (standardized score) showed a twofold reduction

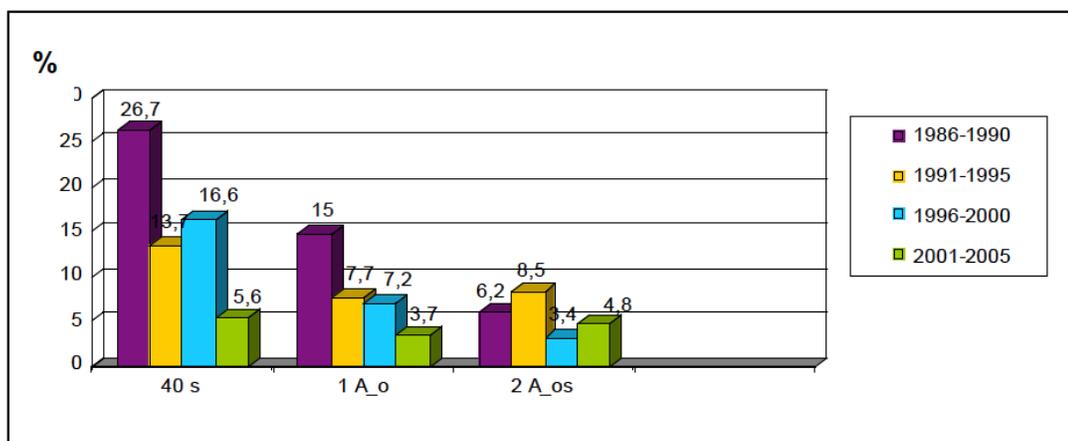
**Table 4: Causes of Rehospitalizations during the 1st Year of Life, 1986-2005**

Causes	1986- 1990	1991- 1995	1996- 2000	2001- 2005
LTI <sup>a</sup> (%)	31 (51.67)	38 (69.09)	65 (69.89)	65 (69.15)
Surgical (%)	10 (16.67)	6 (10.91)	10 (10.75)	4 (4.26)
Other <sup>b</sup> (%)	19 (31.67)	11 (20)	18 (19.35)	25 (26.60)
<i>Total</i>	60	55	93	94

<sup>a</sup>LTI: Lower tract infections.<sup>b</sup>Gastroenteritis, meningitis, seizures, trauma.**Figure 2:** Breastfeeding percentage during the first year of life, 1986-2005.**Table 5: Growth during the 1<sup>st</sup> and 2<sup>nd</sup> Year of Life (YOL), 1986-2005**

	1986- 1990	1991- 1995	1996- 2000	2001- 2005	p-Value
N° 1 <sup>st</sup> YOL	227	177	220	271	
W <sup>a</sup> 40 weeks	2485 ± 508	2629 ± 475	2607 ± 510	2899 ± 520	0,000
Z-Score	- 1,80	- 1,51	- 1,55	- 0,96	0,000
H <sup>a</sup> 40 weeks	45,2± 2,44	45,2 ± 2,3	45,0 ± 3,0	46,6 ± 3,1	0,000
Z-Score	- 2.76	- 2.78	- 2,89	- 2,04	0,000
HC <sup>a</sup> 40 weeks	33,3± 1,62	33,9 ± 1,47	33,9± 1,77	35,0± 1,78	0,000
W 12 months	8650± 1227	8677± 1142	8908± 1091	9016± 1271	0,001
Z-Score	-1.04	-1.08	- 0,86	- 0,79	0,000
H 12 months	70,9 ± 2,97	71,2 ± 3,12	72,6± 2,89	72,6± 3,20	0,000
Z-Score	- 1.37	- 1.27	- 0,79	- 0, 79	0,000
HC 12 months	45,2 ± 1,70	45,7± 1,64	46,1± 1,65	47,0± 1,83	0,000
N° 2 <sup>nd</sup> YOL	160	122	175	208	
W 24 months	11193± 1300	10764± 1411	11303± 1445	11344± 1592	0,007
Z-Score	- 0.87	- 1.10	- 0,85	- 1,11	0,008
H24 months	83,1± 3,50	82,2± 3,88	84,6± 3,48	84,7± 3,76	0,001
Z-Score	- 0.82	- 1,10	- 0,42	- 0,41	0,002
HC 24 months	48,1± 1,64	47,9± 1,70	48,3± 1,55	49,1 ± 1,84	0,001

<sup>a</sup>W: Weight, H: Height, HC:= Head circumference.



**Figure 3:** percentage of very low birth weight infants under 2 SDs for head circumference from 40 weeks of GA up to 2 years of CA, 1986-2005.

for weight at 40 weeks GA and at 12m, and for height at 24 m. All the differences were significant ( $p < 0.05$ ) (Table 5).

Between 1Q and 4Q there was a huge decrease of the number of infants below 2 SD for the HC. At 40 weeks of GA the percentage changed from 26.7% to 5.6% (1Q=26.7 %, 2Q=13.7%, 3Q=16.6% and 4Q=5.6 %), and at the 1<sup>st</sup> YOL from 15% to 3.7% (1Q=15%, 2Q=7.7%, 3Q=7.2% and 4Q=3.7 %) ( $p < 0.01$ ). The difference was minor at the 2<sup>nd</sup> YOL (1Q=6.2%, 2Q=8.5%, 3Q=3.4%, 4Q=4.8%) but still significant ( $p = 0.01$ ) (Figure 3).

**Neurodevelopment**

The NDC mean did not greatly varied along the periods neither for the 1<sup>st</sup> ( $p = 0.07$ ) nor for the 2<sup>nd</sup> YOL ( $p = 0.47$ ).

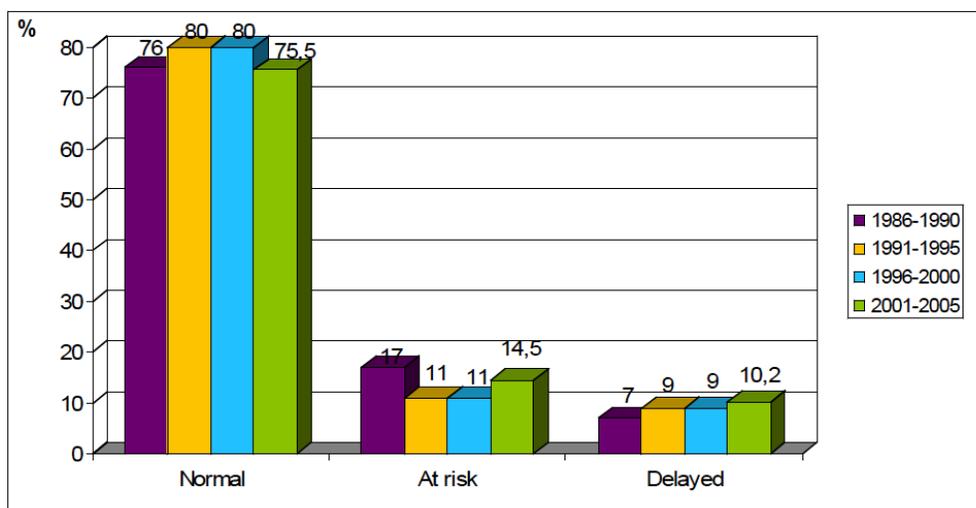
Furthermore, the percentage of children in the three categories (good, at risk or delayed) were not significantly different between periods for neither the 1<sup>st</sup> ( $\chi^2$ ,  $p = 0.91$ ) nor the 2<sup>nd</sup> YOL ( $p = 0.38$ ). 75-80% of infants obtained a normal score both during the 1<sup>st</sup> and 2<sup>nd</sup> YOL (Figures 4 and 5).

**Neurological Sequelae**

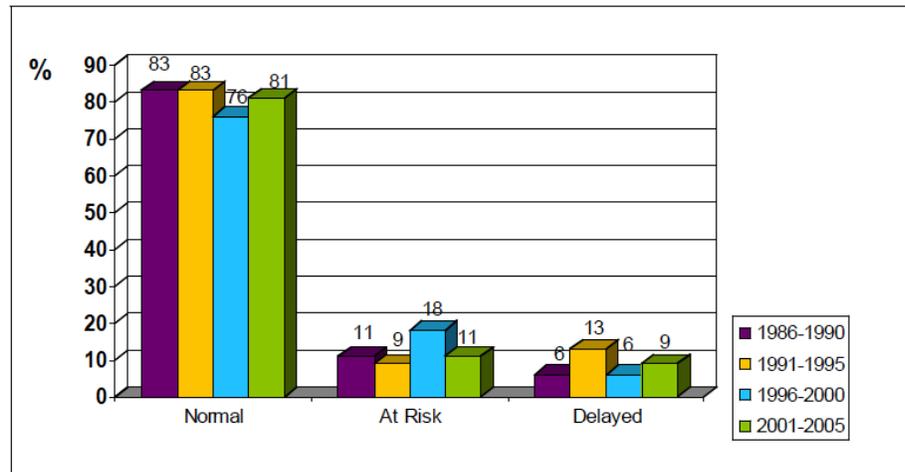
The percentage of major neurological sequelae (range 7 to 11.4%) did not differed along the years (1Q:  $n = 15$ , 9.3%, 2Q:  $n = 14$ , 11.4%, 3Q:  $n = 12$ , 7%, 4Q:  $n = 18$ , 8.6%).

**Neurosensory Disorders**

In the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> quinquenniums blindness was more prevalent than deafness. The opposite occurred in the last quinquennium. There were 4 blind and 1 deaf infants for 1Q, 2 blind and 2 deaf infants for 2Q, 4



**Figure 4:** Neurodevelopment Coefficients of very low birth weight infants during the 1<sup>st</sup> YOL, 1986-2005.



**Figure 5:** Neurodevelopment Coefficients of VLBWI during the 1<sup>st</sup> year of life, 1986-2005.

blind and 1 deaf infants (3 of the 4 blind children had ROP III and 1 had IVH IV) for 3Q, and 1 blind and 5 deaf infants for 4Q.

## DISCUSSION

In this two-decade research (1986-2005) the percentage of PB remained invariable down the years, despite the fact that the survival rate increased a huge quantity for ELBWI, especially after the 90's, concomitantly with changes in obstetrics and neonatology. The unvarying in the PB percentage could be related to a health system that emphasizes intervention over prevention [3, 23]. Conversely, Norman, Morris and Chalmers (2009) noted an augmentation for both spontaneous and induced PB in their temporal trends' study (1980-2004) [12].

The Neonatal Research Network of the National Institute of Child Health and Human Development (NICHD) studied the survival of VLBWI and observed that there was a 54% of survival at 25 weeks of GA during the pre-surfactant era (1987-1988) reaching up to 70% in the post surfactant era (1993-1994) and 72% in the wide-spread surfactant era (1999-2000) [24]. Similarly, in our study the survival rate was 31.5% during the 1<sup>st</sup> quinquennium (pre-surfactant era), increasing to 56% in the post surfactant era when AS were widely used as well.

Arce Casas, Iriondo-Sanz & Krauel-Vidal (2003) observed an important increase in the survival rate between 1988 and 1999 for <1000g infants, specifically 13% for <750g and 46% for 750-999g infants [25]. In the same way, our survival augmented 11% and 22% between 2Q and 3Q. We found even an increase in the <1000g, unlike that study.

Evidence has revealed that the use of AS diminished the incidence of IVH and respiratory distress syndrome. Additionally, pulmonary surfactant greater decreases lungs complications, and a better quality of nutrition further augments survival up to 93% for VLBWI and up to 85% for ELBWI [26, 27]. Correspondingly, our study data revealed that along with a significant reduction in BW and GA, and a twofold increase in survival rates for infants <1000g, there was a steady grow in AS, Sf and PN use especially in the last decade.

An important population based study in preterm infants observed that AS improved survival without increasing morbidity [2]. Also, it has been suggested that 80% of <35 weeks of GA newborns should be given steroids [28]. A Dutch research found that the use of steroids in <32 weeks of GA infants changed from 7% in 1983 to 73% in 1997 [29]. Comparably, the NICHD study observed that between 1987/1988 and 1999/2000 the AS use increased from 16% to 79% [24]. Regionally-wise, the Latin-American neonatal network (NEOCOSUR) informed that the percentage of infants treated with steroids reached 70% during 2001-2005 [30]. Our results showed that the percentage of mothers getting AS to induce infants' lung maturation improved along the years, especially during the last decade, reaching up to 71% linked to the appearance of a policy in 1995.

Similarly, the use of pulmonary surfactant increased each year. Between 2001 and 2005, 48% of children were administered surfactant. NEOCOSUR registered that surfactant was given to 54%-64% of VLBWI [30] and the NICHD described that 57% of them received that treatment in the same period [24].

As regards to PN, the percentage of use rose in the last decade, progressing to 98% between 2001 and 2005. In studies previously done in our hospital comparing conventional vs. aggressive nutrition, it was shown that at 40 weeks of GA the aggressive nutrition group had a weight z-score of -1,19 vs. -1,87 in the control group (conventional nutrition group) [31]. In our study, weight z-score at 40 weeks GA increased from -1.78 in 1Q to -0.94 in 4Q.

BPD places these infants at higher risk of chronic obstructive disease [1]. Our results revealed a progressive increase in the percentage of children with BPD and ROP in the last decade. This could be related to an increase in the survival rate of infants with smaller GA. One third of our children suffered BPD, similar to NEOCOSUR data [31]. In addition, the Dutch study showed an increment of BPD from 6% to 19% (1983 vs. 1997) [29]. Schlapbach, Adams, Proietti *et al.* (2012) explained that BPD was the strongest predictor of adverse outcome, being sepsis the main causative factor, together with low GA, intrauterine growth restriction and absence of AS [2].

IVH and its severity are associated to GA and BW. It occurs in 60% of <1000g BW children and 20% of children between 1,000 and 1,500g [32]. The NICHD detected a significant decrease in the incidence of severe IVH (III and IV) from 18% in 1987 to 11% in 1994. There were also less PVL cases, diminishing from 8 % to 3 [24]. Similarly, a study done by the Central New York Regional Perinatal Center showed a diminishing in IVH from 10% (1985-1086) to 5% (2005-2006). Besides, PVL declined from 4% to 3%. [33]. Our study results demonstrated no major changes along the years. The fact that no cerebral ecographies were performed during the first decade must be taken in consideration. Ecography is considered by many authors as a strong predictor for neurological sequelae [25]. In spite of the fact that the incidence of IVH may decrease, the risk in these population rises with the survival of smaller GA children.

UBI index has been accepted as a useful tool to identify critical needs and classify poverty [22]. The Argentinean Social Debt Survey states that poverty in our country has been structural for many years [34]. In our hospital around 30% of children belonged to homes with unsatisfied basic needs. In this study there was an increase of families in this situation because of the economical crisis that the country underwent in 2001. Regarding mothers' years of schooling there was a small upsurge in the last years. However since primary

education widened from 7 to 9 years in 1996 (high school narrowed down from 5 to 3 years) the mothers' academic level stayed alike. The environmental risk may have influenced growth, development, morbidity and lost to follow-ups. In relation to this last matter, during the 1<sup>st</sup> year of CA our study revealed the best result for 1Q (8.7%) probably connected to the home visits that used to be done during that period. However, these had to cease because of insecurity issues in our patients' neighborhoods. Lost to follow-ups lingered around 20% along the years, comparatively to other study which reported 16% [25]. Furthermore, during the 2<sup>nd</sup> year of CA, there was a rise in the abandonment of the follow-up program during 2Q and 3Q. As a hospital strategy and in order to combat this concern assistance (clothes, food, travel allowances, etc.) has been provided through an organization called "Voluntarias al servicio de hospitales – Damas Rosadas" (Pink ladies) and the hospital cooperative society.

In this research mortality averaged 2.9%, which appears higher than Kugelmann, Reichman, Chistyakov *et al.* (2007) who noted a 0.75% mortality rate between 1995- 2003 [35]. The most prevalent causes were sudden infant death syndrome and respiratory complications.

In our study, despite sending letters to two addresses registered in the clinical charts (the family's plus a relative address) and calling to multiple phone numbers many infants were lost to follow up. This may have influenced the true mortality rate value, since no data was available for these cases. Many of our hospital's families, as stated above, live in poverty which is associated to frequent home moving and phone number changes.

In our research the percentage of rehospitalizations oscillated around 20%-40 % for the 1<sup>st</sup> YOL downing to 4%-7% for the 2<sup>nd</sup> YOL. The major cause was LTI (52% to 69%) increasing in the last decade, whilst survival rate rose for lower GA and BW. These results are consistent with other reports. Ralser, Mueller, Haberland *et al.* (2012) described 40.1% and 24.7% of rehospitalizations for the 1<sup>st</sup> and 2<sup>nd</sup> year respectively. Approximately 40% of them were associated with LTI [14]. In addition, Hayakawa, Schmidt, Rossetto *et al.* (2010) noted that 30.2 % of VLBWI infants were rehospitalized, 56.3 % owing to respiratory complications [35]. Alike results obtained Arce Casas *et al.* (2003) [25].

Human milk is considered the best nutritional source for newborns up to 6 months old by reason of

its benefits including: emotional, intellectual (brain development), physical (infection protection), and cost benefits [36]. A meta-analysis concluded that breastfeeding was associated with better cognitive scores compared to infants fed through formula, especially for VLBWI [37]. We noted that breastfeeding percentages at 40 weeks of GA and at 4 months of CA were important, improving in the last quinquenniums. On the contrary, the perseverance in breastfeeding continued unchanged despite its promotion. In our hospital, the complements to human milk were used until 1996 when a fortified formula designed for preterm infants was incorporated. Since 2003 this formula has been persistently utilized.

Concerning extrauterine growth restriction, Hack *et al.* (1999) described that within VLBWI without major complications 46% stayed under the 3<sup>rd</sup> percentile at 40 weeks of GA, 28% at 8 months and even a proportion remained under the 3<sup>rd</sup> percentile at 3 years of CA. On the contrary, if infants had complications, 91% of them were delayed at 8 months lingering until 3 years of CA [38]. Also, Spanish research revealed that for VLBWI born between 1994 and 1999 HC at 2 years of CA was comparable to term babies. Conversely, height and weight were much lower, especially for ELBWI. They concluded that growth delay appeared to be inevitable for VLBWI [39]. Clark, Thomas and Peabody (2003) observed that the incidence of extrauterine growth restriction was common (28%, 34%, and 16% for W, H, and HC, respectively), increasing with smaller GA and BW. They affirmed that despite advances in this arena due to the incorporation of PN, VLBWI display a weight  $\leq$  the 10<sup>th</sup> percentile nonetheless [40]. Our research showed that infants tended to be better at 40 weeks in the three variables of growth only for the last period, concomitantly with a major PN use. At the 1<sup>st</sup> YOL, results appeared better for the last two quinquenniums. And again, at the 2<sup>nd</sup> YOL, growth slightly improved only in the last quinquennium. It is important to emphasize that diets must be closely monitored since home nutritional habits may be inadequate, particularly for low income households such as the ones in our study.

HC growth has been associated with neurodevelopment, cognition and school performance [41]. Our data demonstrated that only a minor proportion of infants were at 2SD below the mean at 40 weeks of GA and at the 1<sup>st</sup> YOL during the last quinquennium. Besides, HC improved at the 2<sup>nd</sup> YOL for the last two periods.

Malnutrition, low BW, social and emotional factors influence development, increase vulnerability and lessen the quality of life [16]. It has been estimated that over half of infants born at <28 weeks of GA will demonstrate some long-term impairment and 5% of those born at 32–36 weeks [1]. In a study done in Bahia Blanca (Argentina) VLBWI born between 1987 and 2007 were divided in 3 groups: <1000 g, 1001–1250, 1251–1500 g. They found that infants above 1000g BW achieved normal values in the Bayley II Mental and Motor Scales [42]. In this research, 75%–80% of infants displayed a NDC within normal limits and approximately 10% were delayed with no major changes along the years notwithstanding that GA and BW in the last quinquennium were lower. The number of infants with CP may have not change despite new interventions (AS, Sf, PN, etc) due to an increase in survival of the most preterm born infants [1]. In contrast, Bode, D'Eugenio, Forsyth *et al.* (2009) registered a difference between two cohorts, 1985/86 and 2005/06, getting better results in the Bayley scores for the last one. Severe neurodevelopmental impairment decreased from 38% to 19% [33]. Arce Casas *et al.* (2003) noted sequelae in 20.2% of VLBWI at 2 years of age, 9% of them being of severe nature [43]. Similarly, another research described an 11% incidence of severe and 24% of moderate disability [2]. Also, a study of <28 weeks of GA infants born within 1993 and 1998 found that 10–18% suffered CP, and 15%–28% neurodevelopmental difficulties [5].

In our study, early ROP treatment increased in the last years. This intervention is necessary to reduce blindness. In Argentina is ROP the main cause of blindness is [44]. There were 3 blind children in 1Q compared to 1 child in 4Q. Also, the advance in the diagnosis of deafness contributed to the early detection (5 deaf children in 4Q). In the early years of the program there were no OAE or BSEP. Vohr, Wright Dusick *et al.* (2000) detected more vision than hearing impaired infants in their study of almost 1,500 ELBWI [5]. We were not able to do a subgroup analysis for neurosensory sequelae (<1,000g vs. >1,000–1,500) due to the small number of impaired infants for each category in each period.

Research states that for further increasing survival rates without long-term neurodevelopmental or neurosensory severe impairments quality maternity and neonatal care need to improve [1].

More than 20 years of our preterm follow-up program had made an important amount of data

available for this study, therefore contributing to the possibility to evaluate temporal trends. This information indirectly explains the probable impact of interventions such as AS, Sf, PN, etc., and may assist in decision making for health care planning and in setting research priorities.

Unfortunately, this study did not include other institutions with different preterm populations. Furthermore, results demonstrated an important lost to follow-up patients. Another limit was that there were no subgroups neurodevelopmental or neurosensory analysis. ELBWI are known to be different from bigger preterm infants. Moreover, it would be wise to study these infants at school age, since NDCs at two years of CA are not made and cannot be used for prognosis of learning difficulties.

Preterm's follow-up programs are an excellent strategy in order to assess the long term evolution of this patients, as well as to implement early and adequate interventions benefiting not only the child's and his family's quality of life but also the society. Therefore, the information on long-term outcomes remains critical.

## COMPETING INTERESTS

The authors declare no competing interests.

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