

# **The role of 500 grams birthweight in the prognosis of preterm infants born at the limits of viability**

**PhD thesis**

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## **Introduction**

The limit of viability changed greatly over recent decades. For caregivers, it is essential to have up-to-date knowledge; it influences their therapeutic decisions and communication with parents about their children's chances. The outcome of preterm infants is based mostly on their maturity. However, in some cases – e.g. missing early prenatal ultrasound – the calculated gestational age may differ even by weeks from the real gestational age. The difference might alter the outcomes of these infants crucially. In contrast, with ultrasound, birthweight can be assessed more accurately before birth. The changes in the survival of preterm infants were not observable until recent years among infants with a BW <500g. Until the early 2000s, the mortality was high among infants with a BW <500g, and the survivors had an extremely high rate of complications. International literature determined the 500g BW as the limit of viability for a long time.

0.01-0.05% of all pregnancies result in preterm birth with a BW <500g. There is only a limited number of large studies dealing with this population. Numerous studies report a low rate of active care within this group. The exclusion of infants who did not receive intensive care reduces the case numbers further.

Reviewing the literature, we have found that in the last two decades, studies dealing with a BW <500g infants reported controversial survival rates. However, some researchers published higher than 50% - even higher than 60% - survival rates, others have found still low survival in this population.

All of these studies uniformly – with a small variance - reported high rates of early complications. Out of recent publications, a Japanese study has found the most favourable rate of complications. In the Japanese population, only 17% of preterm infants with a BW <500g survived without any major early complication. By the review of the literature, we have found high rates of BPD and ROP among infants with a BW <500g.

To make proper therapeutic decisions, and to know the probable outcomes for these infants, it remains essential to be familiar with the regional and institutional data aside from international literature. The results of third level centres, specialized in the care of periviable infants, may differ from population-based results.

**Objectives:**

- To assess the chance of survival of preterm infants with a BW <500g born between 2006 and 2015, at our institute, the 1<sup>st</sup> Department of Obstetrics and Gynaecology, and to assess the rate of early complications by surviving infants.
- To assess, if any change occurred during the 10-years study period in the survival and complication rates in this population.
- To investigate the possible effect of postnatal protocol changes during the study period on the outcome of preterm infants with a BW <500g.

In parallel, we investigated the preterm infants with a BW <500g in the whole Hungarian population during the study period.

- To assess the survival and complication rates of preterm infants with a BW <500g born between 2006 and 2015 in Hungary.
- To assess, if any change occurred during the 10-years study period in the survival and complication rates in this population.

We also intended to compare the results of the two studies.

- To correlate our institutional data to the Hungarian population results, and to analyse the differences between them.
- To correlate both of our results to international studies.
- To investigate the impact of certain perinatal factors on the survival of preterm infants with a BW <500g.

The main object of our work was to investigate the role of the 500g birthweight margin as a survival determinant factor.

## Methods

With our first study, we analysed the data of 66 preterm infants with a BW <500g, born between January 1<sup>st</sup> 2006 and 31<sup>st</sup> December 2015 at the 1<sup>st</sup> Department of Obstetrics and Gynaecology, and treated at our NICU. We compared the perinatal data of surviving and non-surviving preterm infants, then we compared the data of the 39 infants born between 2006-2010 and the 27 infants born between 2011-2015. We investigated if there is any association between protocol changes and the higher survival rates and lower complication rates.

Then, we examined the data of the preterm infants with a BW <500g, included in the Hungarian NICU database, born between 2006 and 2015. We compared these data with the annual reports (between 2006-2015) of the Hungarian Central Statistical Office (KSH) about live-births, infant mortality, and stillbirths. Infants requiring extrauterine transport to a tertiary level NICU, infants born with congenital malformations were excluded from the study.

Similarly to our institutional study, we compared the survival rate and the complication rates among survivors, born between 2006-2010 vs. 2011-2015. We compared the perinatal factors of surviving and non-surviving infants.

The investigated parameters in both studies are as follows:

*Maternal factors:* maternal age, number of previous births, number of previous pregnancies, number of previous abortions, number of previous miscarriages, ART use.

*Perinatal factors:* cause of preterm birth, method of delivery, multiple pregnancy, gestational age at birth, birthweight, sex of the infant.

*Neonatal factors:* antenatal steroid treatment, Apgar scores at 1 and 5 minutes, surfactant treatment, surfactant dosing, number of ventilator (mechanical ventilation, HFOV) days, non-invasive (CPAP/DUOPAP) ventilator days, need of circulatory support (days).

*Early complications:* bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), spontaneous fractures.

## Statistical analysis

In the case of ordinal variables (Apgar scores at 1 and 5 minutes), the median and interquartile range (IQR) are provided.

The categorical variables were described by frequency along with their 95% confidence interval (95%CI). For continuous endpoints, the mean and the 95% confidence interval were displayed. Instead of statistical probes, the differences between groups, and the 95% confidence intervals were used to describe the difference between groups. When the 95%CI of difference between the two groups does not contain 0, the difference between the two groups is significant. In case of ordinal variables, the difference between the medians was described by Hodges-Lehmann confidence limits. In case of categorical variables, Wald confidence intervals were estimated. For continuous variables, the difference between the means was estimated with 95% confidence intervals by the independent two-sample t-test.

Statistical analysis was performed with the SAS<sup>®</sup> software, University Edition.

## Results

**Institutional results:** In the first 5-years of the study period, between 2006 and 2010, 39 preterm infants with <500 g a BW were born at the 1<sup>st</sup> Department of Obstetrics and Gynaecology. 27 (69.2%) died shortly after birth, 12 of them (30.8%) survived until discharge. In the second 5-years period, between 2011 and 2015, 27 preterm infants with a BW <500g were born at our department. 8 (29.6%) died shortly after birth, 19 (70.4%) survived. The difference between the survival rates of the two periods was statistically significant.

While investigating perinatal factors, we found, that the median of 1 minute Apgar scores was higher in the 2011-2015 group, compared to the 2006-2010 group. There was no difference in the median of 5 minutes Apgar scores, average birthweight, average gestational age. There was no difference between the two groups in terms of antenatal steroid prophylaxis, Caesarean delivery, female sex.

There was no difference between the 2006-2010 and the 2011-2015 group in terms of the number of ventilator days, number of non-invasive ventilator days. However, the duration of the two forms of ventilation combined was higher in the 2006-2010 group. We did not find any difference between the two groups in terms of PDA (requiring treatment), IVH, PVL, ROP (requiring laser photocoagulation), NEC (requiring surgical treatment) rates, nor in the spontaneous fracture rates.

Investigating the whole period, we concluded that the group of surviving infants had a significantly higher mean gestational age. In the surviving group, we found a higher incidence of Caesarean section, and a lower incidence of multiple births, and a lower incidence of premature rupture of membranes. The median values of both 1 and 5 minutes Apgar scores were higher in the surviving groups of preterm infants. The frequency and dosage of surfactant treatment were higher in the surviving group of infants. There was no difference between the surviving and non-surviving groups with respect to maternal age, the number of previous pregnancies, the number of previous births, smoking during pregnancy, ART use.

## **Hungarian results:**

According to the Hungarian Central Statistical Office, 485 preterm infants out of 933617 births were born with a BW <500g between 2006 and 2015 in Hungary. The prevalence of preterm birth with a BW <500g was 0.52 per 1000 livebirths, the number of stillbirths with a BW <500g was 190 during the study period. Between 2006 and 2015, 361 preterm infants with a BW <500 g died within the first year of life. Based on these results, the mortality of preterm infants with a BW <500g was higher than 70%.

In the NICU database, 407 infants were registered with a BW <500g during the study period. 281 infants died, 123 survived (30.2%), the outcome for 3 infants remained unknown, therefore they were excluded from the study. 30 infants required extrauterine transport to a tertiary level NICU, - with only 1 survivor (3.3%) - therefore they were also excluded from the analysis. 10 infants were born with congenital malformations - they were also excluded. After exclusions, 364 preterm infants remained in our study, 122 out of them survived (33.5%).

In the 2006-2010 period, 50 preterm infants survived out of 180 (27.7%), while in the 2011-2015 period 72 infants out of 184 (39.1%) survived. It represents statistically better survival in the second period.

The comparison of the two study periods revealed that the use of antenatal steroid treatment was more common in the second period, just like the frequency of Caesarean delivery, and surfactant treatment. In the first period, the number of multiple pregnancies was lower than in the second period. There was no difference in the mean birthweight, mean gestational age, the mean of 1 and 5 minutes Apgar scores, gender or SGA births.

With the comparison of the survivors in the two periods, we did not find any difference in terms of the incidence of bronchopulmonary dysplasia (neither by the need for supplemental oxygen on the 28<sup>th</sup> postnatal day nor by the need on the 36<sup>th</sup> PMA week. There was no difference in the mean ventilator days between the survivor groups. However, the mean of the non-invasive ventilator days was higher in the second period.

The incidence of mild (Papile I - II) and severe (Papile III - IV) IVHs and the incidence of posthaemorrhagic hydrocephalus did not change over the study period. In the 2011-2015

period, PVL occurred in 25% of survivors, while 64% of survivors required laser photocoagulation due to retinopathy. The incidence of NEC (Bell I-IV) was slightly lower - with statistical significance – in the first period.

With the analysis of the whole 10-years period, we found that the number of previous miscarriages in maternal history was significantly lower in the survivor group. There was no difference between the survivor and the non-survivor group in the following factors: average maternal age, number of previous pregnancies, number of previous births, number of previous abortions, ART use.

The mean gestational age was significantly higher in the survivor group, just like the mean birthweight and the median of 1' and 5' Apgar scores. The rate of SGA infants was significantly higher in the survivor group, just like the rate of Caesarean delivery. Among survivors, antenatal steroid prophylaxis and surfactant treatment were more common. The rate of multiple pregnancies was significantly lower in the survivor group. We did not find any difference in the female sex between the two groups.

## Conclusions

The most important finding of our study was that the survival of preterm infants with a BW <500g improved greatly at our department. In the 2006-2010 period, it was 30.8%, while in 2011-2015 it was more than twice the previous period: 70.4%. The rate of early complications by survivors did not differ in the two periods, therefore the rate of complication-free survivors improved.

In the same period, the survival of preterm infants with a BW <500g improved slightly - not with the rate of our institution - in the whole Hungarian population as well: survival<sub>2006-2010</sub> 27.7% vs. survival<sub>2011-2015</sub>. Among survivors, we did not find any statistically significant difference between the two periods (2006-2010 vs. 2011-2015). In the Hungarian population, the survival of preterm infants with a BW <500g remains under 50%, the rate of early complications is very high among survivors.

In the 2011-2015 period, the survival rate was significantly higher at our department, than in the whole Hungarian population: survival<sub>institutional</sub>: 70.4% vs. survival<sub>Hungarian</sub>: 39.1%. Every early complication occurred frequently among survivors, not only in the whole population but in our department as well. Our NICU has one of the highest admission rates in Hungary. The high admission rate might be linked with better survival.

In line with international results, our studies revealed that the survival of preterm infants with a BW <500g is determined mainly by their maturity. Preterm infants who were born from multiple births had a lower rate of survival. Higher birthweight, antenatal steroid prophylaxis, higher 1 and 5 minutes Apgar scores improved survival, which is also in accordance with international results.

Surfactant administration was more common, and surfactant dosing was higher among surviving infants. The higher survival rate in our department in the 2011-2015 period might be the result of our protocols. In 2010 we switched to prophylactic surfactant treatment, with twice the previous dosage. The better survival rates might be associated with these protocol changes, however, to clarify this, prospective studies should be conducted.

In recent decades, several studies have found higher than 50% survival rates in the < 500g BW population, however, the complication rates remained high by surviving infants. Therefore, the lower than 500g birthweight remains a negative prognostic factor.

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