

# Neurodevelopmental outcome in extremely low birth weight infants in Johannesburg, South Africa

Tanusha Ramdin (✉ [tanusha.ramdin@wits.ac.za](mailto:tanusha.ramdin@wits.ac.za))

University of the Witwatersrand Faculty of Health Sciences <https://orcid.org/0000-0002-9490-6916>

Yoliswa Magadla

University of the Witwatersrand Faculty of Health Sciences

Robin T Sagers

University of the Witwatersrand Faculty of Health Sciences

Aripfani Veronica Mphaphuli

University of the Witwatersrand Faculty of Health Sciences

Rossella M Bandini

University of the Witwatersrand Faculty of Health Sciences

Daynia Elizabeth Ballot

University of the Witwatersrand Faculty of Health Sciences

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## Research article

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# Abstract

**Background:** Improved survival in preterm infants whether due to technological progress or treatment like antenatal steroids, surfactant administration or nasal continuous positive airway pressure (NCPAP) and aggressive resuscitation have raised the question about whether the survivors would be more prone to increased morbidity and adverse neurodevelopmental disability.

**Methods:** This was a prospective follow-up study conducted in the neonatal unit of a tertiary hospital in Johannesburg, South Africa. Bayley scales of infant and toddler development, version III, were conducted on a group of extreme low birth weight infants (ELBWI). The mean composite cognitive, language and motor sub-scales were reported. Infants were considered to be “*at risk*” if the composite subscale score was below 85 and “*disabled*” if the composite subscale score was below 70. Infants identified with cerebral palsy were also reported.

**Results:** The mean birth weight of the study group was 858.5grams (95% CI 839.2- 877.8) and the mean gestational age was 27.5 weeks (95% CI 27.1-27.9). The majority of ELBWI enrolled in the study had at least one Bayley at a mean corrected age of 17.09 months (CI 16.04 to 18.14). The mean composite scores for cognition were 98.4 (CI 95.1-101.7), language 90.0 (CI 87.5-92.6) and motor 97.9 (CI 94.8-101.0). All mean scores fell within the normal range, but the composite language score was the lowest. The study did not diagnose cerebral palsy in any of the infants. The study found 28 (36.3%) infants to be “*at risk*” for neurodevelopmental delay. Significantly more males were classified as “*at risk*” than females (13/25 (52%) vs. 15/52 (28.8%). Late onset sepsis (sepsis 18/37 (48.6%) vs. no sepsis 10/40 (25%)  $p=0.031$ ) and longer duration of ventilation (median of 12 days (IQR 46) vs. median of 4.0 days (IQR 5)  $p=0.048$ ) were significantly associated with an “*at risk*” classification.

**Conclusion:** Rates of early neurodevelopmental impairment have altered minimally despite significant improvements in the overall survival of ELBWI. It is of paramount importance to ensure that early neurodevelopmental outcomes are accurately assessed so as to assist doctors and families in establishing a foundation for advocacy for the immediate intensive care and post discharge follow up.

## Key Points:

- Better survival rates may be associated with increased rates of neurodevelopmental handicap.
- Low middle income countries settings (LMICS) have limited data on long term neurodevelopmental outcome.
- LMICS have limited resources and extreme low birth weight infants (ELBWI) bear enormous financial implications.
- It is critical to provide meaningful information to neonatologists, treating doctors, families and policy makers to aid in decision making regarding the provision of continuing intensive care for ELBWI

## Background

Globally, approximately 15 million of all births are born preterm (less than 37 weeks completed gestational age) annually. One million of these premature infants die due to complications of prematurity and a lack of appropriate healthcare. (1, 2) In South Africa the number of preterm births have increased to one in seven babies- that is approximately 15% of all births in the country. (1, 2)

Advances in neonatal care over the last few decades have improved the survival of the most vulnerable of premature infants. Improved survival in preterm infants whether due to technological progress or treatment like antenatal steroids, surfactant administration or nasal continuous positive airway pressure (NCPAP) and aggressive resuscitation have raised the question about whether the survivors would be more prone to increased morbidity and adverse neurodevelopmental disability. (3)

Improved care in the neonatal intensive settings in many middle and low income countries, is a reflective in the survivors' sequelae in the long term.. Extreme low birth weight infants (ELBWI) are defined as less than 1000 g and survivors can experience a range of short term and long term neurodevelopmental morbidity, which include developmental delay, cerebral palsy, blindness and deafness. (4)

There is a notable difference in the rates of survival and neurodevelopmental impairment in ELBWI in high income country setting (HICS) when compared to LMICS. These differences are attributed to several factors; namely population demographics, antenatal and neonatal care, post- hospital discharge guidelines and resources. (5).

The financial implications of ELBWI are enormous in terms of the immediate neonatal intensive care; the costs, which include equipment, trained medical staff and ongoing long term specialised care. Financial resources play a significant role and this is evident in the disparity in the mortality rates of premature infants less than 28 weeks in LMICS being 70–90% when compared to less than 10% in HICS. (3)

A literature review by Jarjour et al concluded that preterm infants of less than 25 gestational weeks in HICS have a lower probability of survival and nearly half of surviving ELBWI will have significant neurodevelopmental disability on short and long term follow up (4).

The World Health Organization (WHO) reported that three quarters of premature infants can be saved with feasible and low cost-effective care, like antenatal steroids, kangaroo mother care and breastfeeding.(1, 2) A study conducted by Ballot et al at a tertiary hospital in Johannesburg, in a LMICS showed that giving surfactant and NCPAP to infants between 750–900 g improved their survival by 50%. (6). Similarly, a study in Cape Town in a LMICS, reported an increased survival of 75% in infants with a birthweight 500–1000 g who received NCPAP and surfactant therapy. (7) This highlights that a simple intervention provided to ELBWI improved survival.

A later study carried out by Ballot et al at the same hospital in 2013 assessing neurodevelopmental outcomes in very low birth weight infant (VLBWI) with the help of the Bayley Scales of infant and toddler development III (BSID III) showed no difference in a small group of ELBWI versus VLBWI. (8) The ELBWI

also had no evidence of developmental delay. (8) This was in agreement with reports of developmental outcome of ELBWI in India, a low income country. (9)

Premature infants in the first month of life are at risk for cranial injuries ,which include intraventricular haemorrhage (IVH), post haemorrhagic hydrocephalus (PHH) and white matter injury, which are associated with decreasing gestational age. The brain injury of prematurity, negatively impacts on physiological processes namely; neural migration, creation of synapses and myelin sheath and cytological maturation. This occurs while the brain is attempting to recover from hypoxia, ischaemic and inflammatory injuries, which are most common in very premature infants and ELBWI. (4)

In HICS, several studies have shown that improved survival rates in these most vulnerable preterm infants have been accompanied with short and long term complications, including bronchopulmonary dysplasia ( BPD), retinopathy of prematurity (ROP), IVH and white matter injury. (4)

In LMICS there is very limited data on long term neurodevelopmental outcomes of ELBWI. It is vital to accurately assess short term end results and neurodevelopmental disabilities in ELBWI. Understanding these outcomes of prematurity will supply important data to neonatologists, treating doctors, families and policy makers and will guide decision making regarding the provision of continued intensive care for ELBWI. Measuring neuro-developmental outcomes will further assist early intervention programs, supporting families and the establishment of different educational facilities for better future of ELBWI.

A Cochrane review by Spittle *et al* of 25 randomized trials indicated that early intervention has benefits for preterm infants in combined cognitive and motor outcomes. (10) Appropriate early neurodevelopmental intervention may assist in decreasing the burden of a lifetime of functional disability after preterm birth. (10)

The limitations of LMICS reporting of neurodevelopmental outcomes includes the lack of large prospective multicentre cohorts, poor data quality collected, low follow up rates, no proper gestational age's assessment, and lack of an appropriate control group. Furthermore, keeping a control group is expensive and there are limitations on the assessment tools used. The BSID III may also underestimate impairment among extreme preterm infants.(11) Studies have found that the mean score of cognitive and motor using BSID III was close to normal means 96.9–100.4, which is higher than expected when compared to the prior data of similar cohorts test with BSID II. (8)

## Methods

This was a prospective follow-up study of infants with a birth weight below 1000 grams and born between 1 July 2013 and 31 December 2017. The study was conducted at a neonatal unit of a tertiary hospital in Johannesburg, South Africa. Following the patient's discharge, the ELBWIs were requested to attend the study clinic to form part of the study group. The ELBWI study group had attended at least one follow-up study clinic visit and underwent a Bayley assessment. Infants with congenital abnormalities

that were likely to affect neurodevelopment, for example Trisomy 21, were subsequently excluded from the study.

The gestational age was assessed by maternal menstrual history and clinical assessment using the Ballard score. (12)

The ELBWI study group were seen at the study clinic every three months. To ensure a good rate of follow-up, text messages were transmitted to parents as reminder of follow-up appointments. Transport costs were refunded and defaulting patients were traced and rebooked. Where developmental problems were identified, the child was referred for appropriate intervention by allied medicine team.

Developmental assessments using the Bayley scaled of infant and toddler development, version III (BSID III) were conducted. (12) The BSID III evaluation for both the study and control participants were done by an appropriately trained physiotherapist or paediatrician. The BSID III scores were calculated using the age corrected for prematurity. (12) The BSID III assessments were performed at 9 to 12 months and repeated at 15 to 18 months of age. The BSID III assessment would be done at the next visit, if a child defaulted a study clinic visit.

## Statistical Analysis

The data was entered and managed using Research Electronic Data Capture (REDCap™) software, hosted by the University of Witwatersrand. (13) The data was exported into IBM SPSS 23 for statistical analysis. The latest BSID III score for each child was used for analysis. The composite cognitive, language and motor scores were used as outcome variables. If continuous variables were normally distributed, the data was described by mean and 95% confidence intervals (95% CI). Skewed data was described using median and interquartile range. Categorical variables were described using frequency and percentages. Chi Square analysis was used to compare frequencies. A p value of 0.05 was considered significant.

Developmental delay was classified "*at risk*" if a composite BSID III score was below 85 on any of the language, cognitive or motor scales and as "*delayed*" if a composite BSID III score was below 70 on any of the sub- scales. (8)

Cerebral palsy was diagnosed if there was a delay in motor milestones together with abnormal movement and/or posture. (8)

Maternal variables included demographic, obstetric and neonatal variables, which included demographic, birth weight, gestational age and neonatal morbidity.

## Results

Figure 1 shows sample size. Eighty five ELBWI attended the study clinic. Of the 85 ELBWI, 77 had at least one BSID III. The mean birth weight of the study group was 858.5 g (95% CI 839.2-877.8) and the mean

gestational age was 27.5 weeks (95% CI 27.1 – 27.9). The majority of the babies were identified as female 52/77 (67.5%).

We report additional clinical and demographic information in Table 1. Of note, none of the mothers were diagnosed with syphilis or tuberculosis. There were no mothers below 18 years of age. Similarly, no babies had an IVH grade 3 or 4, or periventricular cystic leukomalacia. No babies were treated with an exchange transfusion, underwent ligation of a patent ductus arteriosus or surgery for necrotizing enterocolitis

We performed the BSID III assessment at a mean corrected age of 17.09 months (95% CI 16.04 to 18.14). The mean composite scores are shown in Table 2. All mean scores fell within the normal range, but the composite language score was the lowest. We did not diagnose cerebral palsy in any of the infants.

We found 28 of 77 infants (36.3%) infants to be “*at risk*”- 17 in one domain; 7 in two domains and 4 in three domains. The language domain had the most “*at risk*” infants. Of the 28 “*at risk*” infants, we classified 2 (2.6%) as handicapped – 1 in all three domains and 1 in two domains (motor and language). Significantly more males were classified as “*at risk*” than females (13/25 (52%) vs. 15/52 (28.8%). Similarly, late onset sepsis was significantly associated with an “*at risk*” classification (Sepsis 18/37 (48.6%) vs. no sepsis 10/40 (25%)  $p=0.031$ ). Infants who were found to be “*at risk*” were ventilated for a significantly longer duration than those with a normal developmental outcome (Median of 12. Days (IQR 46) vs. median of 4.0 days (IQR 5)  $p=0.048$ ). No other variables were significantly associated with abnormal developmental outcome in this group.

## Discussion

In LMICS there is a paucity of data on neurodevelopmental outcomes in ELBW infants. Information on long-term neurodevelopmental morbidity is imperative to assist treating doctors in decision making on “who to treat” in ELBWI. Critical decisions in managing extremely premature infants are very challenging. Every centre that cares for high-risk pregnancies should have a consensus approach to manage extremely preterm infants. Outcome data is the foundation required to make guidelines regarding management decisions, together with relevant ethical issues.

This study highlights that the overall composite score for cognitive, language and motor disability was normal in our sample of ELBWI. These results are comparable to composite scores in ELBW and VLBW infants in a study at the same hospital setting. (8). Potential improvement in the rates of neurodevelopmental impairment after extreme preterm birth have been observed in multiple cohorts from recent research papers. (3) Similarly, HICS have shown an improvement in neurodevelopmental outcome,

e.g. The National Institute of Child Health and Disease (NICHD), Swedish EXPRESS study, EPICure study in United Kingdom, National Research Network (NRN) of Japan.(3)

In the current study, two infants had evidence of developmental delay. One infant had delay in all three domains (cognitive, motor and language) and the other infant had delay in two domains (language and motor). There was no evidence of cerebral palsy in the study group. Twenty-eight infants had a score of less than 85 and suggest “*at risk*” for cognitive, language and motor difficulties later on in life. This group of high-risk ELBW infants requires close long-term follow up by a multidisciplinary team comprising of a neonatologist, a physiotherapist, an occupational therapist and a speech therapist.

Composite language scores were lower than other composite scores in our study group. Of note, most of the children in this study were not native English speakers. The interviewer and the child hence interacted with the mother as the medium (8). In premature infants, there is delay in speech and language acquisition, expressive language processing and articulation.(5) There are also lower Bayley scores and deficits in phonological short-term memory. (5) Similarly, a meta-analysis of language outcomes of preterm infants compared with term children have consistently identified significantly increased rates of speech and language delays and impairments. (5, 14, 15)

Overall in the study group of ELBWI, antenatal care was recorded as good. Antenatal steroid use was identified as very low and breastfeeding rates were sub-optimal. Interventions to improve antenatal steroids use and breastfeeding are of utmost importance to further improve ELBWI survival, short term and long-term outcomes.

As the centre where the study was conducted, is a tertiary referral centre, many infants are high-risk deliveries and require delivery by caesarean sections. In this study, most ELBWI required bag-mask ventilation (BMV) at birth. This indicates that ELBW infants are sick and require some assistance to breathe. Respiratory distress syndrome (RDS) was the most common diagnosis and was successfully treated with NCPAP, without ventilation in the neonatal high care unit.

Babies identifying as male gender, with late onset sepsis and prolonged ventilation were associated as being with “*at risk*” for neurodevelopmental delay. Similarly, Rogers et al found being male, early gestational age, infection, steroids given postnatally and high frequency ventilation increased the risk of cerebral palsy in ELBWI. (3)

## **Limitations:**

The study was conducted in a single tertiary referral centre with a relatively small sample size. The results may therefore not be generalizable to ELBWI born and treated in regional and district hospitals with limited facilities.

The sample was skewed towards ELBWI with less risk for poor developmental outcome. The infants that survived were generally well with no ROP, no severe BPD, were ventilated for a short period and had no

surgery for NEC.

Generally the follow up rate of the study group was poor, showing a return of approximately only 30%. However the candidates that elected to continue with the study did so diligently (85–90%). Reasons for the low overall follow up rate were not formally evaluated.

Financial constraints, inability to take time off work and relocation back to home countries or provinces are possible reasons for the low follow up.

Imprecise gestational age determination was another limitation of the study. The gestational age was based on a Ballard assessment in most cases and not accurate first trimester ultrasound.

## **Conclusion:**

Rates of early neurodevelopmental impairment have changed minimally despite marked improvements in overall survival of ELBWI. There are multiple barriers to properly assessing early neurodevelopmental outcomes in LMICS. Overcoming these challenges are critical in assisting doctors and families in establishing a foundation for the advocacy for immediate intensive care, which includes invasive and non-invasive ventilation and post discharge follow up, as well as the need for resources. It is imperative to note that the timeframe of neonatal developmental care and post hospital follow up does not limit itself to between discharge and the age of three years. Patients and families can hugely benefit from family-centred medical, developmental, and social support systems. Future research is required on long-term neurodevelopmental outcome in ELBWI in LMICS.

## **Abbreviations**

**ELBWI** – extreme low birth weight infants

**IQR** – interquartile range

**LMICS** – low and middle-income country setting

**NCPAP** – nasal continuous positive airway pressure

**HICS** – high-income country setting

**WHO** – World Health Organization

**VLBWI** – very low birth weight infants

**BSID III** – Bayley Scale of Infant and Toddler Development III

**IVH** - Intraventricular haemorrhage

**PHH** - post haemorrhagic hydrocephalus

**BPD** – bronchopulmonary hypoplasia

**ROP** – retinopathy of prematurity

**REDCap** – Research Electronic Data Capture

**CI** – confidence interval

**NICHD**- National Institute of Child Health and Disease

**NRN** – National Research Network

**BMV** – bag masked ventilation

**RDS** – Respiratory distress syndrome

## **Declarations**

## **Declarations**

**The authors declare no competing interests.**

### **Ethics approval and consent to participate**

The Human Research Ethics Committee of the University of the Witwatersrand approved the study. (Certificate MR 120623) Written informed consent was obtained from the parents of each participant prior to study enrolment.

## **Consent for publication**

Not applicable.

## **Availability of data and material**

Authors will make the data available upon reasonable request.

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## Authors' contributions

TR performed data collection and wrote up the various drafts for publication. DEB conceptualized the study, performed data collection and analysis, assisted in the write up and review of the various drafts for publication. YM, VM, RS, RB assisted with data collection. RB assisted in the review final draft for publication. All authors have read and approved the final version of this manuscript.

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## Tables

### Table 1

Clinical and demographic characteristics of 77 extremely low birth weight infants assessed with Bayley scales of infant development version 3.

Variable	Frequency	Percentage
Antenatal care (at least one visit)	69	89.6
Antenatal steroid (any number of doses)	46	59.7
Antenatal magnesium sulphate	10	13.0
Chorioamnionitis	2	2.6
Maternal hypertension	33	42.9
Maternal HIV	21	27.3
Maternal Diabetes	1	1.3
Attempted termination of pregnancy	1	1.3
Delivered by Caesarean Section	55	71.4
Bag mask ventilation at birth	38	49.4
Five minute Apgar score below 6	10	13.0
Early onset sepsis (<72 hours)	3	3.9
Intraventricular haemorrhage Grade 1 or 2	14	18.2
Respiratory distress syndrome	74	96.1
Pneumothorax	2	2.6
Any hypoglycaemia <2.6 mmol/l	14	18.2
Any hypernatraemia >155 mmol/l	12	15.6
Metabolic acidosis (any BE>-16 mmol/l)	1	1.3
Nasal CPAP without mechanical ventilation	48	62.33
Mechanical ventilation	13	16.9
Surfactant therapy	63	81.8
Steroids for chronic lung disease	28	36.4
Retinopathy of prematurity stage 3 or more	1	1.3
Surgery (not for NEC)	2	2.6
Patent ductus arteriosus	9	11.7
Necrotising enterocolitis stage 2 or more	4	5.2
Spontaneous intestinal perforation	1	1.3
Blood transfusion	57	74
Late onset sepsis	37	48
Fungal	8/37	21.6
Kangaroo mother care	49	63.6
Breastfed on discharge	42	54.5

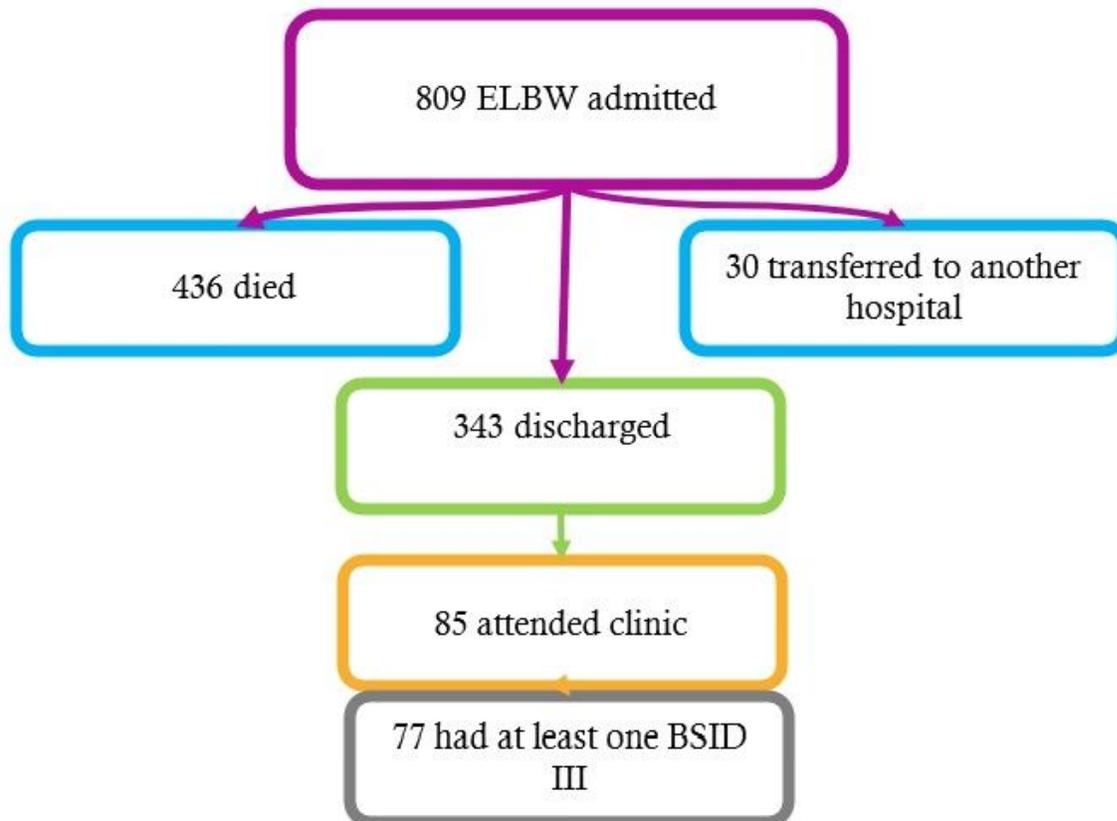
Table 2

Composite score of Bayley scales of infant development version III in 77 extremely low birth weight infants

Domain	Mean Composite Score	95% confidence intervals
Cognitive	98.4	95.1-101.7
Language	90.0	87.5-92.6
Motor	97.9	94.8-101.0

## Figures

**Figure 1: Sample size**



**Figure 1**

Sample size