REVIEW ARTICLE

OUTCOME OF THE EXTREMELY LOW BIRTH WEIGHT INFANTS (LESS THAN 999 GRAMS) : WHAT MESSAGES ARE WE GETTING?

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ABSTRACT

The outcome of the extremely low birth weight (less than 1,000g or ELBW) babies continues to improve. More ELBW babies are surviving, though some of them may have various degrees of impairment or disability. The chance of dying or surviving with a major disability or cerebral palsy declines significantly in recent years in the developed countries. The implication of these findings is that application of neonatal care does not increase the risk of disabled survival as has been often feared but promoted normal survival. Great effort has been put in to achieve good results and better outcome. Developing countries however, will face a problem of achieving similar results because of limited resources or priority of allocation of limited resources, inadequate facilities, lower socio-economic status, poor home environment and lack of follow-up services, training and rehabilitation set-ups or intervention programme.

What is the relevance of these good results in relation to the developing or third world countries? The limit of viability may have to be redefined. Nevertheless, it should be the aim to lower the mortality of these high risk babies and to reduce complications and morbidity of the survivors. Maintenance and control of body temperature, control of infections, blood sugar monitoring, antenatal steroids for the mother in premature labour, resuscitation at birth or even simple nasal continuous positive airway pressure (CPAP) should come a long way in fulfilling these goals.

Those ELBW children who survive without neurological damage may have learning difficulties. It is necessary to find out the reasons for that such as the impact of the home environment on mental development. Do the children have a good background conducive for learning? Are there establishments for intervention programme in the community for these high risk children?

The ratio of neonatal beds per 1,000 deliveries may have to be reviewed now that more ELBW infants are staying in the hospital for a longer period, and surviving.

Keywords: extremely low birth weight (ELBW) infants, outcome of, developing countries.

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Implication of improved survival

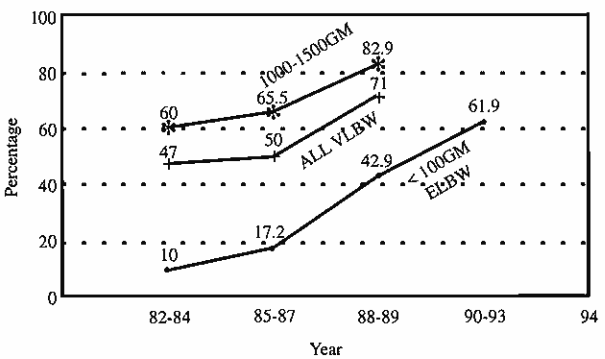
Many centres in the developed countries have recently reported their 'success stories' in the management of the extremely low birth weight (less than 1,000g or ELBW) babies with improved outcome, either in mortality or morbidity. We have also reported the outcome of such babies in Singapore[1]. (Fig 1) What is the relevance of this success in the management of these babies to the developing countries?

The outcome of this special group of patients – the ELBWs – has become a growing concern for the people who take care of these infants. They are the paediatricians, health administrators, educators, rehabilitation specialists, social and community workers, etc. other than their parents. The continued improvement of survival rate of these ELBWs or micropremies as many call them, reflects the realisation of a concept of perinatal-neonatal care and the success in the development of subspecialty in both obstetrics and paediatrics.

Though they constitute only 0.39% of all live births in the neonatal department[1], they occupy most neonatal intensive care beds at any time and spend the longest time in the nursery. Therefore, they consume large amount of the hospital resources. The ELBWs generally range from 22 to 28 weeks' gestational age; some are also intrauterine growth retarded.

It appears that there is an increase in the number of the ELBW infants in recent years. This increase in number in a hospital with tertiary neonatal care service is more apparent than real.

Fig 1 – Survival Rates of VLBW Rates (1982-1989)



VLBW : Very Low Birthweight
ELBW : Extremely Low Birthweight

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They may be due to more referrals of mothers with pregnancy complications, from the surrounding region, to the hospital with tertiary facilities. Also, more foetuses who would have been recorded as abortions or stillbirths previously are now registered as live births. In addition, the obstetrician's less biased attitude toward this group of small babies, say less than 26 weeks in gestation, and increased aggressiveness in the care of these babies such as delivery room resuscitation, may explain an absolute increase in number of ELBWs[2,3].

Just over a decade ago, most reports on the outcome of prematurely born babies were focused on larger babies, weighing less than 2,001g at birth[4]. Survival of infants weighing less than 1,000g at birth was a rarity. Following this, the focus had been shifted and reports of the VLBW (very low birth weight) infants or those weighing less than 1,500g at birth were appearing. More reports of the outcome of babies weighing less than 1,000g began to appear in the recent years[3,5,6]. Sweden, in 1992, reported the national ELBW infant survival rates[7].

The reasons for such a change of focus may be due to increased survivals of ELBW infants and they have now formed a large enough cohort for follow-up study and their long term outcome poses a problem and challenges for the caregivers.

Difficulties in comparing the outcome

When studying or comparing the outcome of the low birth weight infants, the investigators should clearly define the groups of infants they study. For instance, a report of the outcome of VLBW infants invaribly includes the ELBW infants. The findings will therefore depend on the number of ELBW infants that make up the group of VLBW infants because infants weighing between 1,000 to 1,499g would contribute a much better outcome. It is necessary to report the findings under VLBW as well as ELBW infants. Even in reporting of outcome of ELBW infants, the number of babies weighing more than or less than 750g at birth, which form the study cohort, will make the difference.

Other than the differences in the composition of the VLBW or ELBW infants, it is also not easy to compare the outcome of these extremely premature babies from different centres[8]. There are no uniform denominators, time definitions including differing years of study, outcome measures as well as uniform definition of the grades of disabilities. This may explain higher rates of disability in some countries such as the United States[9]. A child with major impairment may be easy to define. However, for 'minor', 'mild', or 'moderate' impairment, how 'mild' is mild? When comparisons of the neonatal outcome are made, one assumes that organisations and facilities of the neonatal centres are similar.

Birth weight or gestational age?

An increasing number of reports of the outcome of ELBW infants based on gestational age are appearing in recent years. Which study of the outcome of these infants, based either on birth weight or on the gestational age, is preferable or more informative? There are advantages in using the birthweight to define the group for evaluation studies because most ELBW infants are born to mothers with uncertain menstrual dates. When it is recommended that aggressive resuscitation is warranted for infants born at 25 weeks[10], how does one, in the developing countries, obtain, at least clinically, an accurate gestational age of the foetus? It may be easier to date the gestational age of the foetus in the developed countries where the technology for doing so is available. However, such method may not be possible or available in the developing countries for a long time to come.

Clinical assessment of gestational age of the ELBW infants after birth is always inaccurate[11] and information on outcome by gestation is sparse and relates to follow-up at relatively early age[12]. These render proper study of the outcome of ELBW children difficult.

Long term neurodevelopmental outcome

More reports on the long term neurodevelopmental outcome of the ELBW infants are appearing[12]. Generally the prospect of a survivor at 8 years having a severe disability was relatively low (4% overall) without a trend towards a higher risk with decreasing gestation. The broad conclusion however, from various reports, for children born before 29 weeks, was that the prevalence of severe disability among survivors was about 14%[12]. Nevertheless, the short-term follow-up study has its deficiency because a two-year follow-up assessment may miss subtle neurological deficits. Some of the 2-year assessment results of ELBW infants were conflicting. It may be unduly pessimistic in some[12-14]. They found an increase in cognitive scores in their children on subsequent follow-up. On the contrary, Collin et al noticed that in the ELBW population, normal infant development was poorly predictive of continued normal development and these children are at substantial risk for ongoing and emerging developmental problems with age[15]. Collin also noted that the methodology in assessment differed somewhat in different studies. As it has been mentioned previously, retrospective study of the outcome of the small babies has its shortcoming and weakness as the conclusions drawn only reflect the standard of care in the earlier years and not the present state of the art in management[15].

It was reported that surviving ELBW infants are at increased risk for adverse long-term neurodevelopmental sequelae[13] and substantial resources are required to produce additional ELBW survivors[17]. Are we getting more handicapped babies now that more ELBW infants are saved by improved neonatal care and advanced medical technology? It is encouraging to note that Kitchen et al reported increased survival rate for ELBW babies, born in 1985-87, in their tertiary centre. It was achieved without increasing the absolute number of severely disabled 2-year-old survivors despite 33% increase in ELBW live births in the hospital[18]. In the Netherlands, a nationwide prospective survey on very preterm and very low birth weight infants at the age of 2 years found that handicap was apparently unrelated to gestational age or birth weight[19]. Even Cooke, in his study of infants of birth weight of less than 1,500g, at three years of age and born between 1980 and 1989, noted that despite improved survival, the chance of survival with major disability or with cerebral palsy was unchanged[20]. These findings were similar to that reported by Stewart more than a decade ago. He reviewed most of the published follow-up data then available and concluded that disability rates had remained largely unchanged over the previous 30 years, while the survival had improved steadily[21]. Yet another meta-analysis study involving 111 reported studies over a 30-year period suggested that it was not possible to determine whether the rate of disability had changed with time[8]. Nevertheless, a trend showed that the chance of dying or surviving with major disability or cerebral palsy declined significantly. The implication of these findings is that application of neonatal care does not increase the risk of disabled survival as has been often feared, but promoted normal survival[20].

There are conflicting reports on the neurodevelopmental outcome of the ELBW infants, according to weight group of

more than or less than 800g. In Kitchen et al's report[18] comparing the babies born in 1977-1982 and in 1985-1987, more infants, weighing 800 to 999g at birth, survived but the rate of neurological disabilities was unchanged when compared with the smaller babies weighing less than 800g at birth, which showed a significant reduction in neurological disabilities in survivors. However, Saigal et al[22] found that improved survival rate without disability was confined to those infants weighing 801-1,000g at birth.

How soon can one tell the neurodevelopmental outcome of ELBW survivors? It remains a problem for the caregivers. Many workers attempt to find reliable predictive factors for neurodevelopmental outcome of preterm infants, though mostly the VLBW infants.

Van de Bor et al concluded in their study of infants of less than 32 weeks' gestation that detection of periventricular leucomalacia with ultrasound showed the best predictive factor for neurodevelopmental outcome[23]. Fazzi et al also reported that neonatal ultrasound examinations seemed to be fundamental in predicting neuromotor, but not cognitive, outcome in the VLBW infants[24]. Further report also confirms the findings[25]. The positive predictive value of intraparenchymal damage, as detected by neonatal cerebral ultrasound, was greater than the positive predictive value of a definitely abnormal neurological examination at one year of age[26].

Other areas of child development

It is important to know whether survivors with neurological deficits improve or worsen with time and what happen to the mental development, keeping in mind that brain development has never remained static. What happens to the long term social and emotional development of the VLBW babies, with or without disabilities? Weiglas Kuperus et al in their study of VLBW children observed that only 35% of the children with a mental delay at 2 years of age had a mental handicap at 3.6 years of age, whereas 35% had a normal cognitive outcome[26]. They therefore cautioned that interpretation of developmental test results in infancy might be misleading. However, a report from South Africa showed that there were more handicaps at 2 years of age when compared with those assessed at 1 year of age[27]. There are very few reports on the impact of home environment or of any form of intervention programme on the physical and mental development of these children[28]. If a neurodevelopmentally normal child does not perform well on follow-up, is it because of poor home environment or unfavourable socioeconomic status? If that is so, something could be and should be done. Can we enhance their development? A study of 985 low birth weight infants by the Infant Health and Development Program in USA to evaluate the efficacy of a comprehensive early intervention in reducing the developmental and health problems of low birth weight premature infants produced encouraging results. In this study, however, larger premature infants were studied and the mean birth weight ranged from 1,727g to 1,947g[29].

School performance

There are some data available from long term follow-up of the ELBW children. We must therefore look at the problems of the ELBWs seriously, especially the real problems of the neurologically normal survivors. The majority of the infants whose gestations were less than 28 weeks are surviving and they are neurologically intact[30]. What happen to these ELBW children, assessed to be normal neurodevelopmentally, when they go to school? Do they have learning problems? What is the effect of socioeconomic status on the child's intelligence? Has the home environment any effect on their mental development[28]? For the children in the developing or third world countries, what is the relevance of these data and their applications? How do these data relate to the prognosis?

Marlow et al found that the under 1,251g infants who were born in 1980 and 1981 and who at the age of 6 years old, attended a normal school, were noticed to be more clumsy, over-active, more easily frightened, and fidgety than term controls. He proposed that longer term follow-up and educational assessment of these premature infants were needed to determine the extent to which immaturity at birth remained a handicap in later life, and to what extent this might be ameliorated by appropriate intervention at school[31]. Saigal et al examined the learning disabilities and school problems of ELBW children at the age of 8 years. These children were considered normal neurologically and intellectually with an IQ of 85 or greater. In these children, the prevalence of learning disabilities was not increased. However, they did less well and utilised more special resources in school[32]. Similar study by Teplin et al in 1991 also noted that though a significant proportion of ELBW children had no severe disabilities, many however had dysfunction likely to affect learning and behaviour in school[33]. The study of neurodevelopmental outcome at 3 years of age by Bowen et al of the neurologically normal ELBW survivals, born between 1985 to 1987 was also reported. They found that there was a significant weakness in the eye and hand coordination skills and a relative strength in hearing and speech skills. Early recognition of this developmental profile may allow implementation of more appropriate preschool programmes for ELBW children[34]. Nishida from Japan in his long-term follow-up of ELBW children also noted poor school performance in spite of the absence of major neurological sequelae and the attainment of average intelligence scores[35]. Halsey et al recently reported their prospective study of ELBW children and they noted weaker performance on all measures prior to school entry among the non-disabled ELBW children. They mentioned that it was unclear whether these data portend emerging school-based disabilities or described a continuing recovery process to be completed in middle childhood. Therefore continued follow-up at 7 and 10 years of age would address these questions[36].

Management - a continuing process after hospital discharge

The management of the ELBW infants does not end on the day of hospital discharge. Another phase of management begins on the day the child goes home. The infant requires intensive training to make up for what he had missed when he was in the neonatal nursery where he was deprived of adequate sensorimotor stimulations and had instead experienced unpleasant stimulations (loud noise, bright light, excessive handling, painful procedures, etc.). Training and learning of the child should become a continuous process. The current neonatal nurseries provide little opportunity or support for early learning as well as psychological well-being[37]. This may have an important bearing on the long-term outcome in mental development.

Economic and psychosocial costs of care

Davies reckoned that the economic and psychosocial costs of caring for ELBW infants are great and she believed these costs to be warranted in developed countries for neonates with a good chance of survival and long-term outcome, which include many neonates with birth weight of less than 750g.

However, she did not believe these costs were warranted when treatment offered little or no hope of even survival up to hospital discharge, as might be the case for neonates weighing 750g or less who required cardiac compression in the delivery room[38]. It was suggested that for infants born at 22 weeks or less and with a birth weight of less than 500g, only comfort care be given[10,39]. What about those babies who were born in the developing or third world countries? Is it necessary to modify the proposal for older and bigger foetuses?

The usefulness of data from the developed countries

It would be ideal to provide the obstetricians with morbidity statistics from their own centres but many do not find it possible. What would happen if one has to rely on published data from other centres, some from other countries, where the definitions of live births, stillbirths, abortions, morbidity and the severity of disabilities, etc. are entirely different?

Would those data have any relevance for the practising doctors in the developing countries? What is behind the success stories, how much have these centres done in order to achieve the improved results, and what is the cost? Many factors are responsible for the improved outcome of the ELBW children, including optimisation of neonatal intensive care, better knowledge of pathophysiology of the premature infants, advent of exogenous surfactant replacement therapy, organised delivery room care with active resuscitative techniques as well as risk identification and efficient transport of the sick infants including *in utero* transfer of the foetus. What about the human resources, which is the most important factor? As mentioned earlier, application of neonatal care does not increase the risk of disabled survival as has been often feared but promotes normal survival[20]. What is the minimum standard required in order to achieve the same 'success'? One should not be carried away with the idea that having a neonatal set-up means uniformly good results or outcome.

Not all the ELBW infants require high-tech neonatal intensive management and some infants survive without resorting to complex and sophisticated equipment. Something should be done for these high risk babies, except those who have not reached the limit of viability. Complications and morbidity among the survivors could be reduced. Simple procedures such as warming devices for maintenance of body temperature, infection control including simple hand-washing, blood glucose monitoring, antenatal steroid for mothers in premature labour, delivery room resuscitation and stabilisation, and nasal continuous positive airway pressures (CPAP), etc. are useful.

The IVF babies

What about the *in vitro* fertilised (IVF) babies? The median length of gestation decreases with multiple births resulting in more VLBW or ELBW infants who make considerable demands on neonatal intensive care facilities. The pregnancy outcome following IVF showed that perinatal mortality increased dramatically with multiple births, especially the higher order of multiple births. It was recommended that restrictions on the numbers of embryos transferred during IVF should reduce the frequency of higher order multiple births[40]. Prevention of prematurity should be the answer but the problems in doing so are enormous and the task formidable. There are reports advocating antenatal corticosteroid to reduce the mortality, frequency of respiratory distress, and intracranial haemorrhage[41]. Such practices are useful at the present time, at least in reducing mortality and morbidity and feasible in the developing countries.

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