

J. B. van Goudoever

## Treatment decisions at the threshold of viability

Received: 7 July 2006 / Accepted: 10 July 2006 / Published online: 19 August 2006  
© European Board and College of Obstetrics and Gynaecology 2006

**Abstract** The survival rate for infants born preterm has improved over the last two decades. However, the incidence of moderate and severe neurodevelopmental disability amongst the surviving infants is high, and these infants require prolonged intensive care. Many countries have developed guidelines how and when to treat these infants. Usually, these guidelines are based upon the outcome data of large studies, but social, cultural and economical factors have a major impact on these guidelines as well. Some European countries have set guidelines at when to start treatment based upon gestational age alone. However, recent data show that ethnicity, gender and birth weight are important determinants for survival and morbidity as well. Thus, policies for initiating and withdrawing intensive care for those born extremely preterm should not be based upon gestational age, but infants should have a chance of proving themselves.

**Keywords** Preterm infants · Withholding treatment

### Introduction

Among the many ethical problems, the one that obstetricians and neonatologists are faced on a regular basis involves the issue of withholding treatment to infants at the threshold of viability. The survival rate for infants born from 22 to 26 weeks of gestation increases with each additional week [1]. However, there is a certain trade-off, whereby survival of extremely preterm infants is achieved at the expense of disability in later life. In addition, the care these infants require is extensive, some times lifelong and costly.

J. B. van Goudoever (✉)  
Division of Neonatology, Department of Pediatrics,  
Erasmus Medical Center,  
Dr Molewaterplein 60,  
3015 Rotterdam, The Netherlands  
e-mail: j.vangoudoever@erasmusmc.nl

### Involvement of the parents in the decision-making process

In the Netherlands, we consider the opinion of the parents critical in the decision to start or withhold treatment to an extremely preterm infant [2]. Most parents are unaware with the complexities of care required for an extremely premature infant in the intensive care unit and after discharge from the hospital. Parents need clear and consistent explanations of what to expect and these should be delivered to them in small and frequent segments so that they can comprehend the issues. Often, time is lacking to provide all the necessary information to the parents at the time of delivery. However, the parents bear the consequences of the birth of an extremely preterm infant. Therefore, it is important that decisions regarding all aspects of birth and the subsequent care of the infant are made jointly by the parents and the physicians. It is also of great importance that the parents receive, as much as possible, appropriate information about the maternal risk of a caesarean section, potential for infant survival and risk of adverse outcome whenever taking decisions upon withholding treatment.

### Current practice

Some countries have set indications for starting treatment to infants born at the threshold of viability based upon the gestational age. Large studies have shown that gestational age is an important determiner in long-term survival and morbidity (Table 1). Gestational age seems often well-established. It is appropriate for the woman with regular menstrual cycles and a known last menstrual period that is confirmed by an early examination. Foetal measurements derived through the use of ultrasonography can be used when the woman is uncertain about the date or her last menstrual period or when the date of anticipated delivery derived from menstrual dating is 2 weeks different from the date derived from ultrasound measurements.

However, sonographic measurements to estimate foetal weight and gestational age is confounded by the inclusion

**Table 1** Neonatal survival (%) by gestational age

Gestational age (weeks)	UK and Ireland [1]	Belgium [7]	Norway [8]	US [9]
22		0	0	21
23	11	6	16	30
24	26	29	44	52
25	44	56	66	76
26		72	72	80

of infants who are growth-restricted [3, 4]. Even in ideal circumstances, the 95% confidence limits for an estimate of foetal weight (and, thus, gestational age) are  $\pm 15$ –20% [5, 6]. A small discrepancy of 100 to 200 g or 1 to 2 weeks in gestational age may have major implications for survival and long-term morbidity (Table 1). Thus, uncertainty about the exact gestational age decreases the already uncertain prognosis of a specific foetus or infant. The uncertainty about the exact gestational age in some instances makes it also questionable whether the set points of starting or withholding treatment should be based upon gestational age alone.

### Other factors besides gestational age that influence mortality rates of extremely premature infants

Birth weight is an important denominator in survival rate. Survival rate is around 10% when birth weight is less than 500 g, whereas the rate increases to approximately 50% for infants with a birth weight of 500–750 g [7–9]. But next to birth weight that has a strong relation to gestational weight, gender and ethnicity is important in predicting neonatal survival.

To illustrate the importance of these variables, three hypothetical cases are compared with either similar gestational age or with a resembling birth weight in Table 2 [10]. The survival rates are based upon mortality rates amongst US and UK- Irish infants born in the mid-1990s [11, 12]. From these data, it is obvious that gestational age should not be the only variable that is taken into account when making decisions on treatment

strategies. Birth weight, ethnicity and gender are pivotal in the decision-making process of withholding treatment to extremely preterm infants whenever parents and physicians want to base this decision on outcome parameters.

### Morbidity rates

The decrease of mortality rates of infants born extremely premature might lead to an increase in morbidity rates. The overall morbidity rate reported in most studies is high in extreme preterm infants. Four large cohort studies show that the number of survivors free of major morbidity range from 13 to 26% when infants are born below a gestational age of 26 weeks [7, 11, 13, 14]. The UK-Ireland EPICure study [15] found approximately 50% of their cohort to have moderate to severe disability in 6-year-old children, similar to other studies [16–18]. There are some data that suggest that morbidity increases with age [19], although severe disability in extremely preterm infants did not alter in time between 30 months and 6 years in the EPICure study [15, 20].

The high chances of morbidity have led to a reserved policy towards the initiation of therapy for extremely premature infants in the Netherlands. From the mid-1990s up to 2004, hardly any infant born before 25–26 weeks of gestation was treated in the Netherlands. A comparison between the different strategies (near universal initiation of intensive care in New Jersey, USA vs selective initiation of intensive care in Leiden, the Netherlands for a comparable group of extremely premature infants in the mid-1980s) revealed that universal initiation resulted in a doubling of survival rate (46 vs 22%), but a four times higher prevalence of disabling cerebral palsy (17.2 vs 3.4%) [21].

However, some studies report much lower rates of severe disability. For example, a study conducted in Stockholm found severe disability in 14% of 3-year-old children born at 24 weeks or less of gestation and in only 9% of children born at 25 or 26 weeks [22]. Those data are supported by another study showing similar results [23]. Some suggest that, although preterm infants have a high prevalence of neurodevelopmental disability, the developing brain recovers [24]. This is supported by a very recent

**Table 2** Different factors affecting the survival rate of extremely preterm infants

	Gestational age of 24 weeks	Gestational age of 24 weeks	Gestational age 28 weeks
Survival rate	68%	68%	94%
Effect of ethnicity	24 wks + Caucasian parents	24 wks + Afro-American parents	28 wks + Hispanic parents
Survival rate	63%	73%	93%
Effect of birth weight	24 weeks + Caucasian parents + 720 g birth weight	24 weeks + Afro-American parents + 770 g birth weight	28 weeks + Hispanic parents + 740 g birth weight
Survival rate	57%	86%	74%
Effect of gender	24 weeks + Caucasian parents + 720 g birth weight + male gender	24 weeks + Afro-American parents + 770 g birth weight + female gender	No additional data on gender available
Survival rate	37%	91%	(74%) <sup>a</sup>

Data presented in this table are based upon [11, 12].

<sup>a</sup>No data available to specify gender effect.

**Table 3** Difference in outcome at 6 years of age of extremely premature born boys and girls surviving the neonatal period

Outcome	24 weeks gestational age		25 weeks gestational age	
	Boys	Girls	Boys	girls
No or mild disability	35%	64%	52%	70%
Severe disability	41%	17%	24%	11%

Data presented in this table are based upon [15].

observation that the majority of extremely preterm-born infants have overcome their early problems at adolescence and young adulthood [25].

### Factors associated with outcome of extremely preterm infants

Cognitive impairment does not seem to correlate with gestational age amongst children born at 23–26 weeks of gestation, but retinopathy of prematurity does [8, 15]. Numerous studies have shown an impact of gender on outcome [7, 11, 15]. Boys perform clearly less than girls (Table 3). There is also an association with ethnicity on the prevalence of retinopathy, with more Caucasian children suffering from retinopathy [11].

There is some evidence that physicians are able to predict later outcome in early life. For instance, Hoekstra et al. [26] showed that approximately 75% of infants with normal brain ultrasounds in the neonatal period developed without major disability at 4 years of age. Those investigations are of utmost importance when discussing continuation or withholding treatment with parents. The usage of NMR-compatible incubators, which can be used while infants are on the ventilator, will help to improve prognostic tools. The combination of imaging techniques in the early postnatal life and long-term outcome is nowadays part of many research projects that should help families and physicians in the decision-making process of management of the birth and subsequent care for an extremely preterm infant.

### Conclusion

The birth of an extremely preterm infant poses a complex issue on several areas for both the family and the involved physicians. Medical, social, ethical and, in some countries, also economical areas may lead to the very difficult discussion whether to start or to withhold treatment. Decisions regarding management of birth and subsequent care should be based upon a fair discussion with parents and caregivers, with appropriate and up-to-date information on the maternal risks and the infant's potential for survival. In addition, the risks on long-term outcome should be thoroughly discussed. Although a decision on the management of the birth and subsequent care is a joint decision of parents and physicians, the parenteral choice

should be respected primarily within the limits of feasibility and appropriateness.

Recent data show that gestational age alone is not an appropriate parameter to make a decision on starting or withholding treatment when an extremely preterm infant is bound to be born. Birth weight, gender and ethnicity seem to influence the long-term outcome. Follow-up into adulthood seems to indicate that a significant majority of former extremely preterm infants have overcome their earlier difficulties to become functional young adults. Most of the medical problems that influence long-term outcome are already apparent in the early neonatal period, suggesting that decisions on withholding treatment seem to be more justified after birth than antenatal.

### Note

After a thorough discussion among physicians in the Netherlands, the policy regarding the management of a threatened birth of an extremely preterm infant has changed. From 2006 onwards, the obstetrician will seek contact with a perinatal centre in case of a threatened birth of an infant with a gestational age of 24 weeks. In general, treatment will be withheld for infants less than 25 weeks of gestation, except for very special occasions. From 25 weeks gestation onwards, in general, treatment will be started, and from 26 weeks onwards treatment will be initiated always.

### References

1. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR (2000) Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 343 (6):378–384 (Aug 10)
2. De Leeuw R, Cuttini M, Nadai M, Berik I, Hansen G, Kucinkas A, Lenoir S, Levin A, Persson J, Rebagliato M, Reid M, Schroell M, de Vonderweid U, EURONIC Study Group (2000) Treatment choices for extremely preterm infants: an international perspective. *J Pediatr* 137(5):608–616
3. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M (1996) A United States national reference for foetal growth. *Obstet Gynecol* 87(2):163–168
4. Arnold CC, Kramer MS, Hobbs CA, McLean FH, Usher RH (1991) Very low birth weight: a problematic cohort for epidemiologic studies of very small or immature neonates. *Am J Epidemiol* 134(6):604–613
5. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK (1985) Estimation of foetal weight with the use of head, body, and femur measurements—a prospective study. *Am J Obstet Gynecol* 151(3):333–337
6. Hadlock FP, Harrist RB, Martinez-Poyer J (1991) How accurate is second trimester foetal dating? *J Ultrasound Med* 10 (10):557–561
7. Vanhaesebrouck P, Allegaert K, Bottu J, Debauche C, Devlieger H, Docx M, Francois A, Haumont D, Lombet J, Rigo J, Smets K, Vanherreweghe I, Van Overmeire B, Van Reempts P, Extremely Preterm Infants in Belgium Study Group (2004) The EPIBEL study: outcomes to discharge from hospital for extremely preterm infants in Belgium. *Pediatrics* 114 (3):663–675

8. Markestad T, Kaaresen PI, Ronnestad A, Reigstad H, Lossius K, Medbo S, Zanussi G, Engelund IE, Skjaerven R, Irgens LM, Norwegian Extreme Prematurity Study Group (2005) Early death, morbidity, and need of treatment among extremely premature infants. *Pediatrics* 115(5):1289–1298
9. Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ, Verter J, Temprosa M, Wright LL, Ehrenkranz RA, Fanaroff AA, Stark A, Carlo W, Tyson JE, Donovan EF, Shankaran S, Stevenson DK (2001) Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. *Pediatrics* 107(1):E1
10. Van Goudoever JB (2004) Te jong on te kiezen (Too young to decide). Inaugural lecture. Erasmus Medical Center, Rotterdam, The Netherlands, ISBN90-9018621-2, September
11. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR (2000) The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics* 106(4):659–671
12. Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J (2003) US birth weight/gestational age-specific neonatal mortality: 1995–1997 rates for whites, Hispanics, and blacks. *Pediatrics* 111(1):e61–e66
13. Chan K, Ohlsson A, Synnes A, Lee DS, Chien LY, Lee SK, Canadian Neonatal Network (2001) Survival, morbidity, and resource use of infants of 25 weeks' gestational age or less. *Am J Obstet Gynecol* 85(1):220–226
14. Cust AE, Darlow BA, Donoghue DA, Australian and New Zealand Neonatal Network (ANZNN) (2003) Outcomes for high risk New Zealand newborn infants in 1998–1999: a population based, national study. *Arch Dis Child Fetal Neonatal Ed* 88(1):F15–F22
15. Marlow N, Wolke D, Bracewell MA, Samara M, EPICure Study Group (2005) Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med* 352(1):9–19
16. Emsley HC, Wardle SP, Sims DG, Chiswick ML, D'Souza SW (1998) Increased survival and deteriorating developmental outcome in 23 to 25 week old gestation infants, 1990–4 compared with 1984–9. *Arch Dis Child Fetal Neonatal Ed* 78(2):F99–F104
17. Doyle LW, Anderson PJ; Victorian Infant Collaborative Study Group (2005) Improved neurosensory outcome at 8 years of age of extremely low birthweight children born in Victoria over three distinct eras. *Arch Dis Child Fetal Neonatal Ed* 90(6):F484–F488
18. Piecuch RE, Leonard CH, Cooper BA, Kilpatrick SJ, Schlueter MA, Sola A (1997) Outcome of infants born at 24–26 weeks' gestation: II. Neurodevelopmental outcome. *Obstet Gynecol* 90(5):809–814
19. McGrath MM, Sullivan MC, Lester BM, Oh W (2000) Longitudinal neurologic follow-up in neonatal intensive care unit survivors with various neonatal morbidities. *Pediatrics* 106(6):1397–1405
20. Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR, EPICure Study Group (2005) The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. *Arch Dis Child Fetal Neonatal Ed* 90(2):F134–F140
21. Lorenz JM, Paneth N, Jetton JR, den Ouden L, Tyson JE (2001) Comparison of management strategies for extreme prematurity in New Jersey and the Netherlands: outcomes and resource expenditure. *Pediatrics* 108(6):1269–1274
22. Finnstrom O, Gaddlin PO, Leijon I, Samuelsson S, Wadsby M (2003) Very-low-birth-weight children at school age: academic achievement, behavior and self-esteem and relation to risk factors. *J Matern Fetal Neonatal Med* 14(2):75–84
23. Serenius F, Ewald U, Farooqi A, Holmgren PA, Hakansson S, Sedin G (2004) Short-term outcome after active perinatal management at 23–25 weeks of gestation. A study from two Swedish perinatal centres. Part 3: neonatal morbidity. *Acta Paediatr* 93(8):1090–1109
24. Ment LR, Vohr B, Allan W, Katz KH, Schneider KC, Westerveld M, Duncan CC, Makuch RW (2003) Change in cognitive function over time in very low-birth-weight infants. *JAMA* 289(6):705–711
25. Saigal S, Stoskopf B, Streiner D, Boyle M, Pinelli J, Paneth N, Goddeeris J (2006) Transition of extremely low-birth-weight infants from adolescence to young adulthood: comparison with normal birth-weight controls. *JAMA* 295(6):667–675
26. Hoekstra RE, Ferrara TB, Couser RJ, Payne NR, Connett JE (2004) Survival and long-term neurodevelopmental outcome of extremely premature infants born at 23–26 weeks' gestational age at a tertiary center. *Pediatrics* 113(1 Pt 1):e1–e6