



Human fetal growth is constrained below optimal for perinatal survival

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ABSTRACT

Objective The use of fetal growth charts assumes that the optimal size at birth is at the 50th birth-weight centile, but interaction between maternal constraints on fetal growth and the risks associated with small and large fetal size at birth may indicate that this assumption is not valid for perinatal mortality rates. The objective of this study was to investigate the distribution and timing (antenatal, intrapartum or neonatal) of perinatal mortality and morbidity in relation to birth weight and gestational age at delivery.

Methods Data from over 1 million births occurring at 28–43 weeks' gestation from singleton pregnancies without congenital abnormalities in the period from 2002 to 2008 were collected from The Netherlands Perinatal Registry. The distribution of perinatal mortality according to birth-weight centile and gestational age at delivery was studied.

Results In the 1 170 534 pregnancies studied, there were 5075 (0.43%) perinatal deaths. The highest perinatal mortality occurred in those with a birth weight below the 2.3rd centile (25.4/1000 births) and the lowest mortality was in those with birth weights between the 80th and 84th centiles (2.4/1000 births), according to routinely used growth charts. Antepartum deaths were lowest in those with birth weight between the 90th and 95th centiles. Data were almost identical when the analysis was restricted to infants born at ≥ 37 weeks' gestation.

Conclusion From an immediate survival perspective, optimal fetal growth requires a birth weight between the 80th and 84th centiles for the population. Median birth weight in the population is, by definition, substantially lower than these centiles, implying that the majority of fetuses exhibit some form of maternal constraint on

growth. This finding is consistent with adaptations that have evolved in humans in conjunction with a large head and bipedalism, to reduce the risk of obstructed delivery. These data also fit remarkably well with those on long-term adult cardiovascular and metabolic health risks, which are lowest in cases with a birth weight around the 90th centile. Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

The evolution of a large head, combined with the changes in pelvic dimensions and orientation associated with bipedalism, constitute a major challenge for vaginal delivery in humans because the fit between the fetal head and the pelvic canal is much tighter than in our closest relative, the chimpanzee¹. Without intervention, obstructed labor is likely to be fatal for the fetus and to increase the risk of urogenital damage and death of the mother. For this reason, we are the only mammal known to utilize a birth assistant. Nonetheless, in the absence of modern medicine, the incidence of perinatal death remains high in some low-income settings². It is believed that human fetal growth is constrained below its genetic potential in all pregnancies, to a greater or lesser degree, to match size at birth to maternal physical characteristics³. The classical studies of Ounsted and Ounsted^{4–6}, reporting on surrogate pregnancy⁷, and a wide range of animal studies^{8–10} support this concept of a strong link between maternal, but not paternal, size and fetal birth weight¹¹. The relationship between size at birth and the health outcome of the offspring is, however, complex. Both impaired and excessive fetal growth lead to an increased risk of perinatal morbidity and mortality. Thus, in small-for-gestational-age (SGA) fetuses, defined as those with a birth weight below the 10th centile, there

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is an increased risk of intrauterine fetal death across all gestational ages compared with non-SGA fetuses, with the highest risk found in those with a birth weight below the 3rd centile^{12–14}. However, while greater fetal growth in late gestation reduces the risk of perinatal death, large-for-gestational-age or macrosomic fetuses (birth weight >90th centile) are at risk of labor complications and thus of perinatal morbidity and mortality^{15,16}.

The use of standardized fetal growth charts assumes that the optimal size at birth for the best outcome is at the 50th centile, but the complex interaction between maternal constraints and the different risks associated with a small or large size at birth suggests that this assumption may not be valid. However, this issue has not been examined in a sufficiently large contemporary population in a high-income setting. The objective of this study was to investigate the distribution and timing of perinatal mortality and morbidity in relation to birth weight and gestational age at delivery.

METHODS

This was a retrospective population-based cohort study. Data on 1 170 127 births between 2002 and 2008 were collected retrospectively from The Netherlands Perinatal Registry. Data on all births occurring between 28 and 43 weeks' gestation from singleton pregnancies in the period 2002–2008 were collected. Twenty-eight weeks was chosen as the lower cut-off point to permit comparison with data from other countries in which there may be differences in registration practices at earlier gestational ages¹⁷. Children with congenital abnormalities were excluded.

Birth weight was displayed in centile groups according to standardized population reference curves, which were based on nationwide data from the year 2002¹⁸. 'Binning' of data according to birth-weight centiles included -2 (2.3rd centile), -1 (16th centile), 0 , $+1$ (84th centile) and $+2$ (97.7th centile) SDs. Gestational age was calculated from the first day of the last menstrual period or from an early ultrasound dating scan. Perinatal death was defined as fetal or neonatal death up to 7 days after delivery: antepartum death was defined as death occurring before labor, intrapartum death as death during labor and neonatal death as death occurring within 0–7 days following live birth. Congenital abnormalities were defined as those recognized at birth, or at first admission, by the neonatologist.

Statistical analysis

The distribution of perinatal mortality according to birth weight was studied. Mortality rates were subdivided into antepartum, intrapartum and neonatal death to assess these relationships separately for the different time periods of occurrence of death. The relationship between perinatal mortality, birth weight and gestational age at delivery was studied. Mortality was expressed as rate (number of deaths per 1000 infants). For perinatal

mortality according to gestational age, the mortality rate at 43 weeks' gestation was not displayed owing to the extremely small number of cases. Given that more than half of perinatal mortality occurred at or after 37 weeks, analysis was carried out separately for both the total data set and for pregnancies delivering at or after 37 weeks. Data of births with missing birth-weight centiles were excluded from the analysis.

RESULTS

We studied 1 170 534 singleton pregnancies delivered between 2002 and 2008 after 28 weeks' gestation and without congenital abnormalities. There were 5075 (0.43%) perinatal deaths. For 407 (0.03%) children, of whom 17 died, birth-weight centiles were not recorded, and these were therefore excluded from the mortality rates. Of all perinatal deaths, 54% occurred at or after 37 weeks' gestation; 29% occurred in infants with a birth weight below the 10th centile, but 64% occurred in infants with a weight between the 10th and 90th centiles, with a similar distribution at all gestational ages (Figure 1). The distribution of perinatal mortality by birth weight is shown in Table 1 and Figure 2a. The distribution according to birth-weight centile (Table 1) corresponds well with that of The Netherlands Perinatal birth-weight chart, which was based on the births in 2002 only¹⁸. The incidence of perinatal death was highest in those with a birth weight below the 2.3rd centile, falling gradually with an increasing birth weight up to the 80th and 90th centiles, at which the lowest death rates occurred. At centiles higher than this, mortality increased again. Perinatal mortality of infants with a birth weight between the 80th and 90th centiles was significantly lower than that of infants with a birth weight between the 50th and 80th centiles or ≥ 90 th centile (chi-square test, $P = 0.02$ and 0.004 , respectively). The distribution of mortality according to birth weight and perinatal timing of death is shown in Figure 2b. Antepartum deaths accounted for 72% of all perinatal deaths and were lowest in infants with a birth weight between the 90th and 95th centiles. Intrapartum and neonatal deaths were lowest between the 80th and 84th centiles. The same patterns were found when data were restricted to infants born at or after 37 weeks' gestation (Figure 3), or to those born between 39 and 40 weeks (data not shown). Perinatal mortality decreased as gestation progressed for all groups (Figure 4). Admission to the neonatal intensive care unit (NICU) and/or a low 5-min Apgar score, representing the morbidity rate, were lowest for those with a birth weight between the 50th and 84th centiles (Figure 5; data restricted to infants born ≥ 37 weeks to avoid the effects of prematurity).

DISCUSSION

This study shows that, in a very large contemporary population of infants without congenital abnormalities born after 28 weeks' gestation in a high-income country,

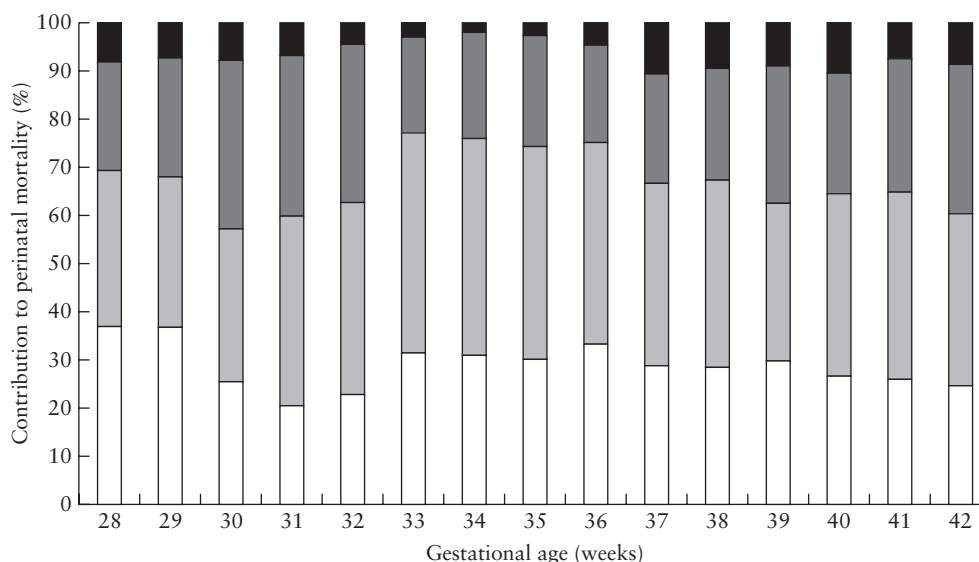


Figure 1 Relative contribution of birth-weight centiles to perinatal mortality according to gestational age at delivery of babies born between 28 and 42 weeks' gestation in The Netherlands during 2002–2008. ■, Birth-weight centile > 90; ■, birth-weight centile 50–90; ■, birth-weight centile 10–50; □, birth-weight centile < 10.

Table 1 Perinatal mortality according to birth-weight centile (p) of babies born after 28 weeks' gestation in The Netherlands from 2002–2008

Birth-weight centile	Total births (n (cumulative %))	Perinatal mortality*			
		Antepartum	Intrapartum	Neonatal	Total*
< p2.3	26 805 (2.29)	540 (20.15)	54 (2.01)	88 (3.28)	682 (25.44)
p2.3–< p5	28 296 (4.71)	247 (8.73)	27 (0.95)	52 (1.84)	326 (11.52)
p5–< p10	52 401 (9.19)	358 (6.83)	28 (0.53)	67 (1.28)	453 (8.64)
p10–< p16	63 805 (14.64)	300 (4.70)	37 (0.58)	73 (1.14)	410 (6.43)
p16–< p20	45 378 (18.52)	170 (3.75)	22 (0.48)	34 (0.75)	226 (4.98)
p20–< p50	353 219 (48.70)	926 (2.62)	114 (0.32)	247 (0.70)	1287 (3.64)
p50–< p80	359 603 (79.44)	686 (1.91)	107 (0.30)	221 (0.61)	1014 (2.82)
p80–< p84	48 139 (83.55)	82 (1.70)	13 (0.27)	21 (0.44)	116 (2.41)
p84–< p90	69 010 (89.45)	99 (1.43)	24 (0.35)	45 (0.65)	168 (2.43)
p90–< p95	57 731 (94.38)	81 (1.40)	20 (0.35)	44 (0.76)	145 (2.51)
p95–< p97.7	32 384 (97.15)	56 (1.73)	9 (0.28)	22 (0.68)	87 (2.69)
≥ p97.7	33 356 (100.00)	100 (3.00)	19 (0.57)	25 (0.75)	144 (4.32)
Total	1 170 127	3645 (3.12)	474 (0.41)	939 (0.80)	5058 (4.32)

*Mortality rate within percentile group per 1000 births.

the median birth weight is substantially lower than is that associated with the lowest perinatal mortality, regardless of gestational age at delivery and perinatal timing of death. In addition, a low Apgar score and/or admission to the NICU were less common in infants with a birth weight between the 50th and 84th centiles. Most perinatal deaths occurred in fetuses with a birth weight in the so-called 'normal' range. For antepartum survival, an even higher birth-weight centile (90th–95th) was optimal, but this was associated with a higher neonatal morbidity and death rate, possibly related to complications during labor. Our findings confirm the hypothesis of the involvement of maternal constraint on fetal growth, a process evolved to facilitate vaginal delivery, in normal contemporary human pregnancies.

Our observations build on those of previous studies. A study conducted in Newcastle in the UK, using Z-scores

for the distribution of birth weight, showed that the lowest stillbirth rate and infant mortality occurred in infants with a Z-score of +1, for both periods 1961–1980 and 1981–2000, during which the overall stillbirth rate in the UK fell from 23.4 to 4.7 per 1000 live births¹⁹. In a larger nationwide study in Norway, the lowest mortality rate was found among those with a birth-weight Z-score between +1 and +2²⁰. In neither study was detailed information given on mortality, in relation to precise centiles or on the mortality pattern of infants born at or after 37 weeks' gestation. Thus, there are currently three studies indicating that the lowest rate of perinatal mortality occurs in infants with a birth weight around 1 SD above the mean, which makes the evidence quite convincing. Similarly, in another study the lowest prevalence of cerebral palsy by Z-score of weight for gestational age was found in infants with a Z-score of +1²¹. Our

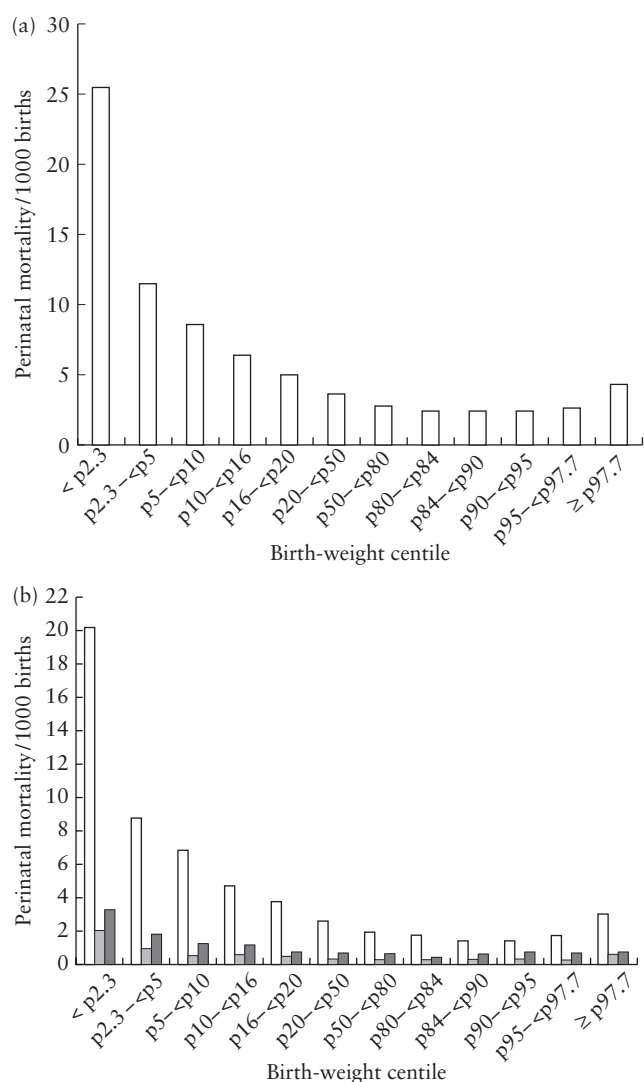


Figure 2 Perinatal mortality according to birth-weight centile (a) and timing of perinatal mortality (b) for babies born between 28 and 42 weeks' gestation in The Netherlands during 2002–2008. □, Antepartum period; ■, intrapartum period; ■ neonatal period.

data also correspond well with those of a recent study of almost 12 000 term fetuses²², in which the Doppler pulsatility index (PI) was measured in the umbilical artery (UA) and fetal middle cerebral artery (MCA), and the cerebroplacental ratio (CPR) was calculated as the ratio MCA-PI:UA-PI. With increasing birth-weight centiles, the UA-PI fell progressively, the MCA-PI increased significantly and the multiples of the median of CPR decreased significantly. Failure to reach their growth potential, defined by the authors as an increased CPR, was only absent in fetuses with a birth weight > 90th centile and was increasingly present at lower centiles²². Also, our data showed the lowest antenatal death rate in infants with a birth weight > 90th centile. In other words, optimal antenatal fetal growth seems to be consistently present only in large-for-gestational age fetuses.

Our finding, that the lowest perinatal mortality and morbidity are not present in infants with a birth weight around the 50th centile, but at a much higher centile,

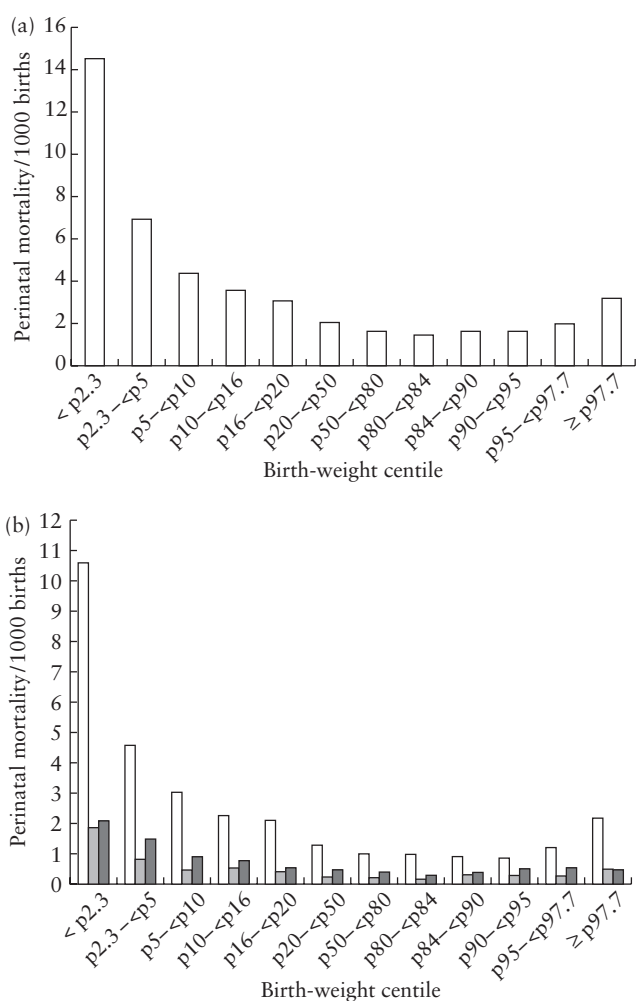


Figure 3 Perinatal mortality according to birth-weight centile (a) and timing of perinatal mortality (b) for babies delivered at or after 37 weeks' gestation in The Netherlands during 2002–2008. □, Antepartum period; ■, intrapartum period; ■ neonatal period.

raises important issues about human development. As this effect did not depend on gestational age, it suggests that it is not linked to the timing of the onset of labor. The protective effect of a higher, although not the highest, birth weight against perinatal mortality is consistent with good nutrition in late gestation and the deposition of fat stores²³. Similarly, the increased mortality rate in the smallest infants may result from inadequate placental function and/or nutrition in late gestation. However, our finding that between these extremes the majority of infants had a lower birth weight than that associated with a low mortality risk suggests that maternal constraint processes operate to reduce late-gestation growth to a degree optimal for the mother rather than her baby³. This may represent a mechanism that has evolved to optimize maternal survival in order to reproduce again as an aspect of Darwinian fitness.

The higher birth weight (centile) favorable for perinatal survival is also associated with a reduced risk of non-communicable disease in adult life. Studies on the Developmental Origins of Health and Disease (DOHaD) concept have shown that birth weight is inversely related,

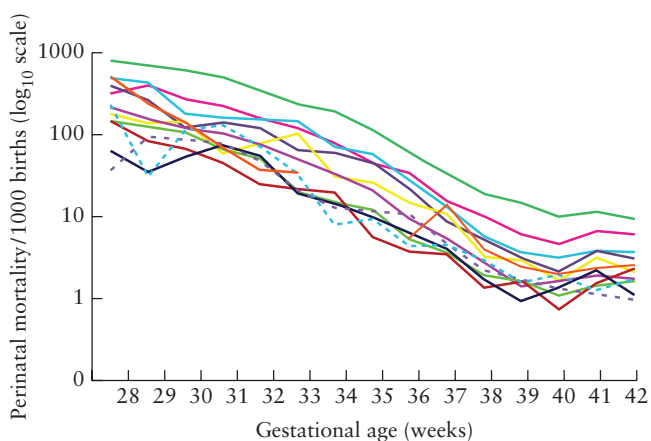


Figure 4 Perinatal mortality rate according to birth-weight centile and gestational age at delivery of babies born at 28–42 weeks' gestation in The Netherlands during 2002–2008. —, < p2.3; —, p2.3–< p5; —, p5–< p10; —, p10–< p16; —, p16–< p20; —, p20–< p50; —, p50–< p80; —, p80–< p84; —, p84–< p90; —, p90–< p95; —, p95–< p97.7; —, \geq p97.7.

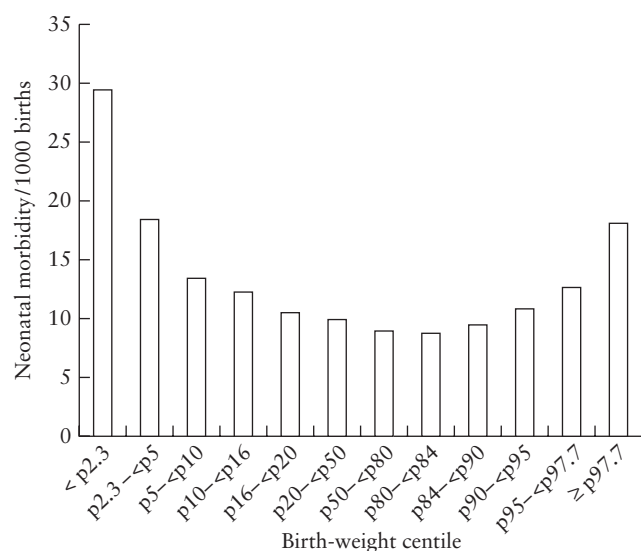


Figure 5 Neonatal morbidity, defined by admission to neonatal intensive care unit and/or 5-min Apgar score < 7, according to birth-weight centile of babies delivered at or after 37 weeks' gestation in The Netherlands during 2002–2008.

in a graded manner, to a risk of later cardiovascular and cerebrovascular death and to the development of impaired glucose tolerance and Type-2 diabetes^{24–28}. Thus, in historical studies in the UK, the lowest risk for developing adult cardiovascular disease was found in infants weighing around 4 kg at birth, approximately the 90th centile at 40 weeks' gestation^{24,26}. A high birth weight, indicative of absence of intrauterine growth restraint, and resulting in a low perinatal mortality, is therefore also favorable for long-term health.

The strength of the present study is the large population size, with information from The Netherlands Perinatal Registry, which contains data on approximately 95% of all births in The Netherlands²⁹. Limitations include the

lack of information on the cause of death, and possible inaccuracies in discriminating between antepartum and intrapartum death³⁰. Moreover, the use of customized growth charts³¹, correcting for ethnicity and maternal height and weight, might have refined our data, but such information is unfortunately not present in The Netherlands Perinatal Registry.

It is sometimes said that birth is the second most-dangerous time in our lives. Our study shows that, from a survival perspective, optimal late-gestation fetal growth requires a live birth weight around the 80–90th centile. Such a high birth weight is favorable not only for short-term survival but also for long-term health. However, normative maternal constraint processes, believed to have evolved for a maternal fitness advantage, result in the majority of fetuses having a lower birth weight than this. This is associated with higher perinatal mortality, even in a high-income country today. When developing risk scores for perinatal mortality, including maternal characteristics such as age, parity, socioeconomic class, body mass index, height, smoking and estimated fetal weight, not only fetal weights < 10th centile should be included, but so should a graded, more sophisticated, risk-centile distribution.

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