

Section 1

Basic Principles

Chapter

1

What Is Optimal Fetal Growth?

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Introduction

Normal fetal growth is usually defined as an estimated fetal weight between the 10th and 90th centiles based on population-specific birth weight centiles corrected for gestational age at delivery, parity, and fetal sex. So-called customized growth charts also correct for maternal ethnicity, weight, and length [1]. Such definitions are based on the fact that both impaired and excessive fetal growth result in an increased risk of perinatal morbidity and mortality. Indeed, in small for gestational age (SGA) fetuses, defined as a birth weight below the 10th centile, there is an increased risk of intrauterine fetal death across all gestational ages [2,3] compared with non-SGA fetuses, with the highest risk in infants with a birth weight below the 3rd centile [4]. Large for gestational age (> 90th centile, macrosomic) fetuses are at risk of labor complications and thus also of increased perinatal morbidity and mortality [5,6]. However, with a focus on too small or too big, it may be forgotten that the majority of perinatal (and especially antepartum) deaths occurs in fetuses with a “normal” weight. Moreover, the use of population-based fetal growth charts assumes that optimal size at birth for outcome is at the 50th centile.

In this chapter, optimal fetal growth/size for perinatal and long-term survival is reviewed in relation to birth weight centiles at birth. The clinical consequences are discussed.

Fetal Growth/Size and Short-Term Perinatal Survival

Several studies have been conducted on perinatal survival in relation to birth weight centiles. A study conducted in Newcastle in the United Kingdom using Z-scores for distribution of birth weight showed that the lowest stillbirth rate and infant mortality occurred in infants with a Z-score of +1, both between 1961–80 and 1981–2000, a period over which the overall

stillbirth rate fell in that region of the UK from 23.4 to 4.7 per 1,000, respectively [7]. In a larger nationwide study in Norway, the lowest mortality was found for a birth weight Z-score between +1 and +2 [8]. Similar results were recently published from Australia [9] and Scotland [10]. In the latter study regarding 780,000 births, the lowest antenatal mortality occurred in fetuses with a birth weight in between the 90th and 97th centiles and in cases with unknown cause, antenatal hemorrhage, or maternal hypertensive disease. In cases of maternal diseases, including diabetes, the stillbirth rate was lowest in fetuses with a weight around the 20th centile. In the most recent study from The Netherlands, distribution of perinatal mortality according to birth weight centile and gestational age was studied in more than 1 million births from singleton pregnancies and non-malformed fetuses between 28 and 43 weeks gestation [11]. There were 5,075 (0.43%) perinatal deaths. The highest mortality occurred in infants with a birth weight below the 2.3rd centile (25.4/1,000 births), and the lowest mortality occurred in infants with birth weights between the 80th and 84th centiles (2.4/1,000 births), according to nationwide birth weight charts. Antenatal deaths were lowest with birth weights between the 90th and 95th centiles. Data were almost identical when analysis was restricted to infants born after 37 weeks or at 39–41 weeks only (Vasak et al.; Figure 1.1) [11]. In term gestations, 63% of perinatal deaths and 61% of antepartum deaths occurred in infants with a so-called normal weight between the 10th and 90th centiles. The majority of perinatal deaths occurred during the antepartum period (72%).

Data on cerebral palsy are also in line with the mortality figures; the lowest prevalence of cerebral palsy by Z-score of weight for gestation was found in infants with a Z-score of +1 [12].

These studies indicate that optimal fetal weight for intact perinatal survival occurs at a much higher

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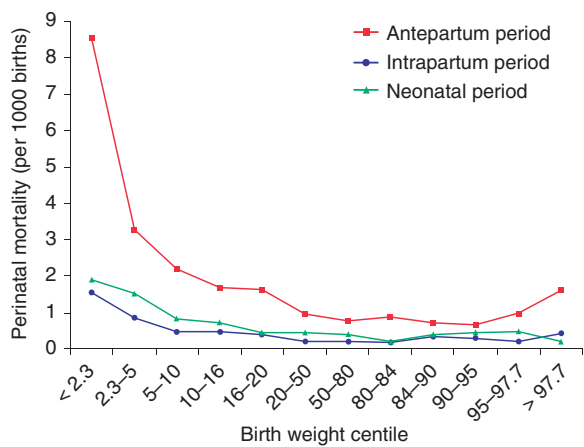


Figure 1.1 Perinatal mortality according to birth weight centile for babies delivered between 39 and 41 weeks' gestation in The Netherlands during 2002–8.

centile than the 50th centile. In fact, perinatal mortality of fetuses with a weight at the 50th centile is 34% higher than that of fetuses weighing in between the 80th and 84th centiles [11]. The lower “optimal weight” for intrapartum and neonatal survival (80th–84th centile), as compared to that of antepartum survival (90th–95th centile), may be explained by intrapartum complications in infants at the highest birth weight centiles. Regarding antepartum survival, it may be concluded that “the bigger the better” [8] and that most infants have a birth weight below optimal for perinatal survival, which seems illogical from an evolutionary perspective. However, mothers also have to survive, and the relatively small pelvis associated with bipedalism and the large human fetal head constitute major obstacles for uncomplicated childbirth. It may therefore well be that maternal factors restrain fetal growth that is below optimal for perinatal survival. In other words, a conflict takes place between mother and fetus, with a compromise as a result. Given the fact that during the whole existence of mankind women have looked after their offspring, such a compromise may have resulted in a net benefit for the infants at the end. In developing countries, this can nowadays still be seen in the poor survival of children whose mothers have died during or directly after childbirth [13,14]. These data also nicely fit with recent Doppler findings of blood flow redistribution to the fetal brain. In a large cohort of third trimester fetuses, it was shown that

the cerebro-placental ratio (CPR) increased progressively with increasing fetal weight centiles whereby signs of redistribution were only consistently absent in cases of an estimated fetal weight > 90th centile [15]. The association between CPR and weight centiles has recently been confirmed in another study [16].

Fetal Growth and Long-Term Survival

The high birth weight (centile) favorable for perinatal survival is also associated with reduced risk of later non-communicable disease. Studies on the Developmental Origins of Health and Disease (DOHaD) concept have shown that birth weight is inversely related in a graded manner to risk of later cardiovascular and cerebrovascular death [17–20] and to impaired glucose tolerance and Type 2 diabetes [21]. Thus, in historical studies in the UK, the lowest risks of adult cardiovascular disease (CVD) were found in infants weighing around 4 kg at birth, approximately the 90th centile at 40 weeks of gestation [17,19]. A high birth weight, indicative of absence of intrauterine growth restraint and resulting in a low perinatal mortality, therefore is also favorable for long-term health.

Clinical Implications

Early stillbirths are generally SGA [3]. So at early gestation, identification of SGA fetuses remains of utmost importance. After approximately 32 weeks of gestation, the majority of stillbirths concerns appropriate for gestation infants [3,11]. Identification of third trimester (SGA) infants remains important since mortality may be reduced when these fetuses have been identified as being small [22,23] (see Chapters 22 and 23 of this volume). However, identification of infants at risk of stillbirth who have a weight within the normal range may prove difficult. Factors to be assessed may include:

- a) Maternal characteristics. In a study from Norway, it has been shown that being SGA increases the risk for stillbirth sevenfold [24]. Other independent risk factors for stillbirth were maternal age > 35 years (RR 4.1), maternal body mass index > 25 (RR 4.7), and maternal education < 10 years (RR 3.5). A combination of risk factors resulted in a dramatic increase in stillbirth risk. For instance, SGA in combination

with maternal overweight resulted in an RR of 71 (univariate analysis). Confidence limits were large due to the relatively low number of inclusions (95% CI: 14–350), but these data indicate that a combination of risk factors may increase detection of fetuses at risk. Such a risk assessment might be made around 36–8 weeks, and if more than one of these variables is abnormal, delivery may be indicated. However, the latter policy has to be tested, preferably in a randomized controlled study.

- b) Uterine artery pulsatility index (UtA-PI). An increased UtA-PI at 20 weeks of gestation has been found to be associated with an Odds ratio of 6.8 for third trimester stillbirth, after correction for maternal weight, body mass index, and smoking, with 50% of all stillbirth cases occurring in the 10% with an abnormal UtA-PI [25].
- c) Cerebro-placental ratio (CPR). In preterm SGA fetuses, an increased PI in the umbilical artery identifies those at highest risk for perinatal death [26]. However, near term the diagnostic value of this tool is limited and significant changes are a late sign of impairment. However, subtle changes may be detected by using the ratio between middle cerebral artery and umbilical artery PI. In SGA term fetuses, it was found that a reduced CPR was associated with a poorer outcome than in cases with a normal ratio [27]. In a high-risk population of term fetuses, pH at delivery was lower in cases with an abnormal CPR, both in SGA and in normally grown fetuses [28]. This suggests that the CPR might be used to identify fetuses at risk of becoming hypoxemic, not only in SGA, but also in fetuses with a weight within the “normal” range. However, in a recent normal population of more than 6,000 fetuses assessed at around 36 weeks of gestation, no predictive value of the CPR was found regarding caesarean section for fetal distress, umbilical artery pH at birth, or Apgar score [16]. Reduced CPR immediately prior to delivery was associated with an increased risk of delivery by emergency caesarean section [29]. The value of the CPR in identifying the risks of intrauterine death or asphyxia in normally grown fetuses is therefore still uncertain.
- d) Longitudinal fetal growth assessment. Single third trimester measurements of fetal growth have not

- been capable of identifying third trimester SGA reliably [30]. Detection of infants at risk with a weight within the normal range may only be possible by longitudinal growth assessment to identify decreasing growth velocity. Such studies are taking place at this moment.
- e) Reduced fetal movements (RFM). RFM remain an important sign of fetal compromise, given the limited predictive values of the other assessment techniques. RFM have been associated with abnormal placental morphology [31]. A study from Norway has shown that structured information given to the mother at around 18 weeks of gestation on the importance of RFM may result in a more than 50% reduction of third trimester fetal deaths in nulliparous women [32].
 - f) Integrated risk assessment. Identification of fetuses at risk for intrauterine death is difficult. On the one hand SGA fetuses should be detected, and on the other hand the larger group of apparently normally grown fetuses at risk of dying in utero should be identified. This will require integrated risk models, including maternal characteristics (BMI, age, socioeconomic situation), Doppler measurements of the maternal and feto-placental circulation, fetal growth assessment, and measurement of biochemical markers of placental function. Most likely a contingent screening is required (e.g., to identify decreasing fetal growth velocity). Models must be first exhaustively tested in the population to which they will be applied, to obviate the risk of unnecessary intervention.

Conclusions

Optimal fetal growth for perinatal and long-term survival is a growth resulting in a birth weight in between the 80th and 90th centiles. This implies that the majority of infants will have a suboptimal fetal growth. Evolutionarily, this may be explained by a compromise between maternal survival, which will be lower in large fetuses, and fetal survival. In the third trimester of pregnancy, the majority of intrauterine deaths occurs in fetuses with a weight within the normal range. Identification of the fetuses at risk will be difficult and requires an integrated risk assessment including sequential measurements.

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Key Points

- The majority of perinatal deaths occurs in fetuses with a weight within the normal range.
- Optimal fetal growth for perinatal and long-term survival is a growth resulting in a birth weight in between the 80th and 90th centiles.
- Identification of fetuses at risk, especially those with a weight within the normal range, remains difficult and requires an integrated risk assessment including sequential measurements.

References

1. Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. *Lancet* 1992; 339(8788):283–7.
2. Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. *Am J Obstet Gynecol* 2012;207(4):318.e1, 318.e6.
3. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: Population based study. *BMJ* 2013;346:f108.
4. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. *N Engl J Med* 1999;340(16):1234–8.
5. Henriksen T. The macrosomic fetus: A challenge in current obstetrics. *Acta Obstet Gynecol Scand* 2008;87(2):134–45.
6. Zhang X, Decker A, Platt RW, Kramer MS. How big is too big? The perinatal consequences of fetal macrosomia. *Am J Obstet Gynecol* 2008;198(5):517.e1, 517.e6.
7. Glinianaia SV, Rankin J, Pearce MS, Parker L, Pless-Mulloli T. Stillbirth and infant mortality in singletons by cause of death, birthweight, gestational age and birthweight-for-gestation, Newcastle upon Tyne 1961–2000. *Paediatr Perinat Epidemiol* 2010;24(4):331–42.
8. Vangen S, Stoltenberg C, Skjaerven R, Magnus P, Harris JR, Stray-Pedersen B. The heavier the better? Birthweight and perinatal mortality in different ethnic groups. *Int J Epidemiol* 2002;31(3):654–60.
9. Francis JH, Permezel M, Davey MA. Perinatal mortality by birthweight centile. *Aust N Z J Obstet Gynaecol* 2014;54(4):354–9.
10. Moraitis AA, Wood AM, Fleming M, Smith GC. Birth weight percentile and the risk of term perinatal death. *Obstet Gynecol* 2014;124(2 Pt 1):274–83.
11. Vasak B, Koenen SV, Koster MP, Hukkelhoven CW, Franx A, Hanson MA, Visser GH. Human fetal growth is constrained below optimal for perinatal survival. *Ultrasound Obstet Gynecol* 2015;45(2):162–7.
12. Jarvis S, Glinianaia SV, Torrioli MG, et al. Cerebral palsy and intrauterine growth in single births: European collaborative study. *Lancet* 2003;362(9390):1106–11.
13. Houle B, Clark SJ, Kahn K, Tollman S, Yamin A. The impacts of maternal mortality and cause of death on children's risk of dying in rural South Africa: Evidence from a population based surveillance study (1992–2013). *Reprod Health* 2015;12 Suppl 1:S7,4755-12-S1-S7. Epub 2015 May 6.
14. Moucheraud C, Worku A, Molla M, Finlay JE, Leaning J, Yamin A. Consequences of maternal mortality on infant and child survival: A 25-year longitudinal analysis in Butajira Ethiopia (1987–2011). *Reprod Health* 2015;12 Suppl 1:S4,4755-12-S1-S4. Epub 2015 May 6.
15. Morales-Rosello J, Khalil A, Morlando M, Papageorgiou A, Bhide A, Thilaganathan B. Changes in fetal Doppler indices as a marker of failure to reach growth potential at term. *Ultrasound Obstet Gynecol* 2014;43(3):303–10.
16. Akolekar R, Syngelaki A, Gallo DM, Poon LC, Nicolaides KH. Umbilical and fetal middle cerebral artery Doppler at 35–37 weeks' gestation in the prediction of adverse perinatal outcome. *Ultrasound Obstet Gynecol* 2015;46(1):82–92.
17. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989;2(8663):577–80.
18. Barker DJ. Fetal origins of coronary heart disease. *BMJ* 1995;311(6998):171–4.
19. Lawlor DA, Ronalds G, Clark H, Smith GD, Leon DA. Birth weight is inversely associated with incident coronary heart disease and stroke among individuals born in the 1950s: Findings from the Aberdeen Children of the 1950s prospective cohort study. *Circulation* 2005;112(10):1414–18.
20. Osmond C, Kajantie E, Forsen TJ, Eriksson JG, Barker DJ. Infant growth and stroke in adult life: The Helsinki birth cohort study. *Stroke* 2007;38(2):264–70.
21. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991;303(6809):1019–22.
22. Gardosi J, Francis A. Adverse pregnancy outcome and association with small for gestational age birthweight by customized and population-based percentiles. *Am J Obstet Gynecol* 2009;201(1):28.e1,28.e8.

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23. Boers KE, Vijgen SM, Bijlenga D, et al. Induction versus expectant monitoring for intrauterine growth restriction at term: Randomised equivalence trial (DIGITAT). *BMJ* 2010;341:c7087. doi:10.1136/bmj.c7087.
24. Froen JF, Gardosi JO, Thurmann A, Francis A, Stray-Pedersen B. Restricted fetal growth in sudden intrauterine unexplained death. *Acta Obstet Gynecol Scand* 2004;83(9):801–7.
25. Singh T, Leslie K, Bhide A, D'Antonio F, Thilaganathan B. Role of second-trimester uterine artery Doppler in assessing stillbirth risk. *Obstet Gynecol* 2012;119(2 Pt 1):256–61.
26. Alfirevic Z, Stampalija T, Gyte GM. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev* 2013; 11:CD007529.
27. Cruz-Martinez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. *Obstet Gynecol* 2011;117(3):618–26.
28. Morales-Rosello J, Khalil A, Morlando M, Bhide A, Papageorghiou A, Thilaganathan B. Poor neonatal acid-base status in term fetuses with low cerebroplacental ratio. *Ultrasound Obstet Gynecol* 2015;45(2):156–61.
29. Prior T, Mullins E, Bennett P, Kumar S. Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: A prospective observational study. *Am J Obstet Gynecol* 2013;208(2):124.e1,124.e6.
30. Bricker L, Medley N, Pratt JJ. Routine ultrasound in late pregnancy (after 24 weeks' gestation). *Cochrane Database Syst Rev* 2015;6:CD001451.
31. Warrander LK, Batra G, Bernatavicius G, et al. Maternal perception of reduced fetal movements is associated with altered placental structure and function. *PLoS One* 2012;7(4):e34851.
32. Saastad E, Tveit JV, Flenady V, Stray-Pedersen B, Fretts RC, Bordahl PE, Froen JF. Implementation of uniform information on fetal movement in a Norwegian population reduced delayed reporting of decreased fetal movement and stillbirths in primiparous women – a clinical quality improvement. *BMC Res Notes* 2010;3(1):2. doi: 10.1186/1756-0500-3-2.