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Twin-Specific Intrauterine 'Growth' Charts Based on Cross-Sectional Birthweight Data

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The assessment of fetal growth is an essential component of good antenatal care, especially for twins. The aims of this study are to develop twin-specific intrauterine 'growth' charts, based on cross-sectional birthweight data, for monochorionic and dichorionic twins according to sex and parity, and to detect twins at risk for neonatal death by comparing the use of twin-specific and singleton charts. The study sample consisted of 76,471 singletons and 8454 twins (4227 pairs) born in East Flanders (Belgium). Birthweights were analyzed using a nonlinear Gaussian regression. After 33 weeks of gestation, the birthweights of twins started to deviate from singletons (difference of 900 grams at 42 weeks). Birthweights of dichorionic twins continued to increase, whereas those of monochorionic twins decreased after week 40 (difference of more than 300 g at 42 weeks). After 31 weeks of gestation, neonatal mortality increased as centile decreased, and was especially high if birthweight was below the twin-specific third centile: .032 (below) versus .007 (above). Using singleton centiles, this was less obvious. In conclusion, twin-specific growth charts, taking chorionicity into account, are more accurate to detect twins at risk for neonatal death. Therefore the presented charts, based on cross-sectional birthweight data, enable an improved assessment of twin growth.

Twin pregnancies carry a high risk with increased perinatal mortality rates compared to singleton pregnancies (Crosignani & Rubin, 2000). In the United States of America, 2.6% of all births are multiples and these pregnancies account for 20% of all low birthweights, for 13% of all preterm deliveries and for 14% of all neonatal deaths (Alexander et al., 1998). Interestingly, twins also have lower mortality rates than singletons of similar weight even after adjusting for gestational age (Kleinman et al., 1991). This suggests that optimal intrauterine growth and development is achieved earlier in gestation for twins than for singletons (Luke et al., 1993; Soucie et al., 2006), presumably because intrauterine growth of twins differs from singletons. The assessment of fetal growth is an essential component of good antenatal care (Gardosi, 2005a). Growth is a dynamic process and can only be evaluated over time (Owen et al., 2001). However, in the absence of serial ultrasound measurements, clinicians often use standards based on cross-sectional birthweight data and use these so called 'growth' charts to differentiate between the small and appropriate for gestational age (SGA and AGA) neonates (Blickstein, 2005).

Gardosi advocates that individualized growth charts are preferable above population-based growth charts, because being SGA can also be a sign of heredity, rather than pathological factors. Pathological factors give rise to intrauterine growth retardation (IUGR; Gardosi, 2005a; Gardosi et al., 1995; Mongelli & Gardosi, 1995), whereas constitutional factors do not. Previous literature has shown that the intrauterine growth in twins deviates from the growth of singletons after 29 weeks of gestation (Alexander et al., 1998; Loos et al., 2005; Luke et al., 1991). Consequently, twin-specific fetal growth curves are important for developing criteria for intrauterine growth retardation and managing high risk situations (Alexander et al., 1998).

Current literature of the intrauterine growth curves of twins only takes one or two factors into

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account: sex and parity (Liu & Blair, 2002), sex and ethnicity (Min et al., 2000), or chorionicity (Min et al., 2000; Senoo et al., 2000). A further step in the development of twin-specific growth curves for twins would be to combine these factors. The data of live-born twins from the East Flanders Prospective Twin Survey (EFPTS; Belgium) provides the opportunity to examine the contribution of chorionicity on the birthweight of twins of Caucasian descent in addition to sex and parity. Furthermore, the EFPTS provides information about survival in the neonatal period, and, therefore, offers the possibility to investigate whether neonatal survival can be predicted by the prenatal growth pattern.

The aims of this study are (1) to present birthweights of twins in comparison to singletons, (2) to estimate intrauterine growth and to develop twin-specific 'growth' charts for monochorionic (MC) and dichorionic (DC) twins according to sex and parity by using cross-sectional birthweight data, and (3) to detect twins at risk for neonatal death by comparing these twin-specific 'growth' charts with singleton 'growth' charts.

Materials and Methods

Twins

The study sample consisted of live-born twin pairs selected from the EFPTS, Belgium (Loos et al., 1998). Between July 1964 and the end of December 2002, the EFPTS registered 6315 twin pairs who met the World Health Organization criteria for live-born infants (birthweight 500 grams or greater or gestational age 22 weeks or greater, if birthweight unknown).

Methods of data collection have previously been described in detail (Gielen et al. 2006, 2007; Loos et al., 1998, 2005). Briefly, a defined set of obstetric and perinatal data (including parity and neonatal survival) were recorded. Placentas were examined within 48 hours after delivery according to a standardized protocol (Derom et al., 1995). Gestational age was reported by the obstetrician, based on the last menstruation or a first trimester ultrasound investigation, and was calculated as the number of completed weeks of pregnancy. Zygosity was determined through sequential analysis based on sex, fetal membranes (chorionicity), umbilical cord blood groups, placental alkaline phosphatase, and, since 1982, DNA fingerprints (Decorte et al., 1990; Vlietinck, 1986). Due to financial stringency, however, DNA fingerprints could not be determined systematically on all twin pairs. Therefore, in this study, only same-sex DC twins with the same markers, reaching a probability of .95 or more, were considered monozygotic. The remaining same-sex DC twins were classified as 'unknown'. Since 1994 no placental examination took place for opposite-sex pairs (n = 917).

Twin pairs of whom one or both children were stillborn (205 pairs) or suffered from major congenital malformation (120 pairs) were excluded (Loos et al., 2001). Twin pairs with missing or inconsistent data (birthweight n = 42, gestational age n = 581, parity n = 47, chorionicity n = 71, mode of conception n = 37, neonatal survival n = 12, maternal age n = 54, placental type and weight n = 832; mainly opposite-sex pairs, or site of insertion of the umbilical cord n = 85; mainly opposite-sex pairs) were excluded (Gielen et al., 2007). Finally, 8454 twins (4227 pairs) were analyzed.

Singletons

Birthweights and gestational ages of singletons of the province of East Flanders (Belgium) were obtained from the Study Center for Perinatal Epidemiology (SPE; personal communication, 1998), a population-based registry. It encompasses all deliveries (birthweight of 500 grams or greater) occurring in this region, except for the very small number of deliveries at home (0.5% and less). Gestational age was calculated as the number of completed weeks of pregnancy. Data of 85,920 live-born singletons registered between 1 January 1993 and 31 December 1998 were available. After exclusion of children with malformations (n = 1181), unknown sex (n = 15), uncertain gestational age (n = 8), a gestational age below 25 weeks or above 42 weeks (n = 29), 76,471 singletons were analyzed.

Ethnicity

Information on ethnicity was obtained from the Study Center for Perinatal Epidemiology (SPE; personal communication, 2006). A vast majority (more than 99%) of the population of the province of East Flanders is of Caucasian origin. Since 1964 the prevalence of people of a foreign descent has increased. In the 2 most recent years of this study, 84.5% was of Belgian origin, 5% of Turkish, and 2.3% of Moroccan origin. The remaining 8.2% was of other origin (mainly Caucasians of Dutch, France and German origin) or unknown origin.

Definitions

Early neonatal death/mortality (abbreviated as neonatal death/mortality) was defined as death/mortality within the first 7 days of life. SGA was defined as less weight than the 10th centile (P10) using the data of the singletons of East Flanders as reference. Preterm delivery was defined as a delivery before the 37th week of gestation, and very preterm delivery as before the 32nd week. Low birthweight (LBW) was defined as birthweight less than 2500 grams; very low birthweight (VLBW) as less than 1500 grams. Discordancy was defined as a birthweight difference of more than 25%, (highest weight–lowest weight)/highest weight.

Statistical Analysis

The contingency χ^2 test was used for comparisons of categorical data. To compare two groups an F test followed by the appropriate t test was used for continuous data and a contingency χ^2 test was used for comparisons of frequencies. Odds ratios and 95% confidence intervals (CI) were calculated to estimate the association between discordancy and neonatal death.

The use of ultrasound to determine gestational age was only available during the second half of this study. Because gestational age based on the last menstruation gives an overestimation as compared to ultrasound investigation (Gardosi, 2005b), we controlled for the mixture of reported gestational ages by year of birth, since this information was available for all twins. For the present study, the year 2002 was used in the presented curves.

The birthweights of pregnancies of different gestational ages were analyzed using a nonlinear Gaussian regression (logistic growth curve). Furthermore, as twins within a pair are more alike than twins between pairs, a random effect was added to the model. Twin-specific and singleton centiles were used to calculate neonatal mortality rates. For detailed information, see the Appendix. The analyses were conducted with the SAS version 8.2 computer package (SAS Institute Inc., Cary, NC, USA) and R (Ihaka & Gentleman, 1996) version 2.0.1 using the growth library (Lindsey, 2001). All reported p values are two-sided and were considered statistically significant when $p \leq .05$.

Results

Birthweights of Twins in Comparison to Singletons

As expected, mean birthweight and gestational age were significantly lower and the frequencies of LBW, VLBW, preterm birth and very preterm birth were significantly higher in twins than in singletons. Additionally, SGA occurred 3.6 times more often in twins. However, when born before 32 weeks of gestation, the prevalence of SGA, LBW and VLBW was equal for both twins and singletons (Table 1).

The birthweight curves of twins and singletons are shown in Figure 1. The curves follow the actual means of individual birthweights per gestational age. The weight of singletons increases up to 42 weeks, whereas the curve of twins shows a dip after 40 weeks of gestation, which is mainly due to the contribution of MC twins (see below). Up to 33 weeks of gestation, the means of twins and singletons are comparable, but the variance of twins is smaller than that of singletons. For both singletons and twins, the maximum weight gain in this period was at 32 weeks of gestation and is about the same (respectively 172 grams/week and 175 grams/week).

Table 1

Characteristics of Live Born singletons and Live Born Twins With No Major Congenital Malformation

	Singletons	All twins	MC twins	DC twins
	n = 76,471	*n* = 8454 (4227 pairs)	*n* = 2144 (1072 pairs)	*n* = 6310 (3155 pairs)
Mean (*SD*)				
Birthweight (grams)	3337 (494)	2462 (536)***	2397 (537)	2484 (534)***
Gestational age (weeks)	39.0 (1.5)	36.4 (2.7) ***	36.4 (2.8)	36.5 (2.6)
Frequencies (%)				
Parity: Primipara	36,272 (47.4%)	4100 (48.5%)	982 (45.8%)	3124 (49.4%)**
Sex: Male	39,009 (51.0%)	4266 (50.5%)	1056 (49.3%)	3216 (50.9%)
Preterm < 37 weeks	3641 (4.8%)	3712 (43.1%)***	960 (44.8%)	2756 (43.6%)
Very preterm < 32 weeks	292 (0.4%)	428 (5.1) ***	130 (6.1%)	298 (4.7) **
SGA	7359 (9.6%)	2937 (34.7%)***	844 (39.4%)	2096 (33.2%)***
≥ 37 weeks	7017 (9.6%)	2294 (48.4%)***	655 (55.3%)	1642 (46.1%)***
< 37 weeks	343 (9.4%)	643 (17.3%)***	189 (19.7%)	454 (16.5%)*
< 32 weeks	26 (8.9%)	39 (9.1%)	10 (7.7%)	29 (9.7%)
LBW < 2500 grams	3148 (4.1%)	4123 (48.8%)***	1143 (53.3%)	2983 (47.2%)***
≥ 37 weeks	1554 (2.3%)	1361 (28.7%)***	398 (33.6%)	963 (27.0%)***
< 37 weeks	1594 (43.8%)	2762 (74.4%)***	745 (77.6%)	2020 (73.3%)**
< 32 weeks	286 (98.0%)	426 (100 %)*	130 (100%)	296 (99.3 %)
VLBW < 1500 grams	301 (0.4%)	421 (5.0%)***	133 (6.2%)	289 (4.6%)**
≥ 37 weeks	10 (0.0%)	15 (0.3%)***	7 (0.6%)	8 (0.2%)*
< 37 weeks	291 (8.0%)	406 (10.9%)***	126 (13.1%)	281 (10.2%)**
< 32 weeks	215 (73.6%)	305 (71.30%)	90 (69.2%)	215 (72.2%)
Discordant (> 25%)			109 (8.9%)	554 (8.8%)
≥ 37 weeks			94 (7.9%)	294 (8.2%)
< 37 weeks			96 (10%)	260 (9.4%)
< 32 weeks			14 (10.8%)	32 (10.7%)

Note: MC = monochorionic, DC = dichorionic, SGA = small for gestational age, (V)LBW = (very) low birthweight.
Comparison singletons — All twins and MC twins–DC twins; *t* test for continuous data, chi square for categorical data: ***< .0001, **< = .01,*< = .05.

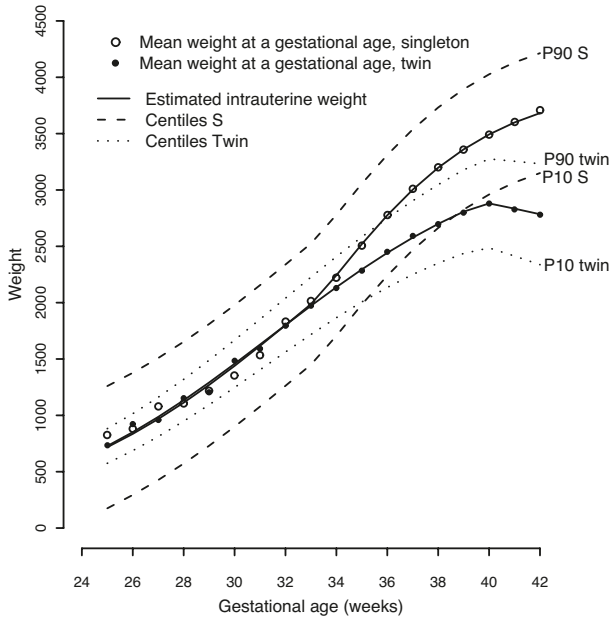

Figure 1

Growth curves of live-born singletons (n = 76,471) and live-born twins (n = 8454, 4227 pairs) based on birthweights.

Note: Legend: P90 = 90th centile, P10 = 10th centile, S = Singleton

After 33 weeks of gestation however, the curves deviate and the birthweights of twins are behind singletons with a maximum weight gain between 33 and 34 weeks: for singletons 280 grams/week, for twins only 170 grams/week. From 33 weeks up to 42 weeks, the birthweight of singletons increases up to 3685 grams, whereas for twins, weight increases up to 3071 grams at 40 weeks and then shows a dip resulting in a weight of 2785 grams (900 grams difference with singletons) at 42 weeks of gestation.

Intrauterine 'Growth' Charts, Based on Cross-Sectional Birthweight Data for MC and DC Twins by Sex and Parity

MC twins had lower birthweights than DC twins, despite the same mean gestational age. Furthermore, they showed more often SGA, LBW and VLBW, but not before 32 weeks of gestation. There was no difference in frequency of discordancy between MC and DC twins throughout gestation (Table 1).

In Figures 2 and 3 separate intrauterine 'growth' charts, based on cross-sectional birthweight data, for MC and DC twins according to sex and parity are presented. The growth pattern of MC twins differs from the growth pattern of DC twins. For DC twins birthweight increases until 42 weeks of gestation, whereas the curve for MC twins drops after 40 weeks. Up to 40 weeks of gestation the curve of MC is lower than the curve of the DC twins (from 47 grams at 25 weeks to a maximum of 70 grams at 32 weeks to 46 grams difference at 39 weeks). But, after 40 weeks the difference increases up to 333 grams at 42 weeks.

Males have higher birthweights than females and multiparity results in higher weight than primiparity. For females, the biggest difference between primipara and multipara is 145 grams at 32 weeks of gestation in advantage to multipara. The difference is 96 grams at 25 weeks and deceases to 91 grams at 42 weeks. For males the biggest difference between primipara and multipara is the same as for females, but one week earlier at 31 weeks. The difference at 25 and 42 weeks is of the same magnitude (25 weeks: 104 grams; 42 weeks: 83 grams). Finally, the largest difference between a female primipara and a male multipara is about 270 grams.

Can These Twin-Specific 'Growth' Charts Be Used to Detect Twins at Risk for Neonatal Death?

Twins who died neonatally had lower birthweights, shorter gestational ages and were more often discordant for birthweight than twins who survived. Furthermore, they were more often born preterm and very preterm, and had more often LBW or VLBW, whereas the overall prevalence of SGA was equal. Before 37 weeks, the prevalence of SGA was higher for twins who died neonatally. The prevalence of neonatal death was equal for MC and DC twins (Table 2). After 32 weeks of gestation, twins who were discordant for birthweight had a greater risk for neonatal death than twins who were not with odds ratios above 6, OR = 6.2, 95% C.I. 2.6–14.4, adjusted (32–37 weeks); OR = 16.9, 95% C.I. 2.8–102, adjusted (after 37 weeks; Table 3).

Figure 4 shows twin-specific curves for twins who survived and twins who died neonatally (presented curve is for a female DC twin of a primipara). Up to 31 weeks of gestation, the curves were the same, but from 31 weeks on the curve of twins who died neonatally deviated. In general, the twins with neonatal death crossed the twin-specific centiles one week earlier than the singleton centiles. The twins with neonatal death crossed the centiles in the following order: first, the twin-specific P10, then the singleton P10, followed immediate by the twin-specific 3rd centile (P3), and 1 week later the singleton P3.

In general, one would expect that the shorter the gestational age or the lower the birthweight centiles, the higher the neonatal mortality rate would be. In Figure 5 we show neonatal mortality rates according to gestational age and both twin-specific and singleton centiles, the former derived from the charts shown in Figure 2 and 3. Between 25 and 32 weeks, the overall mortality rate was 0.26 and not associated with birthweight centiles (data not shown). After 32 weeks the overall neonatal mortality rate was below 0.01 and it is clear that there was a closer relationship between neonatal mortality and twin-specific birthweight centiles rather than singleton centiles. Neonatal mortality increased as centile decreased, and was especially high if birthweight was below the twin-specific P3 (below P3 0.032 vs. above P3 < 0.007; Figure 5). After 37 weeks of gestation, twins with weights below the twin-specific P10, but especially those below the twin-specific P3 centile had higher mortality rates (Figure 5).

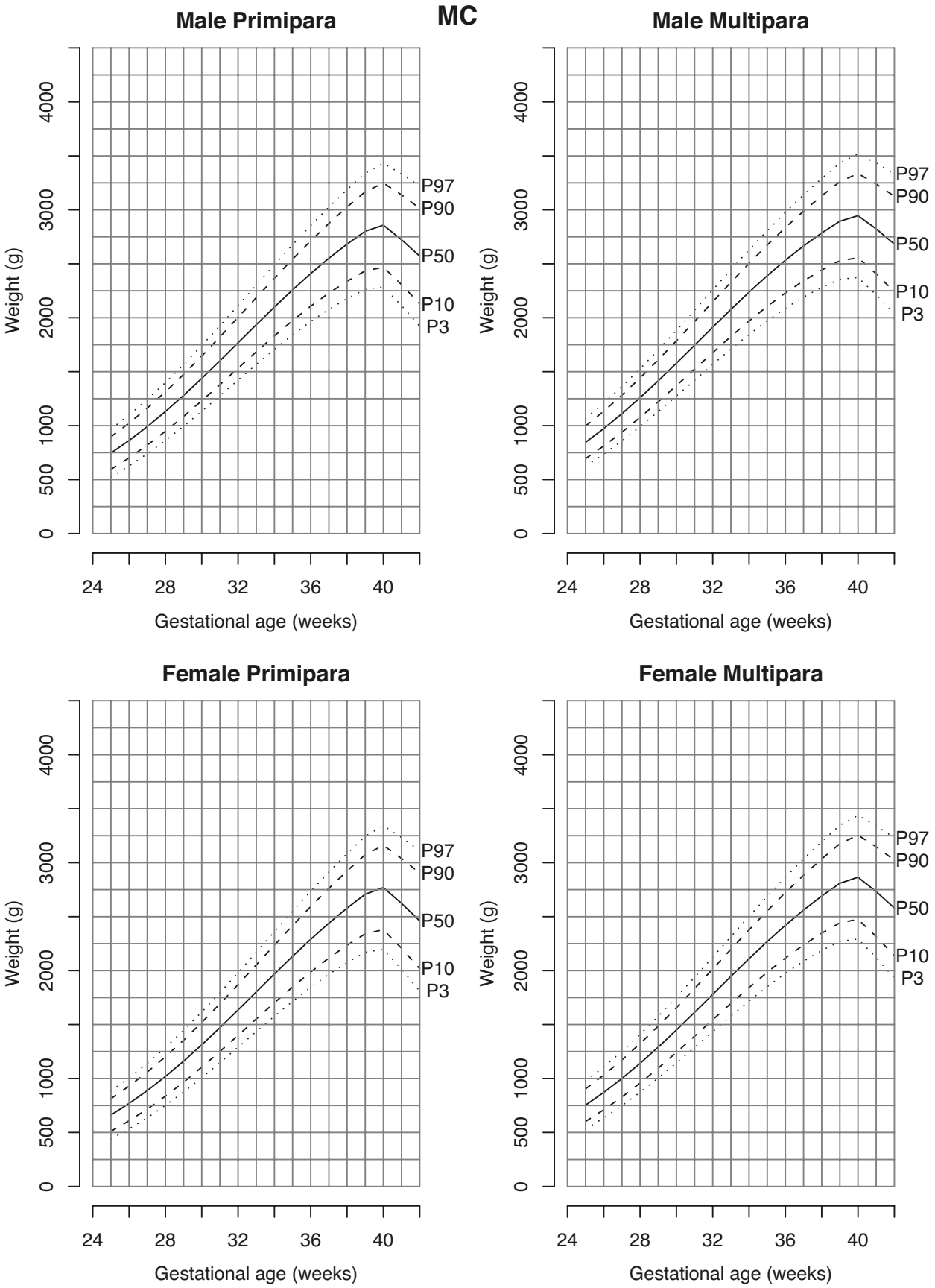

Figure 2

Intrauterine growth charts of live-born MC twins based on birthweights.

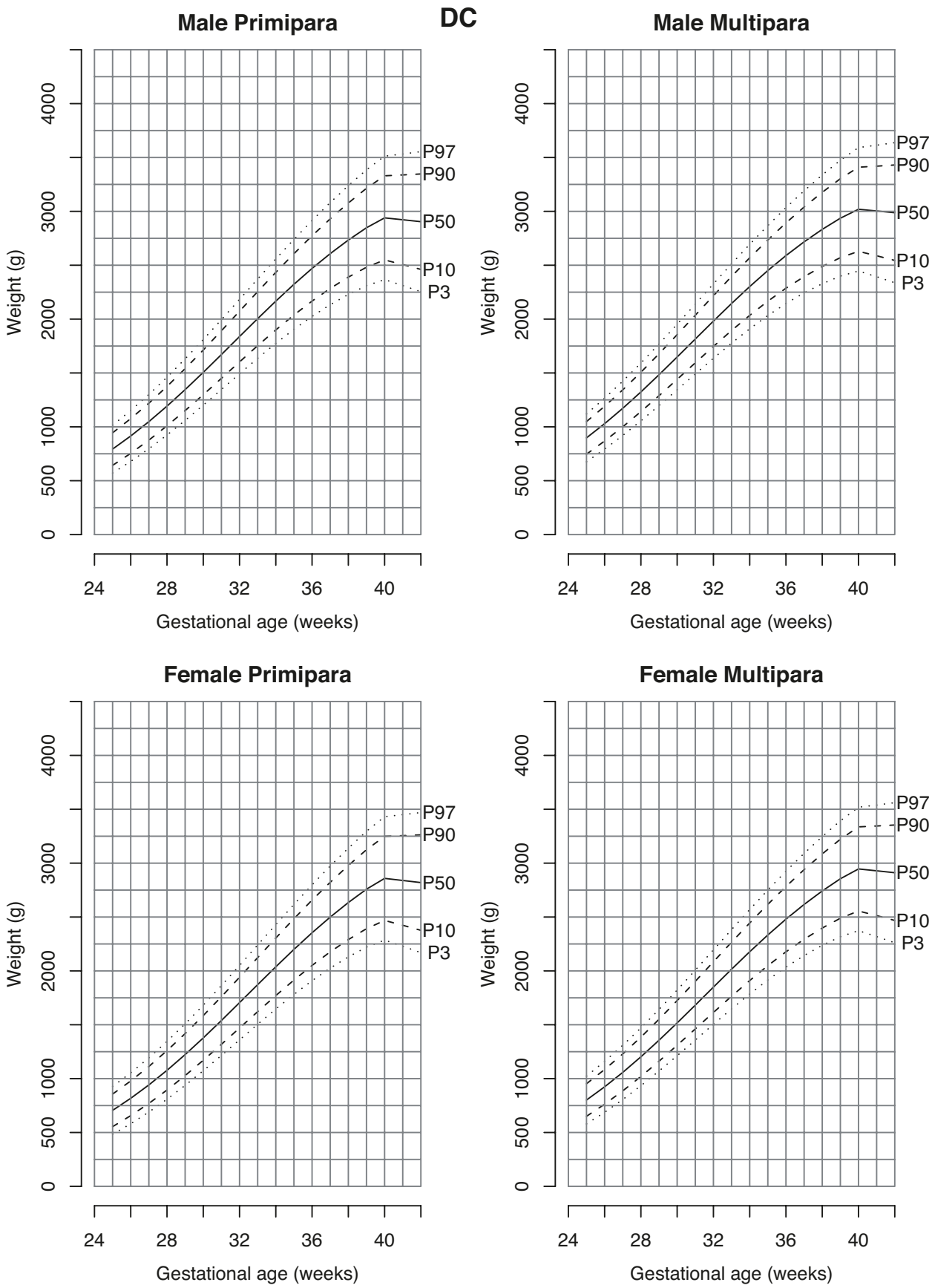

Figure 3

Intrauterine growth charts of live-born DC twins based on birthweights.

Table 2

Characteristics of Live Born Twins With No Major Congenital Malformation According to Neonatal Survival

	Staying alive (*n* = 8319)	Neonatal death (*n* = 145)
Mean (*SD*)		
Birthweight (grams)	2484 (508)	1174 (535)***
Gestational age (weeks)	36.6 (2.5)	28.8 (3.7)***
Frequencies (%)		
Parity: Primiparity	4030 (48.4%)	76 (52.4%)
Sex: Male	4198 (50.5%)	74 (51.0%)
Mode of conception:		
Naturally conceived	6429 (77.3%)	121 (83.5%)
Ovulation stimulation	1008 (12.1%)	14 (9.7%)
In vitro fertilization including ICSI	882 (10.6%)	10 (6.9%)
Monochorionic (MC)	2099 (25.2%)	45 (31.0 %)
≥ 37 weeks	1184 (25.0%)	0 (0%)
≥ 32–37 weeks	820 (25.1%)	10 (38.5%)
< 32 weeks	95 (30.1%)	35 (31.2%)
Preterm < 37 weeks	3578 (43.0%)	138 (95.2%)***
Very preterm < 32 weeks	316 (3.8%)	112 (77.2%)***
SGA	2897 (34.8%)	42 (29.0%)
≥ 37 weeks	2291 (48.3%)	6 (85.7%)*
≥ 32–37 weeks	594 (18.2%)	10 (38.5%)**
< 32 weeks	12 (3.8%)	26 (23.2%)***
LBW	3986 (47.9%)	140 (96.6%)***
VLBW	315 (3.8%)	107 (73.8%)***
Discordant (> 25%)	724 (8.7%)	20 (13.8%)*
≥ 37 weeks	384 (8.1%)	4 (57.1%)*** $
≥ 32–37 weeks	301 (9.2%) MC: 77	9 (34.6%)*** MC: 5***
< 32 weeks	39 (12.3%)	7 (6.3%)$

Note: ICSI = intracytoplasmic sperm injection, SGA = small for gestational age, (V)LBW = (very) low birth weight, $ = only DC twins
t test for continuous data, chi square for categorical data: *** < .0001, ** < = .01,* < = .05

Table 3

Odds Ratios (OR) for Neonatal Death According to Discordancy

Gestational age	OR neonatal death (95% CI) unadjusteds	OR neonatal death (95% CI) Adjusted
All	1.7 (1.06–2.76)	2.37 (1.26–4.45)
≥ 37 weeks	16.73 (2.77–101.06)	16.87 (2.79–102.03)
≥ 32–37 weeks	5.39 (2.37–12.24)	6.17 (2.64–14.43)
< 32 weeks	0.62 (0.26–1.47)	0.50 (0.18–1.40)

Note: Concordancy is reference
Unadjusted = controlled for birth year
Adjusted = controlled for birth year and gestational age; chorionicity was *NS*.

Discussion

This study confirms that growth of twins differs from growth of singletons after 33 weeks of gestation and that birthweights of MC twins differ from birthweights of DC twins, especially after 40 weeks, when mean birthweights falls in MC twins. Therefore separate intrauterine growth charts for MC and DC twins according to sex and parity are presented. Finally, after 32 weeks of gestation, intrauterine growth retardation is not influenced by chorionicity, but twins who died neonatally were more often discordant than twins who survived. Intrauterine growth retardation is an important risk factor for neonatal death. The use of twin-specific centiles may improve the prenatal detection of twins at risk for neonatal death. Neonatal mortality rates are more strongly correlated with twin-specific centiles than with singleton centiles.

As reported before (Alexander et al., 1998; Kleinman et al., 1991; Loos et al., 2005; Luke et al., 1991, 1993), up to 32 weeks of gestation, twins and singletons did not differ according to birthweight and to the frequency of SGA, LBW and VLBW. However, after 33 weeks the weight of twins trailed that of singletons and the curves deviated, implicating that IUGR occurs more frequently in twins after 33 weeks of gestation. Most likely, the leading cause of growth retardation is twinning itself, which can be seen as an adaptation to the fact that two fetuses have to share one uterus. This physiological growth restriction (Blickstein, 2002) might have other outcomes to that

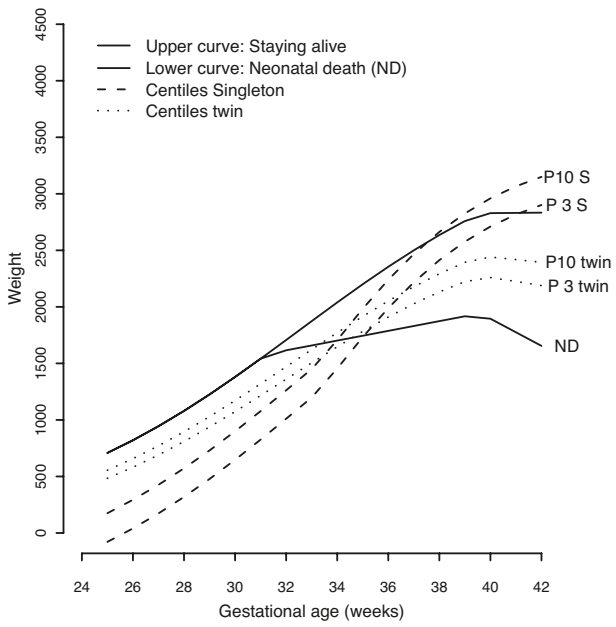

Figure 4

Curves of live-born twins according to neonatal survival based on birthweights.

Note: Legend: P10/P3 twin = 10th/ 3rd twin-specific centile for a dichorionic female twin of primipara, with no neonatal death
P10/P3 S = 10th/ 3rd centile of singletons.

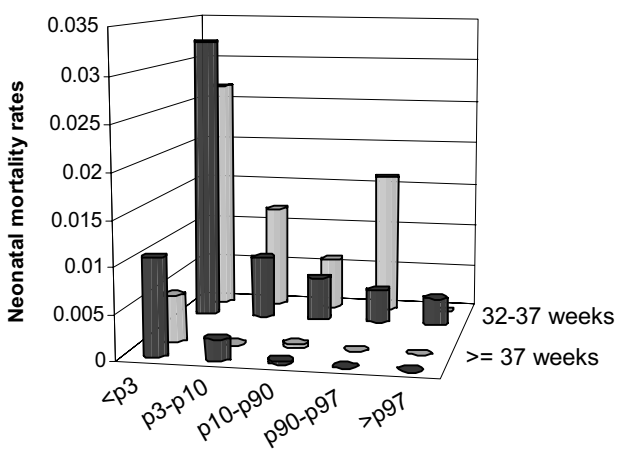

Figure 5

Neonatal twin mortality rates based on twin-specific and singleton centiles.

Note: Mortality rates based on singleton centiles.
Mortality rates based on twin-specific centiles.

of singletons, since twins have a survival advantage as compared to singletons of the same weight, indicating that singletons are not the most accurate reference group (Kleinman et al., 1991). We conclude that growth charts for singletons are not appropriate for twins, and that twin-specific growth charts for twins are needed.

Suboptimal growth (Kleinman et al., 1991; Lubchenco et al., 1963) can be reflected in a lower mean weight and a larger variance at a given gestational age (Hadlock et al., 1985). The fact that the twin population differs from the singleton population can be derived from Figure 1, in which twin birthweights have smaller variances as compared to singletons, which is most obvious before 33 weeks. We speculate that the twin population is more homogeneous with, in general, healthy twins being born after a shorter gestational age (36.4 weeks) and 43.1% preterm births (Table 1). Therefore preterm birth in twins is often seen as a physiological phenomenon (Blickstein, 2005). In the case of singletons, preterm birth would more likely be due to pathological factors (placental dysfunction, maternal hypertension, pre-eclampsia) resulting in larger variances (Hadlock et al., 1985).

Although the variance of twin birthweights is smaller than that of singletons, this does not exclude that prematurity in twins could still be related to suboptimal growth (Kleinman et al., 1991; Lubchenco et al., 1963). There is only one large twin study based on longitudinal sonografic measurements (Min et al., 2000) and neither our mean weight nor variance differed significantly from their findings. This means that for twins, it is appropriate to use birthweights to estimate growth as we did in this study and that our results are not biased by prematurity.

We could not confirm that twins diverge from singletons even before 32 weeks (Alexander et al., 1998). If it is true that suboptimal (pathological) growth leads to preterm birth and to lower mean weights, this will mainly affect the singletons. The singleton weights in this cross-sectional study could therefore be an underestimation of the actual weight of fetuses in ongoing pregnancies with at-term deliveries. Therefore, it is possible that for this study also, the population growth of twins deviates before the 32nd week of gestation.

DC twins are heavier than MC twins. After 40 weeks of gestation, the difference increases (Gielen et al., 2007; Loos et al., 2005). Since chorionicity can easily be determined during a first trimester ultrasound, it can be incorporated in predicting the estimated growth of the twin. Therefore the presented charts (Figure 2: MC twins; Figure 3: DC twins) provide an improved assessment of the growth of an individual twin. MC twins have one placenta and more often a peripheral insertion of the umbilical cord insertion and therefore lower birthweights, implying that these physiological factors determine part of the weight of the twin (Gielen et al., 2007). These placental factors contribute to a better distinction between physiological growth restriction and pathological growth restriction (Gielen et al., 2007). This observation may also have clinical consequences and could explain why MC twins could be at higher risk after 40 weeks of gestation.

The EFPTS records prospectively 98% of all twin births (Loos et al., 1998). Therefore, our sample size

reflects the total population of twins, and because of the large sample size (n = 8454), the variance is small. As a result, the curves and centiles are a very accurate reflection of the growth of twins in the province of East Flanders in Belgium. For the present study cross-sectional data of twin birthweights were analyzed. The strength is that we used actual weights and not estimated weights provided by ultrasound measurements. A disadvantage, however, is that the actual growth is not measured. One could argue that the lower weights of MC twins at the end of gestation (Gielen et al., 2007; Loos et al., 2005) are not due to a decline in weight, but rather to the fact that only relatively small MC twins, with lower growth trajectory, remain in utero beyond 40 weeks. However, DC twins do not show this pattern.

A weakness of the present study is that we could not use information about vascular anastomoses in MC twins, as a possible cause of discordant growth, however MC twins were not more often discordant than DC twins in this study. This could be due to the fact that only live-born twin pairs have been selected, and that therefore MC twin pairs with severe twin-twin transfusion (TTTS) have been excluded, Besides relatively infrequent causes as TTTS, the most common cause for discordant growth is the inability of the intrauterine environment to equally nurture twins (Blickstein & Keith, 2004).

Mode of conception influences the risk of preterm birth (Verstraelen et al., 2005), but not weight given a gestational time (Gielen et al., 2007). Therefore we did not perform different curves for twins who were naturally conceived and twins who were born after subfertility treatment. In general, a cesarean section will be more often performed for IUGR and will lead to a greater percentage of elective preterm deliveries. Former analyses have shown that mode of delivery (vaginal vs. cesarean section) was not associated with the weight of the twin (Gielen et al., 2007). Besides, the prevalence of cesarean sections was higher in twins who survived neonatally (data not shown). Unfortunately, it is not possible to make a further distinction between spontaneous and iatrogenic preterm deliveries.

Up to 32 weeks of gestation prematurity seems to be a more important risk factor for neonatal death than growth, since (1) the birthweight of twins who died neonatally did not differ from twins who survived and (2) mortality rates were not related to centiles. However after 32 weeks of gestation, data from this study suggest that it may be possible to identify twins at risk of neonatal death using twin-specific growth charts. Twins who are at risk for neonatal death are more often growth retarded and discordant, but not more often MC twins. Birthweight of twins who died neonatally crossed the twin-specific P10 one week before the singleton P10. Therefore these twin-specific centiles detect twins at risk earlier in gestation. Up to 37 weeks of gestation, the twin-specific P10 is above the singleton P3, and therefore more accurate to detect SGA. Twin-specific centiles may improve the prediction of SGA. Furthermore, the neonatal mortality rates based on the twin-specific centiles show a clear trend: twins with lower weights have a higher risk of neonatal death. Using singleton centiles, there is no clear trend between 32 and 37 weeks (Figure 5). This confirms that twins with growth restriction are at risk for neonatal death and that twin-specific centiles could provide a more accurate prediction of neonatal death than the mortality rates based on singleton centiles, especially between 32 and 37 weeks of gestation (Figure 5).

In conclusion, we have shown that the growth of twins differs from that of singletons after 32 weeks of gestation and is influenced by chorionicity, sex and parity. Furthermore, since growth of MC twins differs from that of DC twins, not only separate growth charts for twins are needed, but also twin-specific growth charts that take physiological factors like sex, parity and chorionicity into account. Finally, only prenatal growth retardation after 32 weeks of gestation can detect twins at risk for neonatal death. Besides birthweight discordancy, a weight below the twin-specific P10 is an additional risk factor that can predict neonatal death. Therefore the presented twin-specific charts enable an improved assessment of the intrauterine growth of an individual twin.

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Appendix A

The Construction of the Nonlinear Gaussian Regression of This Study

The birthweights of pregnancies of different gestational ages were analyzed using a nonlinear Gaussian regression. The intrauterine growth was best modeled by a logistic growth curve in which time of conception was chosen as time point zero.

Equation: b1/(1 + exp(b2-b3*GA)
in which b1 t/m b3 are the coefficients of the logistic growth curve and GA = gestational age.

Next, the logistic curve was modified to include a change of growth rate (Supplementary Table: Singletons).

Equation: b1/(1 + exp(b2-b3*GA + b3*b4*(GA > b5)*(GA–b5)

in which b4 is the change in growth rate after the time point described by coefficient b5.

For the intrauterine growth charts sex, parity, and chorionicity were entered in the model (Supplementary Table: Twins).

Equation: b1/(1 + exp(b2-b3*GA + b3*b4*(GA > b5)*(GA–b5) + b3*b6*(GA > b7)*(GA–b7)*MC – B*X))

in which b6 is the change in growth rate after the time point described by coefficient b7 for MC twins and where X represents the covariates (sex, parity, chorionicity, birth year) and B the corresponding coefficient.

To predict neonatal survival, information about neonatal death was additionally incorporated (Supplementary Table: Twins [ND included]).

Equation: b1/(1+exp(b2-b3*GA + b3*b4*(GA > b5)*(GA–b5) + b3*b6*(GA > b7)*(GA–b7) *MC + b8*b9*(GA > b9)*(GA-b9)*ND – B*X))

in which b8 and b9 are the coefficients for the twins who die neonatally and ND = neonatal death.

All estimated curves of birthweights of twins and singletons (Figure 1 t/m 4) are based on the estimates of the Supplementary Table. An example of how to use these estimates is shown below.

For both singletons and twins (Gielen et al., 2007) the variance was larger at the end of gestation than at 25 weeks. We therefore allowed the variance to change over time. The increase in variance was different for twins and singletons. For singletons the increase in variance was nonlinear, whereas for twins the variance increased linearly over time. Furthermore, as twins within a pair are more alike than twins between pairs, a random effect was added to the model. Models were compared with the Akaike information criterium (AIC; Akaike 1973). Centiles were computed for the estimated mean birthweight. More details can be found elsewhere (Gielen et al., 2006, 2007). These twin-specific and singleton centiles were used to calculate neonatal mortality rates. The analyses were conducted with the SAS version 8.2 computer package (SAS Institute Inc., Cary, NC, USA) and R (Ihaka & Gentleman, 1996) version 2.0.1 using the growth library (Lindsey, 2001). All reported p values are two-sided and were considered statistically significant when $p \leq .05$.

Example of How to Use the Estimates

For constructing the twin-specific growth charts (Figure 2 and 3), the information about neonatal death is not included in the model. Therefore the equation is:

b1/(1+exp(b2-b3*GA + b3*b4*(GA>b5)*(GA-b5) + b3*b6*(GA>b7)*(GA–b7)*MC - B*X)).

(GA > b5)*(GA-b5) indicates that if gestational age is above b5 then do: gestational age – b5.

If GA is equal or below b5, this becomes zero. In case of an MC twin also do this for b7.

For a male (sex=1) MC (MC=1) twin of a multipara (parity=1), born at 40 weeks of gestation (since conception GA= 38 weeks) in the year 2002 (corresponds to 38, because in 1964 it started at 0) the estimated weight will be:

3570.6647/(1 + exp(5.7879–0.1874*38 + 0.1874*1.0072*(38-37.623) + 0.1874*1.1784*(38-37.9111) – 0.1618 + 0.0784 – 0.1489 – 0.002*38)) = 2945.9077 grams.

Supplementary Table Appendix

Regression Coefficients of Best Fitting Non-Linear Multivariate Gaussian (Logistic) Regression Models for Weight

	Singletons		Twins		Twins (ND included)	
	Coefficient	SE	Coefficient	SE	Coefficient	SE
Coefficients of the logistic curve						
b1 = saturation level at which growth stops	3950.18	42.13	3570.50	67.40	3576.30	79.49
b2 = growth rate	5.87	0.43	5.79	0.16	5.77	0.18
b3 = location parameter	0.19	0.01	0.19	0.006	0.19	0.007
b4 = after inflection point b5						
increase in weight for singletons	–0.55	0.26				
decrease in weight for twins			1.01	0.32	0.98	0.34
b5 = inflection point	31.32	0.26	37.62	0.32	37.60	0.35
b6 = after inflection point b7						
decrease in weight for MC twins			1.18	0.52	1.19	0.53
b7 = inflection point for MC twins			37.91	0.39	37.90	0.39
b8 = after inflection point b9						
decrease in weight for ND					0.74	0.14
b9 = inflection point for ND					29.26	0.67
Covariates (X)						
Male			0.15	0.01	0.15	0.01
Multiparity			0.16	0.01	0.16	0.01
MC			–0.08	0.01	–0.08	0.01
Birth year (form 0 [1964] to 38 [2002])			0.0020	0.0006	0.0020	0.0006

Equation: b1/(1+exp(b2-b3*GA+b3*b4*(GA>b5)*(GA-b5)+b3*b6*(GA>b7)*(GA–b7)*MC+b8*b9*(GA>b9)*(GA-b9)*ND-B*X))

b1 t/m b9 coefficients, GA = Gestational Age (weeks, conception = 0), X = covariates, and B = coefficient of covariates, MC = monochorionic, ND = neonatal death.

Inflection point = weeks of GA.

Note: ND included = information about neonatal death added to the model

Mode of conception, sex of the co-twin was NS.