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Perinatal Outcome of Twins Compared to Singletons of the Same Gestational Age: A Case-Control Study

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Our objective was to determine the perinatal outcome of first- and second-born twins compared to singletons, born at the same gestational age. To that end we conducted a case-control study in Flanders (Northern Belgium). During a 10-year period (01.01.1999–31.12.2008), the entire twin population — 11,154 first- and 11,118 second-born twins (cases) — was compared to 22,228 singletons (controls) with respect to fetal and neonatal (0–27 days) mortality. Only case and control infants of ≥ 500 grams were included, which explained the unequal number of first- and second-born twins. Mothers and their infants of cases and of controls were derived from the Flemish perinatal database and were matched for maternal age and parity, gestational age and gender of the offspring. The main outcome measures were fetal and neonatal mortality according to gestational age. The frequency of fetal death was statistically significantly less frequent in preterm born twins than in singletons, except at term where the reverse was seen in second-born twins compared to controls. After adjustment for congenital malformations, the results stayed unchanged. Below 28 weeks gestation, singletons had a significantly lower neonatal mortality rate than twins that persisted after adjustment for congenital malformations: the first-born twin versus singleton OR 1.71 (1.17–2.51) and second-born versus singleton OR 2.09 (1.43–3.05). Between 28 and 32 weeks, the second-born twin showed a survival advantage over the control singleton. Between 32 and 36 6/7 weeks both twins had a significantly higher survival rate than the corresponding singleton controls. However, after adjustment for congenital malformations, the aforementioned differences between 28 and 36 6/7 weeks disappeared. When at term, twins and singletons had a comparable, though very low, neonatal death rate. These results confirm previous published data. In conclusion, we demonstrated that the neonatal death rate was lower for twins between 32 and 36 weeks (from 28 weeks for the second born twin) when compared to a singleton of the same gestational age. After adjusting for congenital malformations, there was no statistical significant difference.

■ **Keywords:** twins, perinatal death, preterm

Multiple pregnancy is a high risk pregnancy resulting substantially more frequently in preterm birth and in perinatal death (Kiely, 1990). In Flanders, the overall preterm birth rate and the perinatal mortality of twins, between 1999 and 2008, amounted to 57% and 2.8%, respectively (as compared to 6.2% and 0.65%, respectively, in singletons) (annual reports 1999–2008, Flanders–Northern Belgium). A prevailing observation is that gestational age-specific rates of perinatal death at preterm gestation (or in the low birth weight range), are similar or even lower among twins compared to singletons (Gardner et al., 1995; Kilpatrick et al., 1996; Minakami, 1996). We wanted to determine if, in the region of Northern Belgium

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(Flanders) twins have comparable perinatal mortality rates when compared to singletons of the same gestational age. To that purpose we conducted a case-control study.

Methods

Flanders is a region (Northern Belgium) that covers 13,522 km^2, has about six million inhabitants and has its own parliament, government and language. The healthcare system of the region provides general access to services to the entire population, including obstetric care. There are 68 maternity-obstetric units and there are eight neonatal intensive care units (NICU). Ninety-eight per cent of the women receive prenatal care from a gynecologist. Almost all (99.5%) deliveries take place in the 68 units. Each of these is fully equipped. The following data were derived from the existing computer records of the Flemish Study Centre for Perinatal Epidemiology (SPE). The SPE is an independent, regionally funded, centre that registers all births. For each newborn of at least 500 grams, an official perinatal form with obstetric and neonatal items is completed and sent to the SPE, where all data are controlled by an error detection program and feedback with the individual units is given. During the ten year study period (January 1, 1999–December 31, 2008) 633,964 children were born of which 22,272 (3.5%) were a member of a twin of at least 500 grams. For every case mother (giving birth to a twin) the computer searched two control mothers (delivering a singleton) with the same maternal age, parity, gestational age and sex of the infant and that were delivered in the same obstetric unit in order to minimize differences in treatment policies from one unit to another. By doing so, however, the computer program was unable to find an appropriate control for 44 twin children. Of these 44, 25 were born before 32 weeks, 8 died in utero and 6 during the neonatal period. We decided not to exclude these 44 offsprings because we wanted to study the entire Flemish twin population of ≥ 500 grams. There were more first-born than second-born twin infants. That is because the SPE only registered newborn infants of at least 500 grams. The differences were due to twin pregnancies with one infant weighing more and the other weighing less than 500 grams. In such cases only the one with a birth weight of ≥ 500grams was registered. The SPE registration did not record sets of twins where both infants were < 500 grams, nor did we have information on twins where, in early pregnancy, one of the two fetuses underwent a selective feticide for reasons of malformation. The SPE registration takes the birth order and not the presentation for delivery into account.

Gestational age was divided into four categories (weeks): < 28 weeks; 28–31 6/7 weeks; 32–36 6/7 weeks; ≥ 37 weeks.

Fetal mortality refers to stillbirth. It encompasses any death of a fetus with a birth weight of at least 500 g. Neonatal mortality refers to death of a live-born baby within the first 28 days of life. Perinatal mortality is the sum of the fetal and neonatal deaths.

Chi-square tests were used to evaluate the association between discrete variables and Student's *t* tests to evaluate the association between continuous variables. To measure the strength of the associations Odds Ratios (ORs) together with their 95% confidence intervals (CI) are given. The level of statistical significance was set at a probability value of .01.

Results

Table 1 shows the cases and the matched controls. Twin pregnancies were in 35% the result of assisted reproductive techniques (ART). In singleton controls, ART was responsible for 6.5% of pregnancies: OR: 7.7 (CI 7.2–8.2). Hypertensive disorders and/or gestational diabetes amounted to 10.3% in twin mothers and 10.6% in singleton mothers (NS). Infants of twin mothers were significantly more frequently born by means of cesarean section and the frequency of cesarean section for second twins was higher than for first twins (Table 2). Cesarean section and intra-uterine death of one fetus occurred on

TABLE 1

Patient Characteristics

	Mothers of first-born Twin *N* = 11154		Mothers of second-born Twin *N* = 11118		Mothers of singleton control *N* = 22228	
Maternal age (years. *SD*)	30.7 ± 4.6		30.7 ± 4.6		30.6 ± 4.5	
Gestational age (weeks. *SD*)	35.4 ± 2.9		35.4 ± 2.9		35.4 ± 2.9	
< 28 w	318	2.9%	310	2.8%	613	2.8%
28–31 w	742	6.7%	729	6.6%	1456	6.6%
32–36 w	5290	47.4%	5292	47.6%	10568	47.5%
37 w	4804	43.1%	4787	43.1%	9591	43.1%
Parity						
Nulliparity	5676	50.9%	5623	50.6%	11269	50.7%
Multiparity	5478	49.1%	5495	49.4%	10959	49.3%
Male offspring	5737	51.4%	5500	49.5%	11223	50.5%

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TABLE 2

Obstetrical and Perinatal Characteristics of Twin A, Twin B and the Corresponding Singleton

	First-born A		Second-born B		Control		A–C	B–C
	N = 11154		*N* = 11118		*N* = 22228		OR (95% CI)	OR (95% CI)
Total CS*(N/%)	5557	49.8%	5787	52.1%	7206	32.4%	2.07 (1.98–2.17)	2.18 (2.08–2.29)
Birthweight (g ± *SD*)	2375 ± 593		2318 ± 591		2669 ± 748		—	—
Congenital malformation (N/%)	400	3.6%	384	3.5%	1002	4.5%	0.79 (0.70–0.89)	0.76 (0.67–0.86)
Fetal death	123	1.1%	165	1.5%	648	2.9%	0.37 (0.30–0.45)	0.50 (0.42–0.60)
< 28 w	60	18.9%	59	19.0%	220	35.9%	0.42 (0.30–0.58)	0.42 (0.30–0.59)
28–31 w	19	2.6%	20	2.7%	166	11.4%	0.20 (0.12–0.34)	0.22 (0.13–0.36)
32–36 w	32	0.6%	57	1.1%	238	2.3%	0.26 (0.18–0.39)	0.47 (0.35–0.64)
37w	12	0.2%	29	0.6%	24	0.3%	1.00 (0.47–2.08) NS	2.34 (1.37–4.32)
Neonatal death								
(0–27d)	171	1.6%	165	1.5%	301	1.4%	1.11 (0.92–1.35) NS	1.08 (0.89–1.31) NS
< 28w	106	41.1%	107	42.6%	125	31.8%	1.50 (1.06–2.10)	1.59 (1.13–2.24)
28–31w	31	4.3%	21	3.0%	70	5.4%	0.78 (0.49–1.23) NS	0.53 (0.31–0.89)
32–36 w	26	0.5%	29	0.6%	91	0.9%	0.56 (0.35–0.88)	0.63 (0.40–0.97)
37 w	8	0.2%	8	0.2%	15	0.2%	1.06 (0.41–2.67) NS	1.07 (0.42–2.69) NS
Perinatal death without malformation	221	2.1%	259	2.4%	610	2.9%	0.71 (0.61–0.83)	0.84 (0.72–0.97)
Fetal death without malformation	111	1.0%	148	1.3%	467	2.1%	0.47 (0.38–0.58)	0.63 (0.52–0.76)
< 28w	53	18.2%	54	18.8%	117	25.3%	0.66 (0.45–0.96)	0.68 (0.47–1.00)
28–31w	15	2.2%	18	2.7%	130	10.3%	0.20 (0.11–0.35)	0.24 (0.14–0.41)
32–36w	32	0.6%	52	1.0%	198	2.0%	0.32 (0.21–0.47)	0.51 (0.37–0.71)
37w	11	0.2%	24	0.5%	22	0.2%	1.00 (0.46–2.16) NS	2.20 (1.19–4.07)
Early neonatal death	110	1.0%	111	1.0%	143	0.7%	1.52 (1.18–1.97)	1.53 (1.18–1.98)
< 28w	82	34.3%	91	39.1%	81	23.5%	1.71 (1.17–2.51)	2.09 (1.43–3.05)
28–31w	15	2.3%	8	1.2%	27	2.4%	0.96 (0.48–1.89) NS	0.51 (0.21–1.19) NS
32–36w	7	0.1%	7	0.1%	29	0.3%	0.47 (0.19–1.13) NS	0.47 (0.19–1.13) NS
37w	6	0.1%	5	0.1%	6	0.1%	2.00 (0.57–6.90) NS	1.68 (0.45–6.20) NS

Note: * Cesarean section.

95 occasions: in 33 cases the first-born twin and in 62 cases the second-born twin had died.

Congenital malformations were observed significantly less frequently in the first-born and the second-born twin than among singletons. Congenital malformations were less frequently associated with fetal (210/936 = 22%) than with neonatal deaths (273/ 637 = 43%). Overall, there were 288 fetal deaths in twins of which 259 remained (= 90%) after congenital malformations were eliminated. In singletons only 72% (467/648) remained. There were 336 neonatal deaths in twins of which 221 remained (= 66%) after congenital anomalies were excluded. In singletons, less than half (48%, 143/301) of the neonatal deaths remained. Therefore, adjustment of the data after congenital malformations had been eliminated was much more to be felt in singleton-controls than in twin-cases and was much more far-reached for neonatal than for fetal mortality.

In comparison to matched singletons, fetal demise occurred significantly less often in twins. This observation remained firm for every subdivision of preterm birth and after adjustment for congenital malformations (Table 2). In term birth, a different picture emerged: fetal death was now significantly more frequently seen in the second twin than in the corresponding singleton even after congenital anomalies were eliminated. The overall neonatal mortality was comparable in twins and singletons. However, when we looked at the different levels of gestational age at birth, a mixed picture was seen. Compared to controls, first- and second-born twins below 28 weeks' gestation had a significantly higher neonatal death rate that persisted after adjustment for congenital malformations. The second-born twin, between 28 and 31 6/7 weeks' gestation, also showed a lower neonatal death rate compared to the singleton control. This finding became non-significant after elimination of congenital malformations (Table 2). Between 32 and 36 6/7 weeks both first- and second-born twins had a lower neonatal death rate than the corresponding singleton controls. After congenital anomalies were excluded, this observation abated to a non-significant degree. In term birth, the neonatal mortality was comparable, with or without exclusion of congenital anomalies, for cases and controls. After congenital malformations had been excluded, neonatal death was significantly more frequently encountered in twin births which was entirely due to an important difference in neonatal mortality in the extreme preterm births (< 28w).

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Discussion

We compared, during a 10-year period, the fetal and neonatal outcome of the entire twin population of Flanders with matched singletons born at the same gestational age. The fetal death rate of twins was lower than that of singleton controls and the overall neonatal mortality rate of twins did not significantly differ from that of singletons controls except for the extremely preterm (< 28weeks) were twins had a worse neonatal mortality than singletons. Therefore, the well-established overall higher perinatal death rate affecting twins is probably due to their much higher incidence of preterm birth.

Twins and singletons, matched for gestational age, have been previously compared with regard to outcome (Gardner et al., 1995; Kilpatrick et al., 1996; Minakami et al., 1996; Nielsen et al., 1997; Mizrahi et al., 1999; Draper et al., 1999). Results of this comparison did not always point in the same direction. The prospective study carried out by Gardner et al. (1995) showed similar results. In a retrospective cohort study, Kilpatrick et al. (1996) found that twins, when born at 30 weeks or later, had either a comparable or a lower perinatal mortality rate than singletons matched for gestational age. Minakami and Sato (1996) retrospectively studied 88,936 infants born of multifetal pregnancies and found that twins born between 30 and 36 weeks had a lower risk of perinatal death than singletons matched for gestational age. Similar results have been reported when not only gestational age but also birth weight was taken into consideration (Kiely et al., 1990; Draper et al., 1999; Mc Carthy et al., 1981). Our study confirms the data to be found in the literature according to which twins, when compared to singletons, have a higher (< 28w), a lower (32–36w 6/7d) or a comparable neonatal mortality rate. We found a statistically significant lower incidence of fetal demise in twins of either birth order compared to singletons except at term.

Although the birth weight of a twin baby is lower than that of a singleton baby of the same gestational age, neonatal mortality is comparable except for the extreme preterm (< 28w). Twins are programmed to be born preterm, not because of an underlying pathology but because of a limited uterine environment (Blickstein, 2004). Indeed, Blickstein collected data suggesting that at 30–32 weeks the uterine environment is probably performing to its full capacity as at least 80% of sets of multiplets had a total weight greater than a macrosomic singleton at 40 weeks. The frequency of adverse events such as placental abruption and the like is lower than that associated with preterm delivery of singletons (Tucker & Mc Guire, 2004). In preterm twins beyond 31 weeks' gestation, the lungs undergo an earlier in utero maturation than those of singleton fetuses (Leveno et al., 1984). The differences in lung maturation could explain why mortality curves intersect between twins and singletons (Luke et al., 1991). The accelerated maturation is possibly an adaptation to stressful events, such as fetal growth restriction (Amiel-Tison et al., 2004).

Before 28 weeks, our results showed that twins fared worse than singletons. Tyson et al. (2008) found that in extreme premature babies, gestational age alone was not enough to predict survival: higher birth weight for a certain gestational age and being a singleton, among other factors, predisposed to a favourable outcome with intensive care.

Congenital anomalies occur twice as often in twin pregnancies as in singletons (Malone & D'Alton, 2000). Surprisingly, we found less congenital malformations in twins than in the control singletons. Similar findings were reported by Mizrahi et al. (1999). This finding can be attributed to the more frequent and earlier detection of malformations in multiple pregnancies (Mizrahi et al., 1999). The latter are indeed considered to be at higher risk and therefore the object of closer ultrasound surveillance. The selective feticide of a malformed twin fetus, before 20 weeks' gestation or before its weight will have reached 500 g, distorts the true incidence of congenital anomalies and reduces mortality in twins. Unfortunately, we have no data on the incidence of early prenatal invasive techniques such as selective feticide. It is even possible that in this study, an original twin that was reduced to a singleton in early pregnancy, ended up in the singleton control group. An earlier detection of congenital malformations in twins compared to singletons may partly explain our results.

The strengths of this study are, on the one hand, that an entire twin population was examined and, on the other hand and in order to minimize differences in treatment that cases and controls came from the same obstetric unit. This study has several limitations.

First, we could not distinguish monozygotic from dizygotic twins, nor did we analyse separately twins and singletons conceived spontaneously and those conceived by means of assisted reproductive techniques. Perinatal outcome is poorer in monozygotic than in dizygotic, spontaneously conceived, twins (Bryan et al., 1987).

Second, we have no information on the antenatal administration of corticosteroids. The neonatal mortality rate of singletons and twins born after 23 to 29 weeks' gestation is lowered by the administration of steroids (Tyson et al., 2008; Garite et al., 2004).

Third, we used birth order and not order of presentation. This is due to the way the data are collected by the SPE. Depending on practice and the circumstances of the delivery, defining birth order retrospectively can confound the results: on the one hand, both twins may be in trouble and the second-born twin is left behind because it's chances of survival are worse; on the other hand, there is only one twin in trouble (the first-born) and the second-born twin is left behind because it's chances of survival are better. Smith et al. (2007) found no association between birth order and the risk of death among preterm infants

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(< 36 weeks of gestation). They did find an increased risk of perinatal death among second born twins compared to first born twins when born at term (≥ 36 weeks). We had a comparable result in at term born infants where fetal death was higher in the second born than in the singleton control. Sheay et al. (2004) described a 37% higher perinatal mortality in second-born twins compared to first-born twins, even when mortality was examined in strata of gestational age. This was predominantly the result of an almost 2.5-fold increased stillbirth rate. A plausible explanation is that, regardless of delivery route, fetuses that die in utero are typically delivered second, especially when delivered by cesarean section. Indeed, in our study, cesarean delivery was performed in 33 cases when the first-born twin was deceased but in 62 cases when the second-born twin had died. The fact that, when it comes to a cesarean section, it is the obstetrician who determines who will be the first- or the second-born twin flaws the relevance of differentiating the first- from the second-born twin.

Fourth, we had no reliable information on several factors that play a role in perinatal mortality such as socio-economic status, timing of the first antenatal visit or smoking.

In conclusion, our study showed that fetal death occurred less often in twins compared to singletons of the same gestational age, probably due to a better surveillance of twins and an earlier detection of congenital malformations. Neonatal death rates showed a mixed picture: higher in extreme preterm twins (< 28weeks) compared to extreme premature singletons but comparable or lower, depending on whether congenital malformations were taken into consideration, thereafter. It is important in the counseling of future parents to explain that twins are at much higher risk to be born preterm but once born, they do not carry an additional risk (except for the extreme preterm) to that of a singleton born at the same gestational age.

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