A Matched Cohort Comparison of the Outcome of Twin Versus Singleton Pregnancies in Flanders, Belgium

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To compare perinatal outcome of singleton versus twin pregnancies a matched cohort study was performed in Flanders, Belgium. All twins delivered in the region of Flanders during 1998–1999 were compared to singletons, matched for gestational age, fetal sex and maternal parity, resulting in 4384 infants in each group. Above 32 weeks of gestation, birthweight was significantly lower in twins (2095 ± 364 g versus 2315 ± 523 g; $p < 0.001$, 95% confidence interval 193 to 246 g). Perinatal mortality was also significantly lower in twins (1.98% versus 1.26%; odds ratio for twins 0.63; 95% confidence interval 0.53–0.75; $p < 0.001$), this was mostly due to fetal and not to early neonatal mortality. Congenital malformations occurred less frequently in twins (2.5% versus 3.7%; odds ratio for twins 0.80, 95% confidence interval 0.69–0.92; $p = 0.001$). From gestational age of 32 weeks on, respiratory distress syndrome was less frequent in twins (6.7% versus 8.0%; odds ratio for twins 0.81; 95% confidence interval 0.68–0.97; $p = 0.011$). No significant differences were noted with regard to intraventricular haemorrhage, neonatal infections and retinopathy of prematurity. Although twins have a lower birthweight, their outcome is more favorable compared to singletons, when matched for gestational age.

Differences in outcome between singletons and twins have frequently been reported. After correction for gestational age, perinatal mortality has been noted to be less in twins, but this has not been confirmed in other studies (Kiely, 1998; Minakami & Sato, 1996; Rydhstroem & Heraib, 2001). Fetal lung maturation has been said to be accelerated in twins, but this was refuted by other investigators (Winn et al., 1992).

The purpose of the present study was to compare the incidence of hypertension in pregnancy, delivery by cesarean section, perinatal mortality, birthweight, Apgar scores, the need for intensive neonatal care and mechanical ventilation, respiratory distress syndrome, retinopathy of prematurity, intraventricular haemorrhage and convulsions in twins and singletons of comparable gestational age.

Materials and Methods

A matched cohort study was performed in the region of Flanders, Belgium. The Study Centre for Perinatal Epidemiology collects data on all hospital-based deliveries in Flanders (representing the Northern half of Belgium) and has a complete coverage of all hospital deliveries, excluding home deliveries which make up less than 1% of all deliveries in Flanders. Data are linked to the central administration of birth certificates.

All deliveries after a gestational age of 22 weeks or more were included for the period of January 1, 1998 to December 31, 1999. For every twin pregnancy, two control pregnancies were selected. These were the next-born singletons with the same gestational age, fetal sex and maternal parity.

Groups were compared for birthweight; hypertension in pregnancy; cesarean section rate; Apgar scores; fetal, early neonatal and perinatal mortality; need for intensive neonatal care and mechanical ventilation and neonatal morbidity, such as intraventricular haemorrhage, convulsions, infections, respiratory distress syndrome, retinopathy of prematurity and congenital malformations.

Maternal hypertension was defined as a blood pressure > 140/90 mm Hg. Data collection did not allow differentiation between proteinuric and non-proteinuric, chronic or pregnancy-induced hypertension.

Fetal mortality was considered as fetal demise before birth, early neonatal mortality as death before the eighth day after birth. Perinatal mortality was the combination of fetal and early neonatal mortality.

Neonatal morbidity was diagnosed by the neonatologist in charge of the different regional hospitals. Diagnoses were recorded at the moment of discharge of the infant by means of a structured questionnaire. Congenital malformations were not further specified for the analysis.

The results were analysed for the complete groups, and separately for gestational age 24 to 26 6/7 weeks, 28 to 31 6/7 weeks, 32 to 36 6/7 weeks and 37 to 42 weeks gestational age.

Differences between groups were tested by Student *t* test and Chi-square test where appropriate, the significance limit accepted for all statistical analyses was $\alpha = 0.05$.

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The confidence interval of 95% for odds ratios was applied. Multivariate analysis was performed using logistic regression. Statistical analysis was performed with SPSS 10.0.

Results

4384 Twins were compared to 4384 singletons during the study period. Results are presented in Tables 1 to 5.

Birthweight was lower in twins from gestational age 32 weeks; at an earlier gestational age no significant differences existed. Perinatal mortality was not different at a very young gestational age but was lower in twins from 28 to 37 weeks, this difference was mostly due to fetal and not to early neonatal mortality. Logistic regression was performed for fetal mortality including as factors twin or singleton, birthweight and congenital malformations, demonstrating that even taking into account birthweight and congenital malformations, being a twin reduced the risk for fetal mortality (factor –1.56, odds –3.34; 95% confidence interval –2.31 to –4.83, $p < 0.001$). The same was done for early neonatal mortality including as factors twin or singleton, birthweight, congenital malformations, intraventricular bleeding, respiratory distress syndrom; all of which were significant except being a twin or not (factor –0.30; odds 0.74; 95% confidence interval 0.49 to 1.10; $p = 0.46$), confirming that the difference in mortality is due to a difference in fetal mortality.

Maternal hypertension was not more frequent in twin pregnancies. Twins were more frequently born by cesarean section and this was even more the case for term (37–42 weeks) twin pregnancies. A 1-minute Apgar score less than 7 was more frequent in twins; this was mostly seen in twins born between 37 and 42 weeks.

For every gestational age, twins were more frequently transported to a neonatal intensive care unit. No significant differences were noted for respiratory distress syndrome, except for twins from 32 to 36 weeks, who suffered less frequently from respiratory distress syndrome. Although overall the need for mechanical ventilation was not higher in the twin-group, the number of infants needing mechanical ventilation was higher in the younger twins compared to singletons and was lower from 32 weeks on.

The frequency of retinopathy of prematurity, intraventricular haemorrhage and neonatal septicaemia was not different between twins and singletons. Congenital malformations were less frequent in the twin-group.

Discussion

In Flanders a continuing rise in the number of twin deliveries exists, from 14% in 1998 to 19% of all deliveries in 1999. This is thought to be due to the frequent use of artificial reproductive technology. In 1999 only 1.2% of twins were the result of non-assisted "spontaneous" conception.

Our data do not allow to differentiate between monozygotic and dizygotic twins. We did not perform a subanalysis for twins spontaneously conceived or after ovarian stimulation, but other studies have shown that the risk of adverse outcome for twins does not seem to be increased after ovarian stimulation (Olivennes et al., 1996).

This study confirms a lower birthweight in twins after 28 weeks gestational age, some authors have even advocated using twin-adjusted charts for ultrasound-determined fetal growth monitoring (Taylor et al.,1998).

Table1

General Outcome of Twins Versus Matched Singletons

	Twins (n = 4384)		Singletons (n = 4384)		p value	OR	95 % CI
	Mean	*SD*	Mean	*SD*			
Birthweight (grams)	2375	566	2723	729	0.58	—	– 320 to 375[1]
	n	%	*N*	%			
Perinatal mortality	87	2.0	187	4.3	< 0.001	0.63	0.53 to 0.75
Fetal mortality	44	1.0	133	3.0	< 0.001	0.49	0.38 to 0.64
Early neonatal mortality	43	1.0	54	1.2	0.261	0.88	0.71 to 1.11
Maternal morbidity							
Maternal hypertension	428	9.8	438	10.0	0.720	0.99	0.92 to 1.06
Cesarean section primary	1297	29.6	728	17.8	< 0.001	1.35	1.30 to 1.41
Cesarean section secondary	648	14.8	425	9.7	< 0.001	1.24	1.18 to 1.31
Neonatal morbidity							
Apgar score < 7 after 1 minute	712	16.2	594	13.5	< 0.001	1.11	1.05 to 1.17
Apgar score < 7 after 5 minutes	176	4.0	178	4.0	0.914	0.99	0.89 to 1.11
Transfer to neonatal intensive care unit	935	21.3	699	15.9	< 0.001	1.18	1.13 to 1.24
Respiratory distress syndrome	243	5.5	260	5.9	0.435	0.96	0.88 to 1.06
Need for artificial ventilation	298	6.8	296	6.8	0.932	1.00	0.92 to 1.04
Retinopathy of prematurity	24	0.5	20	0.4	0.545	1.09	0.83 to 1.43
Intracerebral haemorrhage	53	1.2	61	1.5	0.306	0.90	0.74 to 1.10
Congenital malformations	109	2.5	163	3.7	0.001	0.80	0.69 to 092
Neonatal septicaemia	150	3.4	168	3.8	0.450	0.89	0.78 to1.13

Notes: *SD* = Standard deviation.
OR = Odds Ratio.
95 % CI = 95 % confidence interval.
[1] 95 % CI = for the difference in population means.

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Table 2

Outcome for Gestational Age 24–27 6/7 Weeks

	Twins (*n* = 78)		Singletons (*n* = 78)		*p* value	OR	95 % CI
	Mean	*SD*	Mean	*SD*			
Birthweight (grams)	822	173	842	184	0.62	—	–20 to 61[1]
	n	%	*n*	%			
Perinatal mortality	33	42.3	35	44.9	0.747	0.95	0.69 to 1.30
Fetal mortality	7	8.9	21	26.9	0.003	0.45	0.23 to 0.87
Early neonatal mortality	26	33.3	14	17.9	0.028	1.45	1.07 to 1.96
Maternal morbidity							
Maternal hypertension	2	2.6	7	9.0	0.086	0.43	0.12 to 1.47
Cesarean section primary	21	26.9	15	19.2	0.254	1.23	0.88 to 1.71
Cesarean section secondary	21	26.9	9	11.5	0.015	1.55	1.14 to 2.09
Neonatal morbidity							
Apgar < 7 after 1 minute	28	35.9	35	44.9	0.253	0.83	0.59 to 1.32
Apgar < 7 after 5 minutes	12	15.4	16	20.5	0.404	0.83	0.52 to 1.32
Transfer to neonatal intensive care unit	66	84.6	47	60.3	0.001	2.09	1.26 to 3.47
Respiratory distress syndrome	42	53.8	35	44.9	0.262	1.20	0.87 to 1.64
Need for artificial ventilation	46	59.0	33	42.3	0.037	1.40	1.01 to 1.94
Retinopathy of prematurity	9	11.5	9	11.5	1.000	1.00	0.62 to 1.63
Intracerebral haemorrhage	18	23.1	18	23.1	1.00	1.00	0.69 to 1.45
Congenital malformations	6	7.7	13	16.7	0.87	0.60	0.30 to 1.19
Neonatal septicaemia	13	16.7	14	17.9	0.869	1.44	1.01 to 2.05

Notes: *SD* = Standard deviation.
OR = Odds Ratio.
95 % CI = 95 % confidence interval.
[1] 95 % CI = for the difference in population means.

Table 3

Outcome for Gestational Age 28–31 6/7 Weeks

	Twins (*n* = 239)		Singletons (*n* =239)		*p* value	OR	95 % CI
	Mean	*SD*	Mean	*SD*			
Birthweight (grams)	1315	304	1359	468	0.7	—	–6 to 94[1]
	n	%	*n*	%			
Perinatal mortality	16	6.7	56	23.4	< 0.001	0.41	0.26 to 0.64
Fetal mortality	9	3.8	44	18.4	< 0.001	0.31	0.77 to 0.57
Early neonatal mortality	7	2.9	12	5.0	0.242	0.73	0.40 to 9.32
Maternal morbidity							
Maternal hypertension	37	15.5	39	16.3	0.802	0.97	0.75 to 1.24
Cesarean section primary	94	39.3	78	32.6	0.127	1.15	0.96 to 1.38
Cesarean section secondary	49	20.5	38	15.9	0.192	1.16	0.94 to 1.43
Neonatal morbidity							
Apgar < 7 after 1 minute	91	38.1	78	32.6	0.214	1.12	0.94 to 1.30
Apgar < 7 after 5 minutes	27	11.3	28	11.7	0.890	0.98	0.74 to 1.30
Transfer to neonatal intensive care unit	209	87.4	166	69.4	< 0.001	1.91	1.40 to 2.62
Respiratory distress syndrome	105	43.9	85	35.6	0.062	1.19	0.99 to 1.42
Need for artificial ventilation	121	50.6	90	37.6	0.004	1.30	1.09 to 1.55
Retinopathy of prematurity	12	5.0	7	2.9	0.242	1.28	0.89 to 1.82
Intracerebral haemorrhage	17	7.1	26	10.9	0.150	0.77	0.53 to 1.13
Congenital malformations	10	4.2	35	14.6	< 0.001	0.42	0.24 to 0.73
Neonatal septicaemia	49	20.5	41	17.1	0.064	1.16	0.94 to 1.43

Notes: *SD* = Standard deviation.
OR = Odds Ratio.
95 % CI = 95 % confidence interval.
[1] 95 % CI = for the difference in population means.

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Table 4

Outcome for Gestational Age 32–36 6/7 Weeks

	Twins (n = 1130)		Singletons (n = 1130)		p value	OR	95 % CI
	Mean	*SD*	Mean	*SD*			
Birthweight (grams)	2095	364	2315	523	< 0.001	—	193 to 246[1]
	n	%	*n*	%			
Perinatal mortality	13	1.1	66	5.8	< 0.001	0.32	0.89 to 0.53
Fetal mortality	11	0.9	43	3.8	< 0.001	0.40	0.24 to 0.68
Early neonatal mortality	2	0.2	23	2.0	< 0.001	0.16	0.04 to 0.60
Maternal morbidity							
Maternal hypertension	165	14.6	167	14.8	0.905	0.99	0.88 to 1.12
Cesarean section primary	298	26.4	240	21.2	0.004	1.15	1.05 to 1.25
Cesarean section secondary	215	19.0	163	14.4	0.003	1.17	1.06 to 1.29
Neonatal morbidity							
Apgar < 7 after 1 minute	247	21.8	210	18.6	0.053	1.10	1.00 to 1.22
Apgar < 7 after 5 minutes	51	4.5	77	6.8	0.018	0.79	0.63 to 0.98
Transfer to neonatal intensive care unit	425	37.6	356	31.5	0.002	1.14	1.05 to 1.24
Respiratory distress syndrome	76	6.7	109	8.0	0.011	0.81	0.68 to 0.97
Need for artificial ventilation	95	8.4	135	11.9	0.005	0.81	0.69 to 0.95
Retinopathy of prematurity	3	0.3	3	0.3	1.000	1.00	0.45 to 2.23
Intracerebral haemorrhage	15	1.3	17	1.5	0.722	0.94	0.65 to 1.36
Congenital malformations	41	3.6	59	5.2	0.066	0.81	0.64 to 1.03
Neonatal septicaemia	58	5.1	78	6.9	0.061	1.15	0.98 to 1.39

Notes: *SD* = Standard deviation.
OR = Odds Ratio.
95 % CI = 95 % confidence interval.
[1]95 % CI = for the difference in population means.

Table 5

Outcome for Gestational Age 37–42 Weeks

	Twins (n = 2102)		Singletons (n = 2102)		p value	OR	95 % CI
	Mean	*SD*	Mean	*SD*			
Birthweight (grams)	2689	392	3160	454	< 0.001	—	446 to 496[1]
	n	%	*n*	%			
Perinatal mortality	7	0.3	7	0.3	1.00	1.0	0.59 to 1.69
Fetal mortality	6	0.3	6	0.3	1.00	1.0	0.57 to 1.76
Early neonatal mortality	1	0.04	1	0.01	1.00	1.0	0.25 to 4.00
Maternal morbidity							
Maternal hypertension	125	5.9	134	6.4	0.564	0.96	0.85 to 1.10
Cesarean section primary	644	30.6	344	16.4	< 0.001	1.44	7.35 to 1.53
Cesarean section secondary	217	10.3	138	6.6	< 0.001	1.25	1.14 to 1.36
Neonatal morbidity							
Apgar < 7 after 1 minute	210	9.9	166	7.9	0.017	1.13	1.03 to 1.24
Apgar < 7 after 5 minutes	48	2.3	35	1.7	0.150	1.16	0.96 to 1.40
Transfer to neonatal intensive care unit	125	5.9	55	2.6	< 0.001	1.41	1.28 to 1.56
Respiratory distress syndrome	3	0.1	10	0.5	0.052	0.46	0.17 to 1.24
Need for artificial ventilation	13	0.6	19	0.9	0.287	0.81	0.53 to 1.23
Retinopathy of prematurity	0	0.0	0	0.0	—	—	—
Intracerebral haemorrhage	2	0.1	1	0.04	0.564	1.33	0.60 to 2.97
Congenital malformations	32	1.5	35	1.7	0.712	0.95	0.74 to 1.23
Neonatal septicaemia	17	0.8	18	0.85	0.564	1.07	0.84 to 1.19

Notes: *SD* = Standard deviation.
OR = Odds Ratio.
95 % CI = 95 % confidence interval.
[1]95 % CI = for the difference in population means.

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Our study participants are matched for gestational age, fetal sex and maternal parity; the influence of these factors on birthweight can be excluded. The data do not confirm the general opinion that maternal hypertensive disorders are more frequent in twin gestation (Campbell & McGillivray, 1999). In this study we can not differentiate between chronic hypertension, pregnancy-induced hypertension and pre-eclampsia. Mizrahi et al. (1999) noted a lower incidence of pregnancy-induced hypertension in twin gestations.

The seemingly high perinatal mortality in singleton pregnancies is to be explained by the process of matching and is not the overall perinatal mortality in Flanders, which was 0.07% in the period studied; a lower perinatal mortality in gestational age-matched twins versus singletons has repeatedly been reported (Friedman et al., 1997; Kiely, 1998; Minikami & Sato 1996; Mizrahi et al., 1999). In our series the difference was more striking for intrauterine (fetal) death. For early neonatal mortality the difference disappeared when taking other factors such as birthweight into account.

A bias is present for fetal mortality as part of the singletons were probably born after induction of labor due to intrauterine fetal demise. The data do not permit to quantify this effect.

It should be remembered that due to prematurity perinatal mortality is in general higher for twins compared to singletons and that twins account for a disproportional amount of preterm births (Gardner et al., 1995). In a matched case-control study such as ours this effect is of course not registered. In 1998, 54% of all twins in Flanders were delivered before 37 weeks gestational age versus 6% of singletons.

More twins are born by cesarean section and the difference is more pronounced after 32 weeks gestational age, this is true both for primary and secondary cesarean section. We believe part of this can be explained by the more frequent non-vertex presentation of the second twin.

Twins are more often admitted to a neonatal intensive care unit. It is remarkable that at a very early gestational age (24–28 weeks) only 40% of singletons are admitted to a neonatal intensive care unit. This does not mean that singletons are less often transported to the intensive care unit when liveborn, the difference can be explained by the higher number of fetal deaths in singletons, who evidently are no longer considered for neonatal intensive care.

A lower prevalence of respiratory distress syndrome in age-matched twins versus singletons has been reported. It is a matter of controversy whether the twin gestation by itself accelerates fetal lung maturation (Friedman et al., 1997; Leveno et al., 1984). In our study we can not exclude confounding factors as differences in the administration of antenatal glucocorticoids.

Compared to singletons, twins had less congenital malformations, this is contradictory to classic teaching but has been reported before (Mizrahi et al., 1999). Even with a lower risk for the individual fetus, the general risk of finding a congenital malformation in one or both twins is higher than the risk for a singleton. In our study 109 fetuses demonstrated a congenital malformation in 2192 twin pregnancies versus 163 fetuses in 4384 singleton pregnancies. This makes the odds ratios to have at least one malformed foetus in twin pregnancy 1.35 (95% confidence interval 1.05 to 1.73). The risk of having a malformed child does not double but increases by 35%.

Conclusion

Twins compared to singletons had a lower fetal and perinatal mortality rate, less respiratory distress syndrome and less congenital malformations. No differences existed for retinopathy of prematurity, intracerebral haemorrhage and neonatal infections.

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