Trends in the prevalence, risk and pregnancy outcome of multiple births with congenital anomaly: a registry-based study in 14 European countries 1984–2007

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Objective To assess the public health consequences of the rise in multiple births with respect to congenital anomalies.

Design Descriptive epidemiological analysis of data from population-based congenital anomaly registries.

Setting Fourteen European countries.

Population A total of 5.4 million births 1984–2007, of which 3% were multiple births.

Methods Cases of congenital anomaly included live births, fetal deaths from 20 weeks of gestation and terminations of pregnancy for fetal anomaly.

Main outcome measures Prevalence rates per 10 000 births and relative risk of congenital anomaly in multiple versus singleton births (1984–2007); proportion prenatally diagnosed, proportion by pregnancy outcome (2000–07). Proportion of pairs where both co-twins were cases.

Results Prevalence of congenital anomalies from multiple births increased from 5.9 (1984–87) to 10.7 per 10 000 births (2004–07).

Relative risk of nonchromosomal anomaly in multiple births was 1.35 (95% CI 1.31–1.39), increasing over time, and of chromosomal anomalies was 0.72 (95% CI 0.65–0.80), decreasing over time. In 11.4% of affected twin pairs both babies had congenital anomalies (2000–07). The prenatal diagnosis rate was similar for multiple and singleton pregnancies. Cases from multiple pregnancies were less likely to be terminations of pregnancy for fetal anomaly, odds ratio 0.41 (95% CI 0.35–0.48) and more likely to be stillbirths and neonatal deaths.

Conclusions The increase in babies who are both from a multiple pregnancy and affected by a congenital anomaly has implications for prenatal and postnatal service provision. The contribution of assisted reproductive technologies to the increase in risk needs further research. The deficit of chromosomal anomalies among multiple births has relevance for prenatal risk counselling.

Keywords Concordance, congenital anomalies, multiple births, pregnancy outcomes, twins.

Introduction

The proportion of multiple births has risen in the last 30 years, through changes in maternal age[1] and the introduction of assisted reproductive therapies (ART).[2,3] This rise is mainly in dizygotic or multizygotic deliveries (DZ), because monozygotic (MZ) twinning is not strongly associated with either maternal age or ART.[2,3] There is evidence that multiple births have an increased risk of congenital anomaly relative to singleton births.[4–11] The excess in congenital anomalies has been associated with the splitting of the zygote[4,6] and with vascular accidents as a result of blood clots or other debris moving across a shared or joined placenta[9] in MZ twins. Epidemiological studies have found an excess risk of anomaly in MZ twins relative to DZ twins, with the risk for DZ twins being similar to that in singletons.[4,6,9] However, there is emerging evidence that babies conceived through ART have an excess risk of congenital anomalies,[12–14] which may independently contribute to the risk of congenital anomaly among DZ twins.

The combination of twin pregnancy and congenital anomaly can pose particular problems for the management of the pregnancy and birth, where one or all of the fetuses/babies in a multiple pregnancy are affected. Little is known on a population basis about the rates of prenatal diagnosis[15–18] and in utero and neonatal survival[19,20] in twin pregnancies with congenital anomaly relative to singletons with congenital anomaly.

This paper investigates how the change in the proportion of multiple births over a 24-year period (1984–2007) in European countries has affected the prevalence of congenital anomalies from multiple births, and the relative risk of congenital anomaly in multiple versus singleton births. It also investigates whether multiple pregnancy status affects the likelihood of prenatal diagnosis of a fetus with congenital anomaly, and whether babies with congenital anomaly from multiple pregnancies have a different outcome in terms of in utero and early neonatal survival from their singleton counterparts (2000–07). The proportion of twin pairs concordant for any type of congenital anomaly is assessed, as well as the impact of concordance on the likelihood of prenatal diagnosis or terminations of pregnancy for fetal anomaly (TOPFA).

Methods

European Surveillance of Congenital Anomalies (EUROCAT) collects standardised data across Europe that can be used to assess changes in the epidemiology of congenital anomalies and associated risk factors. The EUROCAT central database contains data on congenital anomaly cases from population-based congenital anomaly registries.[21] The methods of registry case ascertainment are fully described elsewhere.[22] The database includes congenital anomaly cases among live births (LB), fetal deaths after 20 weeks of gestation (FD), and all prenatally diagnosed cases resulting in termination of pregnancy (TOPFA) at any gestational age. Congenital anomaly cases diagnosed in spontaneous abortion before 20 completed weeks of gestation are not included. Nineteen registries in 14 countries participated in this study (Table 1), all of which could provide data on multiple birth status for both their cases and the population.[23] These registries covered a population of 5.4 million births between 1984 and 2007. Not all registries cover the early part of the study period (Table 1) and only 13 registries in eight countries (Table 1) could provide data on like-sex and unlike-sex twin pairs in the denominator data used to estimate zygosity proportions in the population. Fourteen registries in eight countries (Table 1) were able to provide the maternal age distribution of multiple and singleton denominator births. The period 2000–07, covering a population of 3.2 million births, was analysed as the most recent data.

A 'case' in this paper refers to fetus/baby diagnosed with a congenital anomaly. Congenital anomalies are coded within the range 740–759 in the International Classification of Diseases, version 9 (ICD9) or in the Q chapter in version 10 (ICD10).[24] The EUROCAT Data Management Programme assigns all major congenital anomalies to subgroups according to their ICD codes.[21] The analysis presented here uses only the subgroups 'all anomalies', 'all nonchromosomal anomalies' (i.e. cases where no chromosomal syndrome was diagnosed) and 'chromosomal anomalies'. Cases with only minor anomalies, or patent ductus arteriosus in preterm infants, are excluded according to a specific list of exclusions.[21]

Cases were classified as prenatally or postnatally diagnosed, and according to pregnancy outcome (LB, FD, TOPFA) and early neonatal death (deaths within 1 week) among LB.

Multiple birth is defined for cases in EUROCAT guidelines according to the 'number of babies/fetuses delivered'.[21] As the diagnosis of multiple birth is often made on early ultrasound scans, with subsequent loss of one fetus,[25,26] the registries were surveyed to ascertain how the EUROCAT guidelines are interpreted in case of early loss of a co-twin. Fourteen centres were able to check their data and of the 3980 cases from multiple births recorded, only 22 (0.55%) were singletons at delivery. Denominator data were provided by the registries or were requested directly from national birth registries. They are provided as LB and stillbirths (SB) and reflect civil registration of births in the area and country where the registry is situated. For births (denominators), multiple birth is defined as declared at civil registration.

Conjoined twins are included as multiple birth cases, but the pair is only counted as one case. The prevalence of

Table 1. Study population (countries and years), number and proportion of births covered by registries and % multiple, no. of congenital anomaly cases registered and % from multiple births, 1984–2007

Country	Percentage of country covered by EUROCAT registries in study	Years for which case and denominator data are available	Total denominator births and percentage multiple	Total number of congenital anomaly cases and percentage multiple
Poland (Wielkopolska)*	9.8%	1999–2007	316 838 (2.27%)	7314 (3.43%)
Italy (Tuscany)	5.5%	2004–2007	119 482 (2.43%)	2352 (3.23%)
Germany (Saxony-Anhalt)	2.6%	2000–2007	140 710 (2.69%)	4593 (4.01%)
Malta*,**	100%	1999–2007	36 412 (2.80%)	1160 (3.19%)
Hungary*	100%	1998–2002	561 911 (2.73%)	12 580 (2.80%)
UK^ (four registries: NorCAS, WANDA, CARIS, CAROBB)*,**	16.3%	1989–2007	1 110 594 (2.94%)	29 601 (3.62%)
Austria (Styria)	13.4%	1985–2007	275 733 (2.41%)	7849 (4.37%)
Ireland^^ (Three registries: Dublin, Cork and Kerry, South east Ireland)*,**	62.7%	1984–2007	647 348 (2.72%)	15 073 (2.89%)
Switzerland (Vaud)	10.3%	1989–2007	142 366 (2.85%)	5371 (4.60%)
Belgium (Antwerp)*,**	16.5%	1990–2007	256 747 (3.63%)	6532 (5.28%)
France (Paris)*	3.2%	1984–2007	814 569 (3.36%)	24 754 (3.82%)
Northern Netherlands**	9.7%	1984–2007	420 045 (3.28%)	10 737 (3.97%
Norway*,**	100%	1999–2006	464 992 (3.66%)	17 261 (4.77%)
Denmark (Odense)**	8.5%	1984–2007	130 323 (3.58%)	3182 (5.09%)
Total		1984–2007	5 438 072 (3.00%)	148 359 (3.83%)

*Maternal age denominators available at the time of analysis.
**Like-sex data available (in Ireland this is for two out of the three registries).
^Years included NorCAS 2000–2007, WANDA 1994–2007, Wales 1998–2007 and CAROBB 1991–2007.
^^Dublin 1984–2007, Cork and Kerry 1996–2004, South east Ireland 1997–2007.

conjoined twins was calculated separately, and conjoined twins were included in the analysis of nonchromosomal cases.

EUROCAT data enable linkage of babies with congenital anomalies from a multiple set where more than one is affected. After a careful check for possible duplications, concordant twins were defined as twin pairs where both of the fetuses/babies in the pair had a congenital anomaly within the subgroup of analysis (e.g. for the nonchromosomal anomaly subgroup, a concordant pair is one where both babies have any nonchromosomal anomaly, but not necessarily the same specific type of anomaly). When examining concordance only twin pairs were used, excluding higher-order multiple births and conjoined twin pairs. Concordance analyses were pair-based rather than case-based.

Statistical analysis

Statistical analysis was performed using STATA version 9.0 (Statacorp LP, College Station, TX, USA).

Proportions of MZ and DZ twins among all (denominator) births were calculated for those registries with denominators giving like-sex and unlike-sex twin pairs using the Weinberg rule: number of MZ pairs = total pairs − 2 (unlike-sex pairs). This rule has been validated using population-based twin registries where zygosity is known.[27,28]

The *proportion* of congenital anomaly cases among multiple births (live and still) was calculated as: [No. of congenital anomaly cases (LB+FD+TOPFA) that were from multiple births or pregnancies × 100]/[Total no. of multiple births (LB + SB) in the population].

The *prevalence* of congenital anomaly from multiple births per 10 000 births (live and still) in the population was calculated as: [No. of congenital anomaly cases (LB+FD+TOPFA) that were from multiple births or pregnancies × 10 000]/(Total no. LB+SB in the population).

Relative risks (RR) with 95% confidence intervals (95% CI) were estimated using Poisson regression to represent the ratio of the proportion of congenital anomalies among multiple births relative to the proportion among singleton births. The RRs were adjusted for country (Table 1) and time. Data were categorised into six 4-year time periods (1984–87, 1988–91, 1992–95, 1996–99, 2000–03 and 2004–07) for the analysis of time trends. Poisson regression was

used because of the rarity of the events studied and the possibility of no events happening within a given time period.[29]

A subanalysis was performed, adjusting for maternal age (<20, 20–24, 25–29, 30–34, 35–39, 40–44 and >44 years) for those countries for which maternal age denominators were available.

Logistic regression was used to estimate odds ratios (OR) adjusted for country when analysing the odds of prenatal diagnosis and of various pregnancy outcomes. These analyses used case data only because they compared multiple cases with singleton cases. Odds of SB (versus LB) and early neonatal death (versus surviving LB) in multiple versus singleton pregnancies were also analysed, stratified by gestational age (≤ 35 weeks or ≥ 36 weeks of gestation). Although preterm birth is usually defined as before 37 weeks, 36 weeks was used because placental maturation occurs earlier in multiple pregnancies.[30, 31]

The proportion of concordant pairs was calculated for twin pairs only and for 2000–07 only as: (Pairs where both babies or fetuses were cases × 100)/(No. of twin pairs from which at least one case was diagnosed).

Results

Of the 5.4 million births during the 24-year study period, 3.00% of babies were from multiple births (Table 1), varying by country (Table 1). Of the 148 359 births involving major congenital anomalies recorded in this population, 3.83% were from multiple births (Table 1, see Supplementary material, Appendix S1 for 2000–07 only). Chromo-

somal anomalies represented 12.8% of congenital anomalies among singleton births, and 7.43% among multiple births. The prevalence of conjoined twins was 0.19 per 10 000 births ($n = 103$).

Trends in multiple births and zygosity in the denominator (births) data

The percentage of babies who were from multiple births rose from 2.32% to 3.09% between 1984–87 and 2004–07 (Figure 1). The rise, which mainly occurred in the late 1980s and plateaued thereafter, varied between countries (Figure 1). The estimated proportion of MZ twins among all births varied between 0.76% and 0.96% but showed no overall trend, whereas the proportion of DZ twins among all births rose, with a similar plateau, from 1.43% to 1.93% (Figure 2).

Trends in prevalence of congenital anomaly in multiple births and relative risk compared with singleton births 1984–2007

The prevalence of cases of congenital anomaly from multiple births increased from 5.60 per 10 000 births in 1984–87 to 10.9 per 10 000 in 2004–07, peaking at 11.5 per 10 000 births in 2000–03 ($P < 0.001$, Table 2), with variation between countries (Figure 3). Nonchromosomal anomalies from multiple births increased from 5.03 per 10 000 births to 10.0 per 10 000 births over the same period ($P < 0.001$, Table 2). The prevalence of chromosomal anomalies from multiple births increased from 0.58 per 10 000 births to 0.90 per 10 000 births ($P = 0.037$, Table 2).

The proportion of congenital anomaly cases in multiple births was 3.49% (95% CI 3.40–3.55%) compared with
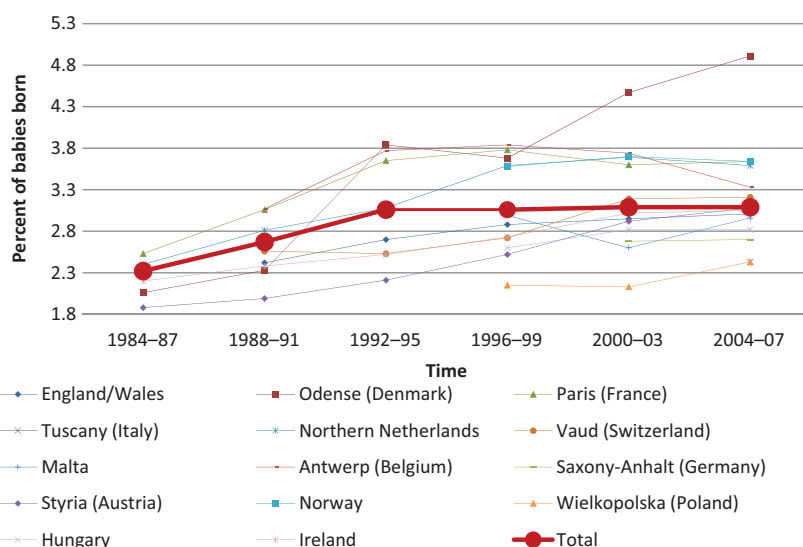

Figure 1. Proportion (%) of multiple births in the EUROCAT population: 1984–2007.
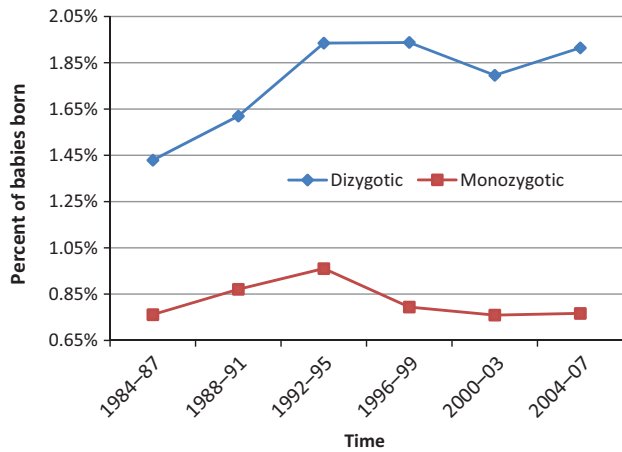
Figure 2. Estimated proportion of births (babies) who were monozygotic and dizygotic twins: 1984–2007 (see Table 1 for registries with data on like-sex and unlike-sex births on which this figure is based, using Weinberg rule).

2.70% (95% CI 2.69–2.72%) in singleton births. The relative risk of congenital anomaly in multiple versus singleton births adjusted for country and time (adjRR) was 1.27 (95% CI 1.24–1.30) (Table 2).

The proportion of nonchromosomal congenital anomaly cases in multiple births was 3.23% (95% CI 3.14–3.328%) compared with 2.35% (95% CI 2.34–2.37%) in singleton births. Relative risk of nonchromosomal anomaly in multiple versus singleton births, adjusted for country and time, was adjRR 1.35 (95% CI 1.31–1.39) overall, increasing over time from adjRR 1.06 (95% CI 0.92–1.22) for 1984–87 to adjRR 1.41 (95% CI 1.34–1.48) for 2004–07 (Figure 4).

The overall proportion of chromosomal anomalies in multiple births was 0.26% (95% CI 0.24–0.29%) compared with 0.35% (95% CI 0.34–0.35%) in singleton births. Relative risk of chromosomal anomalies in multiple versus singleton births, adjusted for country and time, was adjRR 0.72 (95% CI 0.65–0.80), decreasing over time from adjRR

Table 2. Number and prevalence of cases from multiple births per 10 000 births and proportion (%) of cases in multiple and singleton births for all, nonchromosomal and chromosomal cases and RR of cases in multiple relative to singleton births 1984–2007, by 4-year time period

	Congenital anomaly cases from multiple pregnancies				Congenital anomaly cases from singleton pregnancies		RR congenital anomaly in multiple relative to singleton births*	
Year-groups	Number	Prev/10 000 births	95% CI	% multiple births	Number	% singleton births	RR	95% CI
All congenital anomaly cases								
1984–87	185	5.60	4.85–6.47	2.41	7359	2.28	1.06	0.91–1.22
1988–91	350	8.58	7.72–9.52	3.19	10 543	2.65	1.19	1.07–1.33
1992–95	581	11.3	10.4–12.2	3.67	13 905	2.79	1.31	1.20–1.42
1996–99	1040	10.1	9.45–10.7	3.28	26 847	2.68	1.20	1.13–1.27
2000–03	1934	11.5	11.0–12.1	3.74	46 042	2.83	1.30	1.25–1.36
2004–07	1603	10.9	10.4–11.5	3.55	37 968	2.66	1.31	1.24–1.38
Total	5695	10.5	10.2–10.8	3.49	142 664	2.70	1.27	1.24–1.30
Nonchromosomal anomalies								
1984–87	166	5.03	4.32–5.85	2.16	6539	2.03	1.07	0.92–1.25
1988–91	320	7.82	7.01–8.72	2.91	9221	2.31	1.25	1.12–1.39
1992–95	528	10.3	9.42–11.2	3.34	12 014	2.41	1.37	1.26–1.50
1996–99	948	9.16	8.59–9.76	2.99	23 430	2.33	1.26	1.18–1.34
2000–03	1883	10.9	10.4–11.4	3.54	40 629	2.50	1.40	1.34–1.47
2004–07	1472	10.1	9.51–10.5	3.26	32 386	2.27	1.41	1.34–1.48
Total	5268	9.68	9.42–9.95	3.23	124 219	2.35	1.35	1.31–1.39
Chromosomal anomalies								
1984–87	19	0.58	0.37–0.90	0.25	820	0.25	0.97	0.61–1.52
1988–91	30	0.73	0.49–1.05	0.27	1322	0.33	0.83	0.58–1.18
1992–95	53	1.03	0.79–1.35	0.33	1891	0.38	0.87	0.66–1.14
1996–99	92	0.89	0.72–1.09	0.29	3417	0.34	0.81	0.66–1.01
2000–03	101	0.60	0.50–0.73	0.20	5413	0.33	0.57	0.47–0.70
2004–07	131	0.90	0.76–1.06	0.29	5582	0.39	0.71	0.60–0.78
Total	426	0.79	0.71–0.86	0.26	18 445	0.35	0.72	0.65–0.80

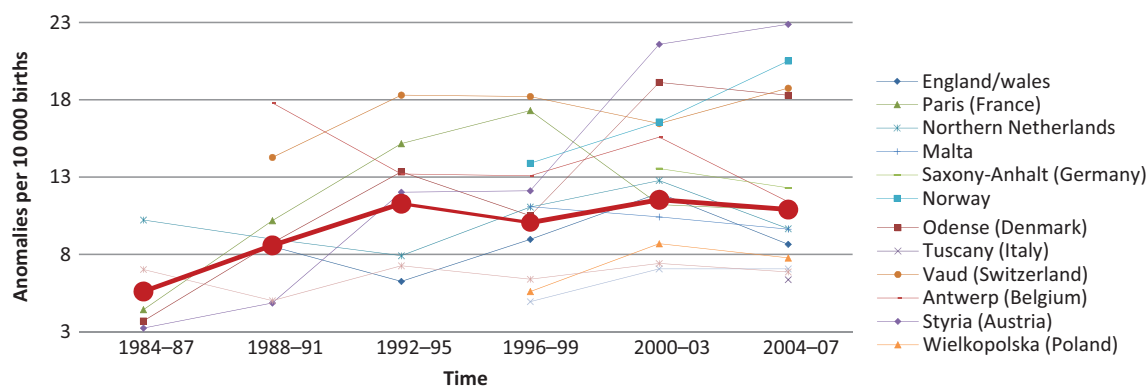*Adjusted for country, total adjusted for country and time.

Figure 3. Prevalence of congenital anomaly cases from multiple births per 10 000 births: 1984–2007.
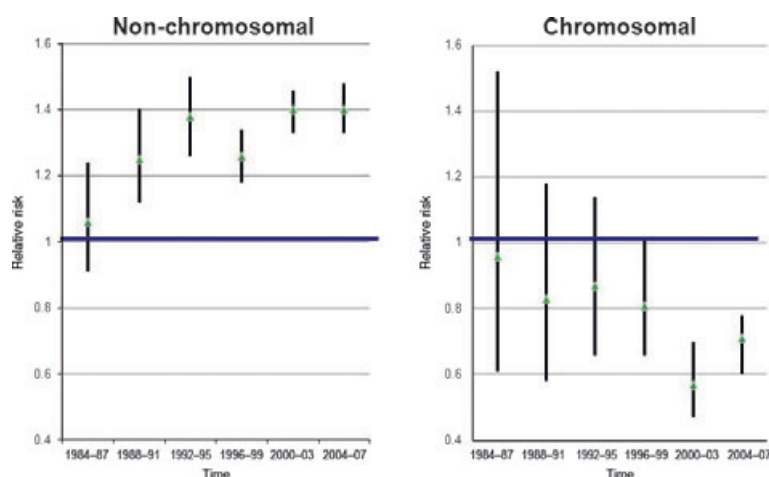

Figure 4. Risk of congenital anomaly in babies from multiple births relative to singletons: 1984–2007, for nonchromosomal and chromosomal anomalies separately.

0.97 (95% CI 0.61–1.52) for 1984–87 to adjRR 0.71 (95% CI 0.60–0.78) for 2004–07 (Figure 4).

A subanalysis of RR adjusted for maternal age was performed for countries with maternal age denominator data. This adjustment resulted in almost no change for nonchromosomal anomalies [a change from unadjusted RR 1.31 (95% CI 1.26–1.36) to adjRR 1.33 (1.28–1.38)] and an increased risk deficit for chromosomal anomalies [unadjusted OR 0.72 (95% CI 0.40–0.81) to adjOR 0.64 (95% CI 0.57–0.72)].

Concordance 2000–07

The 2000–07 data for twin pairs with at least one nonchromosomal case (*n* = 2665), showed a proportion of concordant pairs (where both babies were diagnosed with a nonchromosomal congenital anomaly) of 11.6%. Converted to babies, this means that 20.8% of cases with a nonchromosomal anomaly from a multiple birth have an affected co-twin.

For pairs with at least one chromosomal anomaly case (*n* = 217), 5.53% of pairs were concordant. In terms of babies, 10.5% of cases with a chromosomal anomaly from a multiple birth are from a concordant pair.

There were seven pairs (0.2% of all affected twin pairs) where one baby had a chromosomal anomaly and the other had a nonchromosomal anomaly. In total, concordance for all twin pairs with at least one congenital anomaly case was 11.4%.

Prenatal diagnosis 2000–07

Prenatal diagnosis did not significantly differ between cases from multiple births and singleton pregnancies [adjOR 0.97 (95% CI 0.89–1.06)], but were less likely to result in TOPFA [adjOR 0.41 (95% CI 0.35–0.48)]. This was found for both nonchromosomal and chromosomal anomalies, but chromosomal anomalies had a particularly reduced TOPFA frequency [adjOR 0.21 (95% CI 0.14–0.31), Table 3].

Of prenatally diagnosed nonconcordant pairs where one baby had a nonchromosomal anomaly, 16.2% (n = 89 pairs) resulted in TOPFA (i.e. selective feticide), compared with 26.6% (n = 34 pairs) in concordant pairs. For chromosomal anomalies, these proportions were 48.1% (n = 50) for nonconcordant, and 22.2% (n = 2) for concordant pairs.

Pregnancy outcome 2000–07

Of congenital anomaly cases from multiple pregnancies, 88.7% resulted in an LB, compared with 84.4% for singletons (Table 4). The greater proportion of LB in cases from multiple births was mainly explained by the lower TOPFA proportion in multiple births.

Babies with congenital anomalies from multiple births were born at earlier gestational ages than those from singleton births with 51.5% of cases from multiple births (once TOPFAs were excluded) born before 36 weeks of gestation compared with 11.3% of those from singleton births (Table 4). Gestational age <36 weeks was associated with greater mortality (both SB and early neonatal death) than gestational age $\geq$ 36 weeks for both multiple and singleton congenital anomaly cases, but mortality was lower for multiple than singleton congenital anomaly cases born before 36 weeks of gestation (Table 4).

Babies from multiple births with congenital anomalies were more than twice as likely to be SB than LB compared with their singleton counterparts [OR 2.55 (95% CI 2.16–3.02), Table 4], and more than twice as likely to be early neonatal deaths rather than surviving LB [OR 2.36 (95% CI 1.97–2.82), Table 4]. Overall, the increased SB and neonatal death rate for multiple births with congenital anomaly was a combination of mortality associated with more

preterm birth, and greater mortality than singletons among term births (Table 4).

Patterns of mortality differences were similar for nonchromosomal and chromosomal cases (data not shown, available on request).

Discussion

Interpretation of main findings

Within the European population studied, there was an approximately 50% rise in the multiple birth rate, reflecting trends reported by EUROPERISTAT,[32] accompanied by a 70% rise in prevalence of congenital anomaly cases from multiple births from 1984 to 2007. Most of the rise happened in the 1980s. The risk of congenital anomalies was 27% higher in multiple births than singleton births and this excess risk also increased over time, again mainly in the 1980s.

If excess congenital anomaly risk were associated with MZ twinning alone, given that the rise in the rate of multiple births is in the rate of DZ twins, we should find a decrease over time in the relative risk of congenital anomaly in multiple (MZ + DZ) versus singleton birth, whereas we find the contrary—an increase. This suggests that DZ twins may also be at higher risk of congenital anomaly, and it is possible that this risk increase is related to ART[12,13] or to parental characteristics associated with ART,[14] rather than with multiple birth status per se. If ART is associated with some of the excess risk identified, then the increasing adoption of single-embryo-transfer policies[33] may simply redistribute the risk of congenital anomaly to singletons.

In contrast with nonchromosomal anomalies, we found a deficit of chromosomal cases from multiple births.

Table 3. Numbers and proportions of prenatally diagnosed (PD) cases, number and proportion of terminations of pregnancy for fetal anomaly (TOPFA), and OR comparing cases from multiple births with singleton cases, 12 European countries*, 2000–07

Congenital anomaly group	PD/TOPFA	Number and proportion (%) among singleton births	Number and proportion (%) among multiple births	OR (95% CI) **
All congenital anomalies	Prenatal diagnosis	21 696 (34.0)	858 (32.9)	0.97 (0.89–1.06)
	TOPFA following prenatal diagnosis	9559 (44.0)	213 (24.8)	0.41 (0.35–0.48)
Nonchromosomal anomalies	Prenatal diagnosis	15 688 (28.9)	737 (30.7)	1.08 (0.99–1.18)
	TOPFA following prenatal diagnosis	4779 (30.5)	159 (21.6)	0.60 (0.50–0.72)
Chromosomal anomalies	Prenatal diagnosis	6025 (62.8)	121 (59.6)	0.94 (0.68–1.31)
	TOPFA following prenatal diagnosis	4780 (79.3)	54 (44.6)	0.21 (0.14–0.31)

*Norwegian and Hungarian data excluded because prenatal diagnosis data were not available.
**Adjusted for country.

Table 4. Numbers and proportions of cases by pregnancy outcome and OR comparing cases from multiple births with singleton cases 2000–07

Outcome	Singletons				Multiple births				AdjOR* (95% CI), excluding TOPFA		
	Total number and proportion (%)	Excluding TOPFA			Total number and proportion (%)	Excluding TOPFA			Total	≤35 weeks	≥36 weeks
		Proportion (%)	n (%) ≤35 weeks	n (%) ≥36 weeks		Proportion (%)	Number and (%) ≤35 weeks	Number and (%) ≥36 weeks			
Livebirths	73 376 (84.4)	73 376 (98.0)	6912 (86.6)	62 298 (99.4)	3191 (88.7)	3191 (95.2)	1563 (93.5)	1529 (97.0)	1.00	1.00	1.00
Stillbirths	1485 (1.84)	1485 (1.98)	1074 (13.4)	390 (0.60)	160 (4.60)	160 (4.77)	108 (6.46)	47 (2.98)	2.55 (2.16–3.02)	0.45 (0.37–0.56)	5.01 (3.68–6.84)
Early neonatal deaths**	1432 (2.51)	—	603 (11.0)	829 (1.6)	145 (5.45)	—	103 (7.57)	42 (3.28)	2.36 (1.97–2.81)	0.70 (0.56–0.88)	2.05 (1.49–2.81)
TOPFAs	11 389 (13.7)	—	—	—	233 (6.63)	—	—	—	—	—	—

*All ORs adjusted for country.
**Early neonatal death is based on live births only.

A deficit has been previously reported[4,7] but nevertheless seems not to be widely known. We found that the main reduction was in number of concordant pairs/cases from MZ twins. Given the paucity of evidence on multiple births for use in prenatal screening algorithms,[17] this finding is being further detailed in a study on Down syndrome, which enlarges the study population further. Interpretation is complex, as it involves consideration of maternal age, zygosity and ART including egg donation, use of eggs frozen at a younger maternal age and preimplantation diagnosis. The low concordance we find suggests selective loss of affected fetuses in early pregnancy, before diagnosis, particularly in concordant MZ twins.[34]

Despite the greater technical and organisational problems in twin or multiple pregnancies,[15–18] prenatal diagnosis rates for congenital anomalies were similar between cases from singleton and multiple pregnancies. After prenatal diagnosis, termination was much less likely to be the outcome in multiple than singleton pregnancies as an unaffected co-twin must often be considered. Cases from multiple births were more likely to die in the perinatal period than their singleton counterparts, partly associated with their much greater preterm delivery rate and partly associated with higher mortality rates at term. The balance of congenital anomaly and survival is complex as it is confounded by the obstetric choices that surround multiple births.[35–37] Moreover, because of the lower TOPFA rate, the proportion of lethal and very severe anomaly cases surviving to LB or SB is likely to be higher in multiple birth cases, so affecting perinatal mortality rates.[9] Concordant pairs were more likely to result in termination than cases from nonconcordant pairs, presumably as the need to consider the co-twin is lessened. The difference in outcomes between cases from multiple and singleton births suggests that, although single embryo transfer may not influence the overall number of congenital anomaly cases, it may affect the pregnancy outcomes for those cases from ART pregnancies.

Strengths and limitations

The strengths of this study relate to its large population coverage in Europe, with high-quality diagnostic data on congenital anomalies that were collected from multiple sources and coded consistently. The main study limitation relates to the lack of individual information on zygosity, for both cases and births, and the lack of systematic data on ART for cases and for births. An important methodological issue in this type of study is the definition of a multiple birth. Earlier in pregnancy, more pregnancies are multiple; some of these experience loss of one fetus leading to a singleton delivery.[38] We validated our case data to make sure that 'multiple' status was at delivery, not early pregnancy, and would therefore be comparable to data from birth registrations.

There are differences between registries in ascertainment of congenital anomaly cases, because of differences in screening and diagnosis, and differences in completeness of access to appropriate medical records,[22, 39] and so we stratified analyses for registry. Multiple birth status for cases may sometimes have been unstated in the medical records leading to slight underestimation of RR. Multiple births may be subject to more prenatal screening[18] than singletons (although we found a similar prenatal diagnosis rate) or more paediatric examination because of longer hospital stays associated with preterm birth, but our data concern major anomalies that are normally diagnosed prenatally or neonatally.

Implications for service provision

The co-occurrence of multiple birth and congenital anomaly among liveborn infants places particular demands on parents and health services. This may be even more relevant for the one in nine affected twin pairs where both babies are affected by a congenital anomaly. Parental interactions encouraging normal development are more difficult with twins[40] and such interaction may be particularly important for babies with a congenital anomaly, potentially requiring ongoing treatment.[41,42] Extra specialised help should be put in place for affected families, recognising that there are now nearly twice as many affected families than there were 20 years ago, although absolute numbers are small, at one per 1000 births.

Women with MZ twin pregnancies can be counselled that they have a small excess risk of a major congenital anomaly (per baby), usually with only one baby affected, but a lower risk of chromosomal anomaly (per baby), compared with women with singleton pregnancies. For women with DZ pregnancies, further research is needed to determine whether any excess risk of nonchromosomal congenital anomaly is limited to those following ART.

Conclusions

We found a small excess risk of nonchromosomal congenital anomaly in multiple births, an excess that increased particularly during the 1980s, possibly because of ART. We found a lower risk of chromosomal anomaly among multiple births than singletons, which needs further investigation before it can be fully taken into account for prenatal screening. The rate of prenatal diagnosis was similar for multiple and singleton pregnancies, but TOPFA following prenatal diagnosis was much less commonly chosen in multiple pregnancies, and this, as well as the higher preterm rate, contributed to higher SB and neonatal mortality. The co-occurrence of multiple birth and congenital anomalies is now twice as common as in the mid-1980s, at 1 per 1000 babies. A single-embryo-transfer policy may not reduce the number of babies with congenital anomalies in the population, but may affect pregnancy course and neonatal outcome and reduce the extra demands placed on services and on parents by co-occurrence of multiple birth and congenital anomaly.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Number of births and proportion(%) which are multiple births; number of congenital anomaly (CA) cases from multiple births; proportion (%) congenital anomaly cases in multiple and in singleton births and Relative Risk (RR), by country 2000-2007. ■

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