**Congenital anomalies in twins: a register-based study**

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Congenital anomalies in twins: a register-based study

Running title: Congenital anomalies in twins

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Abstract

BACKGROUND: The risk of congenital anomalies in twins is higher than in singletons, but it is less well reported in relation to chorionicity. The aim of this study was to describe the prevalence of congenital anomalies in twin pregnancies by chorionicity and by major subtype and compare the rates with those in singletons. METHODS: The study population included 2329 twin pregnancies (4658 twins) and 147,655 singletons delivered in the Northeast of England during 1998-2002. Data were obtained from the population-based Northern Multiple Pregnancy Register and Northern Congenital Abnormality Survey. RESULTS: The rate of congenital anomalies in twins was 405.8 per 10,000 twins vs 238.2 per 10,000 singletons [RR=1.7, 95% confidence interval (CI) 1.5-2.0]. In twins with known chorionicity (84.8% of all twins), the prevalence of congenital anomalies in monochorionic twins (633.6 per 10,000) was nearly twice that in dichorionic (343.7 per 10,000; RR=1.8, 95% CI 1.3-2.5). There was an increased rate of congenital anomalies in twin compared to singleton pregnancies for all major types of anomalies, except chromosomal abnormalities. CONCLUSIONS: This study using high quality, population-based data on multiple pregnancies and congenital anomalies found that twins, particularly monochorionic, have a higher risk of congenital anomalies than singletons.

Word count: 197

Key words: twin pregnancies/congenital anomalies/chorionicity/Northern Multiple Pregnancy Register/Northern Congenital Abnormality Survey (NorCAS)
Introduction

The rate of multiple births continues to increase due to the combined effect of a rise in maternal age and increased use of assisted reproductive technologies (ART) (Blondel and Kaminski, 2002; Derom et al., 1995). The contribution of twins following ART to the increasing trend in total multiple birth rates is rising over time (Derom et al., 1995; Human Fertilisation and Embryology Authority, 2007) Thus according to the UK Human Fertilisation and Embryology Authority, around 25 percent of all twins in the UK were conceived as a result of in vitro fertilisation (IVF) treatment. In the Northern region of England the twinning rate has increased from 9.8 per 1000 maternities in 1990 to 12.0 in 1994 (Glinianaia et al., 1998), and more recently to 16.7 per 1000 maternities in 2002 (Ward Platt et al., 2006). Multiple births are well known to carry a higher risk of perinatal mortality (Glinianaia et al., 2000), preterm birth (Papiernik, 1995) and cerebral palsy (Glinianaia et al., 2002; Pharoah, 2006). The risk of congenital anomalies among these pregnancies, although known to be higher compared to singletons (Li et al., 2003; Mastroiacovo et al., 1999; Meyers et al., 1995), is less well documented, in particular in relation to chorionicity.

This study describes the prevalence of congenital anomalies in twin pregnancies by chorionicity and by major anomaly subtype, using data from two population-based prospective surveys; the Northern Multiple Pregnancy Register (MPR) and the Northern Congenital Abnormality Survey (NorCAS).
Methods

The MPR was established in 1998 to capture details on all multiple pregnancies in the former Northern Region (1993 boundaries), comprising the counties of north Cumbria, Northumberland, Tyne and Wear, Durham & Darlington, and Teesside. Details on data collection are described elsewhere (Glinianaia et al., 2001). Ascertainment is from the earliest antenatal scan on which a multiple pregnancy is detected, and then successively at the time of the 20 week anomaly scan and at delivery. The records are linked to the long standing Perinatal Mortality Survey database (PMS) (Northern Regional Health Authority Coordinating Group, 1984) and the NorCAS (Northern Regional Survey Steering Group, 1992; Rankin, 2007; Richmond and Atkins, 2005), both of which are housed at the Regional Maternity Survey Office (RMSO). NorCAS collects data on all congenital anomalies arising within the population of the former Northern region. Data on congenital anomalies occurring in late miscarriages (≥20 weeks), terminations of pregnancy for fetal anomaly, stillbirths and livebirths whether diagnosed antenatally or not, are notified to NorCAS. For the purpose of this paper congenital anomalies resulting in late miscarriages were not included in the analysis (see Definitions). Cases are notified from multiple sources, are coded to ICD-10, and the EUROCAT (European Surveillance of Congenital Anomalies, a network of 38 congenital anomaly registers in 20 European countries) exclusion list for minor anomalies is employed (http://www.eurocat.ulster.ac.uk/). Final diagnosis of chorionicity for like-sex twin pregnancies is based on placental examination and histology; or, when there is no pathologic examination of placenta, on appropriate first trimester antenatal ultrasound determination.

Information on zygosity is not available in the MPR.

The number of total births for the former Northern Region population was obtained from the Office for National Statistics. The denominator for singletons in the current analysis was calculated by subtracting the number of multiple births registered in the MPR from the
total number of births and then by adding the number of terminations for a congenital anomaly in singletons registered in the NorCAS.

In line with current UK law, the RMSO cannot capture data on the use of ART in relation to these pregnancies.

**Definitions**

A *stillbirth* was defined as the birth of a dead fetus at 24 or more completed weeks of gestation, the legal cut-off in gestational age for stillbirth in England and Wales since in October 1992. *Twin maternities* are defined as twin pregnancies with at least one live birth or stillbirth, including pregnancies where there has been a fetal loss before 24 completed weeks of gestation. *The twinning rate* is defined as the number of twin maternities per 1000 total maternities with at least one livebirth or stillbirth. The *total prevalence rate* of congenital anomalies in *all registered twin pregnancies* is calculated per 10,000 twins irrespective of their outcome (Table II). The *total prevalence rate* of congenital anomalies *in singletons* is the number of anomaly-affected pregnancies resulting in terminations of pregnancy, stillbirths and livebirths per 10,000 singleton stillbirths, livebirths and terminations of pregnancy (for fetal anomaly); late miscarriages are not included in this calculation due to the lack of denominator data for late miscarriages. For comparison with singletons in Table III, the prevalence rate of congenital anomalies in twins is calculated per 10,000 twins resulting in either termination of pregnancy, stillbirth or livebirth of at least one co-twin (twin pregnancies resulting in a spontaneous abortion of both twins are excluded, n=99); this exclusion explains a slight discrepancy in the number of congenital anomalies and the denominator in twins between Tables II and III.

**Ethics and consent**
The RMSO is part of the North East Public Health Observatory and data is processed in accordance with its Security and Confidentiality policy. The RMSO has ethics approval (04/MRE04/25) to undertake studies involving the use of its data.

Statistical analysis

For descriptive statistical analysis we used SPSS for Windows version 14.0. Rate ratios (RR) with 95% confidence intervals (95% CI) are presented, with statistical significance being accepted at the 5% level.
Results

There was a total of 2175 twin maternities during the five years, giving a twinning rate of 14.6 per 1000 maternities. The twinning rate increased from 13.6 per 1000 maternities in 1998 to 16.7 in 2002 (Table I).

Of all twin pregnancies 2084 (89.5%) were diagnosed before 19 weeks of gestation (65.2% before 13 weeks), with no significant change over the five years. Chorionicity in twin maternities was unknown for 68 (15.8%) maternities in 1998 but this had improved to 42 (8.7%) in 2002 (Table I). Over this time the ratio of dichorionic (DC) to monochorionic (MC) twins remained similar. There was also no change in the ratio of like-sex (LS) to unlike-sex (ULS) twins. For 1998-2002, chorionicity data were missing for 246 (11.3%) of 2175 twin maternities. The proportion of missing data increased to 353 (15.2%) of 2329 twin pregnancies, which also included pregnancies with early loss of both twins where the determination of chorionicity is fallible.

Congenital anomalies in twin pregnancies

Congenital anomalies complicated 163 pregnancies, involving 182 individuals (390.7 per 10,000 registered twins) (Table II). Of these, 20 twins with anomalies were stillbirths, eleven were terminated pregnancies; three spontaneous abortions, there was one selective reduction and 138 live born twins with 117 (84.8%) still alive at one year. The prevalence in live born twins was 331.4 per 10,000 livebirths.

Table II shows that the most common types of congenital anomalies were: cardiovascular anomalies (51, 28.0%), anomalies of the central nervous system (24, 13.2%), genito-urinary system (25, 13.7%), chromosomal anomalies (21, 11.5%), musculoskeletal (19, 10.4%) and others (31, 17.0%) including facial clefting, oesophageal atresia, other anomalies of the digestive system, syndromes (2.7%) and multiple anomalies (2.2%). Of anomalies
related to twinning (6%), there were four sets of conjoined twins and three fetuses were affected by the TRAP sequence.

Chorionicity was known for 143 (87.7%) of 163 twin pregnancies with congenital anomalies. Table II shows that in twins with known chorionicity, the prevalence of congenital anomalies in MC twins (633.6/10,000) was significantly higher than that in DC twins (343.7/10,000) (RR=1.8, 95% CI 1.3–2.5). The analysis by major congenital anomaly type revealed that in addition to the expected contribution of anomalies related to twinning, the excess risk in MC twins was attributable to anomalies of the central nervous system, chromosomal and musculoskeletal anomalies. The numbers were sometimes too small to reach statistical significance, as for example in the case of chromosomal anomalies, and the confidence intervals were wide. The prevalence in twin pregnancies with unknown chorionicity was 297.5 per 10,000. Given that chorionicity data are incomplete; these rates must be treated with caution. Even if all twins of unknown chorionicity were assumed to be dichorionic, the relative risk of congenital anomalies in MC twins was still higher compared to DC twins (RR=1.9, 95% CI 1.4-2.6). Among 20 twin pregnancies with unknown chorionicity 12 were like-sex twin pairs.

For comparison with studies which do not have chorionicity data we also present the prevalence of congenital anomalies for LS twins, which can contain both MC and DC pregnancies, and ULS twins, containing only DC twin pairs. For LS pairs the rate was higher (439.2 per 10,000) than for ULS pairs (313.8 per 10,000) (RR=1.4, 95% CI 1.0-2.0), but the relative risk was lower than for MC versus DC pairs. As 261 twin pregnancies of the 2329 recorded twin pregnancies (11.2%) resulted in an early spontaneous fetal loss of at least one twin or a termination of pregnancy, the number of twins with unknown sex pairing (205 pairs) was substantial. The prevalence of congenital anomalies in these pregnancies was 317.1 per 10,000.
Twins were discordant for a congenital anomaly in the majority (144 out of 163) of pregnancies affected by an anomaly, including 33 out of 434 MC pregnancies. Nineteen pregnancies (11.6%) had both twins affected by a congenital anomaly; eleven of these were MC pregnancies, in ten of MC pregnancies co-twins had concordant types of anomalies.

**Twin-singleton comparisons**

Table III shows the total rates of congenital anomalies in both twins and singletons; the risk of a congenital anomaly in a twin pregnancy was 70% higher that in a singleton pregnancy, when anomalies related to the twinning process (conjoined twins and twins affected by the Twin Reversed Arterial Perfusion (TRAP) sequence, i.e. acardiac twins) were also included. The higher risk for twins was not reduced greatly when these twin-specific anomalies were excluded [RR=1.61 (1.38-1.87)] for comparison with other studies. The prevalence rate in live born singletons was 188.1 per 10,000.

Table III also demonstrates that twins had higher rates of all major types of congenital anomalies than singletons, except chromosomal anomalies. A separate comparison of the total rates between singletons and twins of different chorionicity revealed that the excess risk of congenital anomalies observed in twins was largely attributed to the excess risk in MC twins (RR=2.3, 95% CI 1.7-3.0) even when anomalies specific to MC twinning were excluded. However, even in DC twins the rate of congenital anomalies was significantly higher than that in singletons (RR=1.4, 95% CI 1.2-1.8). The risk of congenital anomalies in LS twin pairs was higher (RR=1.7, 95% CI 1.4-2.1) than in ULS twin pairs 1.3 (95% CI 1.0-1.8) compared to singletons.
Discussion

This study using high quality, prospectively collected data from population-based registers of twins and congenital anomalies reports an increased rate of congenital anomalies in twin compared to singleton pregnancies for all major types of anomalies, except chromosomal abnormalities. There was a two-fold increased prevalence of congenital anomalies in MC twins compared to singletons; however, congenital anomalies were also more common in DC twins than in singletons. Among twin pregnancies, the rate of congenital anomalies was nearly doubled in MC compared to DC twin pairs.

Our findings confirm earlier studies reporting a higher rate of total congenital anomalies in twins compared to singletons (Doyle, 1996; Jaikrishan et al., 1999; Kato and Fujiki, 1992; Li et al., 2003; Luke and Keith, 1990; Mastroiacovo et al., 1999; Myrianthropoulos, 1976; Spellacy et al., 1990; Zimo et al., 1998). Some studies found that the total rate of anomalies did not differ significantly between twins and singletons (Campana and Roubicek, 1996; Doyle et al., 1991; Ghai and Vidyasagar, 1988; Little and Nevin, 1989; Ramos-Arroyo, 1991; Windham and Bjerkedal, 1984), however, some specific major anomalies were significantly more common in twins than in singletons (Doyle et al., 1991; Windham and Bjerkedal, 1984).

Our observation that the most common anomalies in both twins and singletons were cardiovascular anomalies and the relative risk was higher for twins than singletons confirms previous reports (Kallen, 1986; Li et al., 2003; Little and Nevin, 1989; Mastroiacovo et al., 1999; Pradat, 1992; Windham and Bjerkedal, 1984). We found that anomalies of the central nervous system were more common in twins than in singletons, a finding consistent with some earlier reports (Doyle et al., 1991; Li et al., 2003; Mastroiacovo et al., 1999; Myrianthropoulos, 1976) but not with others (Kallen, 1986; Little and Nevin, 1989), which observed excess rates in twins for hydrocephaly (Kallen, 1986) but not for neural tube defects (Kallen, 1986; Little and Nevin, 1989). Anomalies of the digestive system, in particular gut

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atresias, are also reported to be more common in twins (Doyle et al., 1991; Kallen, 1986; Li et al., 2003; Mastroiacovo et al., 1999). There were only seven cases of isolated gut atresias in twins in our study but the prevalence was significantly higher than in singletons. Our data also confirmed the findings of previous studies reporting higher rates of anomalies of the genitourinary (Kallen, 1986; Li et al., 2003; Mastroiacovo et al., 1999) and musculoskeletal (Li et al., 2003; Mastroiacovo et al., 1999) systems in twins compared to singletons. The rates of chromosomal abnormalities were similar in twins and singletons as was found by Li and colleagues (Li et al., 2003). In earlier studies the prevalence of Down syndrome in twins was reported to be lower than in singletons (Doyle et al., 1991; Kallen, 1986; Myrianthopoulos, 1976; Windham and Bjerkedal, 1984). However, some studies excluded chromosomal abnormalities from their analysis due to the presumed confounding effect of advanced maternal age associated with dizygotic twinning (Mastroiacovo et al., 1999).

The variations in the prevalence rates of congenital anomalies between studies may partly be explained by the differences in definitions and inclusion criteria for anomalies and outcomes examined. Some were based on register data which collected congenital anomalies in live born children only and included such anomalies as congenital dislocation of hip, talipes, patent ductus arteriosus or undescended testes, (Li et al., 2003) which our study excluded. Although the differences in inclusion criteria will affect the overall rate and rates by major malformation type, it should not influence the rate ratios as long as inclusion criteria are consistent for both singletons and twins. However, the timing of registration of a twin pregnancy will affect the rate ratios: the earlier a twin pregnancy is registered the higher is the number of diagnosed early fetal losses including those with congenital anomalies and, consequently, the lower is the number of twin pregnancies registered as singleton. Thus it has been hypothesised that some congenital anomalies and cerebral palsy of unknown aetiology may be attributable to ischaemic organ damage caused by feto-fetal transfusion in a
monochorionic multiple pregnancy or perhaps (even in apparent singletons) to early, unrecognized or unrecorded loss of one conceptus (the so-called ‘vanishing’ twin) in a monochorionic pregnancy (Pharoah, 2007; Pharoah, 2005). A major strength of our study is ascertainment of a multiple pregnancy from the earliest antenatal scan where available and the inclusion of congenital anomalies irrespective of pregnancy outcome.

Few studies were able to examine congenital anomalies in twins by chorionicity or zygosity, however, many congenital brain, cardiac, renal, intestinal and other anomalies in twins are more common in monozygotic (MZ) twins (Chen et al., 1992; Meyers et al., 1995; Myrianthopoulos, 1976; Pharoah, 2002). The elevated risk of congenital anomalies was confined to LS twins when sex of the twin pair was used as a proxy for zygosity estimation (Campana and Roubicek, 1996; Layde et al., 1980; Ramos-Arroyo, 1991). In contrast to other studies, Little et al. (Little and Nevin, 1989) did not find markedly higher rates amongst LS (287.8/10,000) compared to ULS twins (252.3/10,000). However, the excess rate they found for cardiovascular anomalies was confined to LS twins.

In our study the risk of congenital anomalies in MC twins was nearly twice as high as in DC twins, which remained stable when twins with unknown chorionicity were added to DC twins. The increased risk of anomalies in MC twins was over twice higher than in singletons. With few reported exceptions, MC twin pregnancies are also MZ, and only about one third of MZ pregnancies are DC (Machin, 2007). A number of mechanisms have been proposed for the higher rate of anomalies in MC and MZ twins (Phelan and Hall, 2006). Vascular anastomoses between the circulations supplying MC twins are associated with a variety of disruptive anomalies, in particular twin reversed arterial perfusion (so-called acardiac twins), and those due to hypoxic-ischaemic injury resulting from sudden changes of flow through the anastomoses (such as might occur following death of one twin) (Pharoah, 2005). MZ twinning itself can be regarded as an abnormality of morphogenesis (Jones, 2006), and some
early primary malformations may develop due to the same (poorly understood) aetiological mechanisms; such malformations have a predilection for midline structures, eg sirenomelia, cloacal anomalies and holoprosencephaly (Phelan and Hall, 2006).

Our study also showed an increased risk of anomalies in DC twins compared to singletons, although the excess risk was smaller than between MC twins and singletons. This can be partially explained by the fact that a third of MZ twins, which are known to be associated with a higher risk of anomalies, are DC. It can also be speculated that the excess risk of congenital anomalies in both DC and MC twins compared to singletons may be partly accounted for by surveillance bias as during pregnancy and after birth, twins, as a high risk group, are followed with increased surveillance intensity compared to singletons. However, there is currently no evidence that this is a major contributing factor to the higher risk of major congenital anomalies in twins.

Wider use of ART contributing to the growing proportion of twin pregnancies may also, to some extent, contribute to the increased rate of congenital anomalies in twins compared to singletons (Bergh et al., 1999), although some studies found an increased rate in IVF-conceived singletons (McDonald et al., 2005; Zhu et al., 2006) but not twins (McDonald et al., 2005; Zhu et al., 2006). It is still not clear to what extent the excess risk of congenital anomalies in ART treated pregnancies is due to the underlying infertility and to what extent it is due to the treatment itself. Unfortunately, in our study we were not able to investigate the effect of the use of ART on the rates of congenital anomalies as in line with current UK law, the register cannot capture these data.

The major strength of our study is the availability of reliable chorionicity data which allows us to evaluate the contribution of monochorionicity and monozygosity to the excess rate of congenital anomalies in twins. Although some studies based on data from several registries are larger and statistically more powerful, the lack of information on the sex of a co-
twin, and, in particular, on chorionicity, is a serious limitation (Mastroiacovo et al., 1999). Our study based on five-year regional data is insufficiently powerful to compare prevalence rates for specific congenital anomalies; however, it is able to present the comparison for major congenital malformation groups and to examine for concordance in relation to chorionicity.

In conclusion, our population-based study shows that twins, in particular monochorionic, have an increased risk of congenital anomalies than singletons. Among twin pregnancies, the rate of congenital anomalies in MC twin pairs was nearly twice that in DC pairs.
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References


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Table I. Multiple pregnancies, maternities, and twinning rates in the Northern Region, 1998-2002

<table>
<thead>
<tr>
<th></th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Twin pregnancies</strong></td>
<td>477</td>
<td>449</td>
<td>466</td>
<td>439</td>
<td>498</td>
<td>2329</td>
</tr>
<tr>
<td><strong>Twin maternities</strong></td>
<td>431</td>
<td>416</td>
<td>427</td>
<td>420</td>
<td>481</td>
<td>2175</td>
</tr>
<tr>
<td><strong>Dichorionic twin maternities</strong></td>
<td>289 (67.1)</td>
<td>286 (68.8)</td>
<td>299 (70.0)</td>
<td>306 (72.9)</td>
<td>344 (71.5)</td>
<td>1524 (70.1)</td>
</tr>
<tr>
<td><strong>Monochorionic twin maternities</strong></td>
<td>74 (17.2)</td>
<td>73 (17.5)</td>
<td>77 (18.0)</td>
<td>86 (20.5)</td>
<td>95 (19.8)</td>
<td>405 (18.6)</td>
</tr>
<tr>
<td><strong>Twinning rate /1000 maternities</strong></td>
<td>13.6</td>
<td>13.6</td>
<td>14.6</td>
<td>14.7</td>
<td>16.7</td>
<td>14.6</td>
</tr>
<tr>
<td><strong>Total maternities</strong></td>
<td>31737</td>
<td>30653</td>
<td>29334</td>
<td>28613</td>
<td>28886</td>
<td>149223</td>
</tr>
</tbody>
</table>

Note: Maternities are pregnancies with at least one live birth or stillbirth.

The total number of twin maternities exceeds the sum of the dichorionic and monochorionic maternities due to a number of maternities with unknown chorionicity (reduced from 15.8% in 1998 to 8.7% in 2002).
Table II. Types of congenital anomaly, rates and rate ratios (RR) for monochorionic (MC) and dichorionic (DC) twins by major anomaly group, 1998-2002

<table>
<thead>
<tr>
<th>Type of anomaly</th>
<th>DC n (sets) rates</th>
<th>MC n (sets) rates</th>
<th>RR 95% CI</th>
<th>All twins n (sets) rates</th>
</tr>
</thead>
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<tr>
<td><strong>Anomalies associated with twinning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>conjoined twins</td>
<td>—</td>
<td>11 (7) 126.7</td>
<td>—</td>
<td>11 (7) 23.6</td>
</tr>
<tr>
<td>TRAP sequence (acardiac twins)</td>
<td>—</td>
<td>8 (4)</td>
<td>—</td>
<td>8 (4)</td>
</tr>
<tr>
<td><strong>Chromosomal anomalies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trisomy 21</td>
<td>6 (5)</td>
<td>2 (1)</td>
<td>1.8 (0.7-4.7)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>trisomy 18</td>
<td>2 (2)</td>
<td>2 (1)</td>
<td>—</td>
<td>5 (4)</td>
</tr>
<tr>
<td>other</td>
<td>4 (4)</td>
<td>2 (2)</td>
<td>—</td>
<td>8 (8)</td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neural tube defects</td>
<td>6 (6)</td>
<td>5 (5)</td>
<td>3.2 (1.3-7.8)</td>
<td>14 (13)</td>
</tr>
<tr>
<td>other</td>
<td>4 (4)</td>
<td>4 (3)</td>
<td>—</td>
<td>10 (9)</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>isolated VSD</td>
<td>16 (16)</td>
<td>6 (6)</td>
<td>0.9 (0.4-1.8)</td>
<td>24 (24)</td>
</tr>
<tr>
<td>other</td>
<td>20 (18)</td>
<td>3 (3)</td>
<td>—</td>
<td>27 (25)</td>
</tr>
<tr>
<td><strong>Genito-urinary system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>renal dysplasia</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>0.9 (0.4-2.5)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>hydronephrosis</td>
<td>9 (9)</td>
<td>1 (1)</td>
<td>—</td>
<td>11 (11)</td>
</tr>
<tr>
<td>other</td>
<td>7 (6)</td>
<td>2 (2)</td>
<td>—</td>
<td>9 (8)</td>
</tr>
</tbody>
</table>
Musculoskeletal system | 8 (6) 25.9 | 9 (6) 103.7 | 4.0 (1.6-10.3) | 19 (14) 40.8
Other anomalies | 21 (20) 68.1 | 6 (5) 69.1 | 1.0 (0.4-2.5) | 31 (29) 66.6
Total with congenital anomalies | 106 (99) 343.7 | 55 (44) 633.6 | 1.8 (1.3-2.5) | 182 (163) 390.7
Denominator | 3084 | 868 | 4658

**Note:** TRAP, Twin Reversed Arterial Perfusion; VSD, ventricular septal defect; RR are given for major groups of anomalies only due to small numbers of individual anomalies.

*The number of all twins with congenital anomalies exceeds the number of DC and MC twins as there are 20 twin sets with unknown chorionicity. Other anomalies combine facial clefts, anomalies of eye, ear, face and neck, anomalies of respiratory, digestive system, syndromes and multiple anomalies. The total number of twins exceeds the sum of DC and MC twins because chorionicity was unknown for 353 pregnancies (706 twins).*
Table III. Rates of congenital anomaly in twins and singletons per 10,000 by major anomaly type and rate ratios (RR), 1998-2002

<table>
<thead>
<tr>
<th>Type of anomaly</th>
<th>Twins</th>
<th>Singletons</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>24</td>
<td>326</td>
<td>2.44 (1.61-3.69)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>51</td>
<td>1146</td>
<td>1.47 (1.11-1.95)</td>
</tr>
<tr>
<td>Chromosomal</td>
<td>20</td>
<td>649</td>
<td>1.02 (0.65-1.59)</td>
</tr>
<tr>
<td>Genito-urinary system</td>
<td>25</td>
<td>427</td>
<td>1.94 (1.30-2.90)</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>19</td>
<td>292</td>
<td>2.15 (1.36-3.42)</td>
</tr>
<tr>
<td>Other anomalies</td>
<td>31</td>
<td>677</td>
<td>1.52 (1.06-2.17)</td>
</tr>
<tr>
<td>Twin-specific anomalies</td>
<td>11</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>181</td>
<td>3517</td>
<td>1.70 (1.47-1.97)</td>
</tr>
</tbody>
</table>

**Denominator**

<table>
<thead>
<tr>
<th>Twins</th>
<th>4460^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singletons</td>
<td>147655^d</td>
</tr>
</tbody>
</table>

Note: ^a anomalies related to the twinning process (conjoined twins and twins affected by the Twin Reversed Arterial Perfusion (TRAP) sequence, acardiac twin).

^b The prevalence rate in twins is calculated per 10,000 twins resulting in either termination of pregnancy for fetal anomaly, stillbirth or livebirth of at least one co-twin (twin pregnancies resulting in spontaneous abortions of both twins were excluded).

^c Anomaly-affected pregnancies resulted in spontaneous abortions were not included [191 out of 3708 (5.2%)].

^d Includes singleton stillbirths, livebirths and terminations of pregnancy for fetal anomaly only.