INTRODUCTION

The prevalence of twinning and higher order multiple births is high and is increasing in many countries, due at least in part to fertility-enhancing medical therapies. About 1 in 40-45 births is a twin; it is thus important to investigate whether the twinning status confers a higher risk for morbidity and mortality, particularly early in life. Birth defects are a major cause of morbidity and mortality in the pediatric age-group. The purpose of this review is to consider the evidence for an increased risk of some birth defects associated with twinning, using data from the literature and the Italian Multicentre Birth Defects Registry (IPIMC), to illustrate some of the challenging aspects of the study of birth defects in twins, and to suggest some guidelines for future investigations.

What’s in a twin

Twins are a heterogeneous group. They may differ in origin and genetic similarity, as for monozygotic (MZ) and dizygotic (DZ) twins; and in placentation (monochorial monoamniotic, monochorial diamniotic, dichorial with separate or fused placentae). Likewise, birth defects are known to be heterogeneous in presentation, pathogenesis, and etiology. Thus, the question raised here is not whether or not birth defects ‘in general’ are more common in twins, but rather whether or not there are any specific types of defects that are more frequent among specific types of twins. To maintain the generality of the discussion, this review will focus on those structural defects which are not unique to twins; conjoined twins and arcadia, defects which are unique to the twinning process, will not be discussed.
What should be in a twin study

Twin studies of birth defects have often yielded inconclusive or contradictory results. A critical evaluation of these studies and the potential offered by the new technologies has enabled us to conceive an ideal study of birth defects in twins. This ideal study should address a wide range of issues, including the following ones:

Firstly, the diagnosis of twinning should be made as early as possible, even early in pregnancy. In a substantial proportion of twin pregnancies, one embryo or fetus dies early in gestation and goes undetected, so that the remaining twin is misclassified as a singleton. This misclassification will usually lead to an underestimation of the difference in birth defect rates in twins, or in a specific type of twin, that is more likely to experience an early demise. Improved technologies, including high-resolution ultrasound scanning, can greatly improve sensitivity in the diagnosis of a twin pregnancy.

Secondly, the diagnosis of zygosity must be accurate. In the majority of twin studies, the diagnosis of MZ versus DZ twinning has been based on sex-concordance of the twin sibship. New genetic technologies can have a major impact on the diagnosis of zygosity. 'DNA fingerprinting', using probes for highly polymorphic regions of the DNA, can define with close-to-absolute certainty the zygosity of twin pairs [14, 25]. These DNA-based methods are very precise, need only minute amounts of any biologic specimen, and can also be utilized for demised fetuses.

Thirdly, the type of placenta should be identified. There is evidence that some birth defects, possibly those thought to be caused by vascular anomalies, differ in frequency even among MZ twin pairs, depending on whether the MZ pair was mono or dichorionic. Moreover, the type of placentation could be a marker of the time of separation of the MZ twin pair, with dichorionic pairs having experienced earlier separation than monochorionic: this in turn could be related to a specific risk for some birth defects. Many studies do not report the type of placentation. However, since the identification of most types of placenta is not difficult for well-trained personnel, it should be strongly encouraged.

Fourthly, an adequate number of twins should be studied. A sufficient sample-size can prove to be much larger than might be expected. As an example, we may calculate the sample-size of a study to detect a two-to-fivefold increase of the most common types of birth defects among monochorionic MZ twins, using a cohort approach. From Table 1 it can be seen that to detect a two-fold increase of anencephaly compared to singletons (singleton rate, 5 per 10,000 births), over 20,000 monochorionic MZ twins have to be studied; to detect a five-fold increase, over 2,000 have to be studied. These numbers, which increase with the rareness of the defect, are much higher than those found in the twin studies published to date. Thus, it is not surprising that some studies report inconclusive or contradictory findings. It follows that any major twin study must be collaborative in nature, with all the additional issues that a collaborative study entails.

In addition, the comparison group should be adequate. Ideally, the study should be population-based, so that both twins and singletons come from the same population. If this is not the case, the design of the study should be such as to allow the comparison
Table 1 - Minimum sample-size of twins (MZ or DZ) to detect a two-or five-fold increase in the rate of selected defects compared to singletons, using a cohort approach and a ratio of case: controls of 1:100

<table>
<thead>
<tr>
<th>Birth Defect</th>
<th>Rate in singletons</th>
<th>Number of twins to detect a relative increase among twins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2-fold</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>1: 2,000</td>
<td>22,092</td>
</tr>
<tr>
<td>Cleft lip</td>
<td>1: 1,200</td>
<td>13,802</td>
</tr>
<tr>
<td>Esophageal atresia</td>
<td>1: 3,000</td>
<td>36,829</td>
</tr>
<tr>
<td>Limb deficiency preaxial</td>
<td>1:12,000</td>
<td>110,514</td>
</tr>
</tbody>
</table>

group, usually singletons, to be representative of the population from which the twins are derived. Though seemingly simple, this concept may not be easy to apply consistently, especially in collaborative studies.

Lastly, birth defects should be ascertained in the same way among twins and the comparison group. Twins may be more likely to undergo extensive examination because of the general knowledge that they may be at higher risk for structural defects or deformities, or because they tend to stay in hospital longer. This type of ascertainment bias cannot be adjusted for in the analysis of data; it has to be minimized during the examination of the patients and data collection, using, for instance, the same methods of examination and the same period of follow-up in both groups. Sufficient additional data should be recorded to correct for possible confounders during the analysis; these would include such factors as maternal age (chromosomal anomalies) and gestational age at birth (hydrocephaly).

In summary, an ideal study should detect all twins early in pregnancy, identify their zygosity and type of placentation and evaluate them in the same manner as the adequate comparison groups drawn from the same population; moreover, the study should allow for the control of confounding factors, and enrol sufficient numbers for the study to have adequate statistical power to detect reasonable differences in risk for specific birth defects among twins and twin subgroups. Such a study has yet to be made; however, it is theoretically feasible, given the technology currently available, adequate planning, a long-term approach, and widespread cooperation.

What is in a twin study?

To date, we have one small study on spontaneous abortions and a series of studies on births. All of them have one or more of the problems we mentioned in the previous paragraph, most often a small sample size and an incomplete or absent diagnosis of zygosity. This situation does not permit firm conclusionis on specific risks, but only hypotheses, though for some birth defects, the hypotheses are plausible and probably sound.
Birth defects in embryos and fetuses: general remarks

To our knowledge, there has only been one study of birth defects in aborted twins [38]. Among 1,939 complete spontaneously aborted embryos and fetuses, 53 pairs of twins were identified (25 embryos, 26 fetuses and one pair with 1 embryo and 1 fetus). Among the 37 pairs for which zygosity was determined, 35 were MZ; of these, in 21 pairs both twins had birth defects, in 4 pairs, 1 member was affected, and in 10 pairs both members were normal. Thus, the overall birth-defect rate among MZ twins was 66% (46/70), and it was higher among embryos (88%) than in fetuses (30%). Figures for DZ pairs could not be computed as there were only 2 DZ twin pairs among those with known zygosity.

Considering all 53 twin pairs, and disregarding zygosity, the birth-defect rate among embryos was 88% and among fetuses 22%, a very similar rate to that observed among singleton abortuses in the same sample specimens, which for embryos was 84% and for fetuses 26%. This small study does not provide evidence that twin embryos or fetuses have an higher incidence of defects compared to singletons. However, even in this small study, the concordance for birth defects among twin pairs appears remarkable.

Defects in newborns: general remarks

Frequency. In most studies, birth defects have been found to be about 1.5 times more common in twins than in singletons [6, 35]. Those studies that did not identify differences in rates usually had some of the methodological problems addressed above.

Frequency by zygosity. Most studies suggest that the increased frequency of birth defects in twins is mainly confined to MZ twins [6, 35]. In a few studies this has been shown directly by determining the zygosity of the twin pairs; in most however, the evidence is indirect, and stems from the comparison between like-sex (LS) and unlike-sex (US) twin pairs. The four studies [8, 9, 13, 45] in which zygosity was determined are summarized in Table 2. The larger of the four [45] is shown in more detail in Table 3.

MZ twins are not at higher risk for all types of birth defects. To identify which specific defects are more frequent in MZ twins it is necessary to have larger groups, and the studies where zygosity is known are simply not large enough. For this reason we had to rely on additional data, including the few epidemiological studies, which only provide information on the sex of pairs, and the unpublished data of the IPIMC registry. Table 4

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Rate MZ</th>
<th>Rate DZ</th>
<th>RR MZ/DZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myrianthopoulos [45]</td>
<td>24.1</td>
<td>14.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Cameron et al [8]</td>
<td>3.7</td>
<td>2.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Corney et al [13]</td>
<td>5.3</td>
<td>3.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Chen et al [9]</td>
<td>2.7</td>
<td>1.0</td>
<td>2.7</td>
</tr>
</tbody>
</table>
Table 3 - Birth prevalence (per 100 births) of birth defects in twins, by zygosity, and in singletons [45]

<table>
<thead>
<tr>
<th></th>
<th>Malformed infants</th>
<th>Total infants</th>
<th>Birth prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singletons</td>
<td>8,288</td>
<td>53,257</td>
<td>15.6</td>
</tr>
<tr>
<td>Twins, total</td>
<td>219</td>
<td>1,195</td>
<td>18.3</td>
</tr>
<tr>
<td>Monozygotic</td>
<td>90</td>
<td>373</td>
<td>24.1</td>
</tr>
<tr>
<td>Dizygotic</td>
<td>91</td>
<td>617</td>
<td>14.8</td>
</tr>
<tr>
<td>Zygosity unknown</td>
<td>38</td>
<td>205</td>
<td>18.5</td>
</tr>
</tbody>
</table>

Table 4 - List of defects found to be more frequent among MZ or like-sex twins in the review of Schinzel et al [52] and in at least two large epidemiological studies

- Anencephaly
- Encephalocele
- Hydrocephaly
- Holoprosencephaly
- Cleft lip/palate
- Oesophageal atresia
- Anal atresia
- Intestinal atresia
- Cardio-vascular, total
- Single umbilical artery
- Renal agenesis
- Hypospadias
- Spine malformations
- Sirenomelia
- Exstrophy of the cloaca
- Asplenia situs inversus
- Sacrococcygeal teratoma
- VATER phenotype

Frequency by placentation. In studies in which placentation was identified, no significant difference in birth defect rates among different types of placentation has been reported [13, 43], with the possible exception of one study [8] that found a marginally higher frequency of congenital heart disease in monochorionic versus dichorionic MZ twins (Table 5). Placentation may however play a role, as some anomalies, such as acardia and those disruptions discussed later have been frequently reported in monochorionic MZ twins and directly related to placental vascular anastomosis between the twins' circulations.

Table 5 - Rate of CHD according to zygosity and type of placenta. (Modified from Cameron [8])

<table>
<thead>
<tr>
<th>Zygosity</th>
<th>Placenta</th>
<th>No. of infants</th>
<th>No. of cases</th>
<th>Rate per 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ</td>
<td>Dichorionic</td>
<td>264</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>MZ</td>
<td>Monochorionic</td>
<td>626</td>
<td>8</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Specific defects

Neural tube defects

This topic has been reviewed extensively by Little and Elwood [18]. Pooling all available data, the frequency of anencephaly was 1.15 (1.02-1.30) and that of cephalocele 3.48 (1.96-6.17) times higher in twins than in singletons. Spina bifida did not seem to be more frequent. An analysis separating LS and US twin pairs was not carried out. In at least three studies where this separate analysis was made, a higher rate of anencephaly was found in LS twins compared to US twins or singletons [22, 27, 56]; one of the studies [27] also found an increased frequency of cephalocele. The risk for spina bifida was not found to be increased in any study.

In Little and Elwood’s review [18], the concordance rates for anencephaly and spina bifida were higher in LS than in US twin pairs (6.1% vs. 3.9% for anencephaly, and 7.7% vs. 2.2% for spina bifida), a difference that just reached statistical significance. This suggests a common, possibly genetic etiologic factor. However, the lack of information on zygosity, sex type, and spontaneous fetal loss in this sample does not allow any firm conclusions to be drawn, and it is possible that the concordance may have a non-genetic explanation.

Holoprosencephaly

In their review, Schinzel et al [52] suggested that holoprosencephaly may be more frequent in MZ twins. An excess of twins was found in a few other studies [28, 40]. In one study [40], among 106 infants with holoprosencephaly, 9 were twins; 2 were from a US pair and 7 were from a LS pair. It was thus estimated that holoprosencephaly could affect 1 in 1,483 twin pregnancies, almost 10 times the rate in singletons. In all 9 affected cases the other twin was normal. Out of the other 9 twin sibships (8 pairs and 1 triplet) reviewed by Cohen [11], in which at least one twin had holoprosencephaly, 4 were MZ, and one of these had a concordant MCA pattern possibly indicating an unrecognized syndrome. Of the 5 DZ pairs, 2 were concordant; in one of these, holoprosencephaly was probably due to a recessive condition.

Hydrocephaly

Hydrocephaly has been observed more frequently in twins in many studies [6, 15, 30, 36, 50]. Some authors suggest that the increase is confined to LS twins, and the only report with possibly an excess among US twins [33] is based on only 1 affected case. An important caveat is related to the fact that twins are more likely to be born prematurely compared to singletons; as hydrocephaly is more frequent among premature births, the excess of hydrocephaly should be analysed taking into account birthweight and gestational age. In fact, in one study [30] that controlled for these two factors, the excess of hydrocephaly was explained in great part, though not entirely, by the prematurity and low birthweight of the twins.
Structural Congenital Defects in Multiple Births

Congenital heart defects

Differences in the prevalence of congenital heart defects in singletons and twins are difficult to interpret because of the well-known pitfalls in cardiovascular diagnosis during the perinatal period and the possible ascertainment bias in twins. Moreover, some heart defects such as patent ductus arteriosus are much more frequent among premature births; as twins are more often prematurely born compared to singletons, gestational age should be considered in the analysis. An excess of heart defects in twins has been found in most studies [4, 6, 15, 27, 35, 36, 48, 50]. Specific heart defects are more difficult to study because of the smaller sample-size and the high proportion of unspecified diagnosis reported in many studies. Patent ductus arteriosus, ventricular septal defects and tetralogy of Fallot have been reported by Layde et al [33]. Patent ductus arteriosus, anomalies of umbilical vessels, cardiac murmurs and other or unspecified defects were reported by Doyle et al [15]. Other anomalies of the circulatory system, not otherwise specified, were reported by Little and Nevin [37]. Looping abnormalities, which may indicate disturbances of laterality, were reported by Berg et al [4]. All studies consistently report that the excess is attributable to MZ twins or LS twins.

The high ratio of MZ to DZ twins found among clinical series collected in pediatric cardiology units [1, 7, 56] is consistent with these findings. There may be an excess of females among affected twins [1, 4, 30, 36]. Lastly, in all studies the concordance rate for congenital heart defects has been consistently low [1, 8, 33, 56].

Orofacial clefts

While in most studies there is no clear-cut difference in the frequency of oral clefts between twins and singletons [15, 17, 22, 30, 50, 54, 58], in other studies an excess of cleft lip with or without cleft palate (CLP) has been found in MZ twins [45] and in LS twins [27, 33, 36]. The different results among the studies are consistent with a small increase in risk for CLP among MZ twins that will be difficult to detect if CLP is lumped together with cleft palate, and no distinction is made between MZ and DZ twins. A recent review of concordance among Danish twins with CLP indicates a concordance rate of 42% for MZ twin pairs and 2% for DZ twin pairs [10], suggesting a major genetic influence in the etiology of this defect.

Hypospadias

In the largest collaborative international study on hypospadias and twinning [29], hypospadias was more frequent among LS twins (71 observed vs. 54 expected). Interestingly, the male twin in US pairs appeared to be at an even lower risk for hypospadias than a singleton (12 observed vs. 22 expected). This study suggested that the increased risk in LS male pairs may not be restricted to MZ twins but may be true also for DZ twins. It appears that, compared to a singleton pregnancy, the presence of two males in the same pregnancy increases the risk of hypospadias while the presence of one female lowers it. It is tempting to speculate that the reported endocrine imbalance in twin gestations, in which a lower production of chorionic gonadotrophin per male fetus has been reported [20], may play a causal role in the pathogenesis of the defect.
Alimentary tract atresia

Some large studies reported a high rate of esophageal atresia, anal atresia, and intestinal atresia in twins [27, 35], and the excess was limited to LS twins. An association has been reported between intestinal atresias, namely jejunal/ileal, and exposure to methylene blue injected intra-amniotically at 15-17 weeks gestation to identify the amniotic sacs [24, 46]. Indirect evidence of this association comes from two clusters of isolated intestinal atresias reported among older mothers of twins [27, 32].

Single umbilical artery

The prevalence in twins of single umbilical artery (SUA) was 2.3%, 3-4 times higher than in singletons [23, 34]. Most twins with SUA are discordant for the anomaly, and are usually the smallest of the pair [5, 31, 34]. Studies based on autopsies found an increased risk for additional birth defects when a SUA was present both in singletons and twins and more among MZ than DZ twins; this may be related at least in part to the overall increased mortality among MZ twins [23, 53].

VATER phenotype

Schinzel et al in their review of the literature, Källén [30] in the Swedish register, and ourselves in the IPIMC registry [27] have found tha the VATER phenotype as well as each of the major component defects (vertebral defects, anorectal atresia, esophageal atresia, and radial limb anomalies) are more prevalent among MZ or LS twins than among singletons. About half of all cases of sirenomelia, which may be part of the VATER phenotypic spectrum, are twins. It has been suggested that primitive streak anomalies resulting in MZ twinning could also affect the development of the axial mesoderm, which in turn may lead to an increased risk of the types of birth defects found in the VATER phenotype.

Deformations or positional defects

Deformations are often caused by intrauterine crowding, particularly in the latter part of gestation; thus, twins should be more likely to suffer from positional defects, such as minor foot anomalies, molding of cranio-facial structures, and skull asymmetry. These defects may cause diagnostic uncertainty during the early phenotypic determination of zygosity, since MZ twins may not appear identical at birth. Some of the minor deformities may be related to abnormal fetal positioning, especially in breech presentation of one of the twins. These defects tend to be transient and reversible, and adequate growth after birth is normal [52]. The prevalence of these defects is not well known, as even large epidemiological studies often do not record them, and given the pathogenesis, it should theoretically be similar in DZ and MZ twins. The data available, however, is somewhat contradictory. Some severe deformations, such as talipes, have been reported to be both more prevalent [15, 30, 33, 50] and less prevalent [22] in twins compared to singletons. Moreover, the concordance rate for both talipes and hip dysplasia is 10 to 15 times higher in MZ than in DZ twin pairs [22]. These reports suggest that the etiology of these defects is probably not purely mechanical, and that other factors may interact with intrauterine crowding and constraints.
Disruptions or vascular defects

MZ twins share placental blood circulation in about 75% of cases producing variable degrees of vascular anastomoses. Monochorionic twins pregnancies are more likely to suffer single fetal deaths after 20 weeks of gestation, above the rate of 0.5-6.8% that has been reported among all multiple gestations [3, 16, 21]. Following the demise of one twin, emboli or thromboplastin-rich blood may enter the circulation of the survivor, causing ischemia and disruptive lesions in the developing organs [3]. In one study [44], 3.6% of near-term MZ twin pregnancies had some evidence of a demised cotwin, and the survivor had about a 0.5% risk of developing disruptive brain lesions. There are a number of defects that have been attributed to vascular disruptive events and many of them have been reported following single twin death [2, 26, 39, 51, 52] (Table 6). At times, only careful examination of the placenta and membranes can provide any evidence of a deceased cotwin. The clinical recommendation is that when there is evidence indicating the intra-uterine demise of one twin in a twin pregnancy, the surviving cotwin should be carefully monitored for the presence of birth defects, and particularly for those thought to be caused by vascular disruptive events.

Table 6 - Examples of disruptions secondary to in-utero death of one twin

<table>
<thead>
<tr>
<th>Aplasia cutis</th>
<th>Terminal limb defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porencephalic cyst</td>
<td>Horseshoe kidney</td>
</tr>
<tr>
<td>Hydranencephaly</td>
<td>Splenogonadal fusion</td>
</tr>
<tr>
<td>Cerebellar necrosis</td>
<td>Intestinal atresia</td>
</tr>
<tr>
<td>Hemifacial microsomia</td>
<td>Appendiceal atresia</td>
</tr>
</tbody>
</table>

Concordance and discordance

When one twin is affected by a birth defect, it is important to know what the chances are of the cotwin being affected. The available data, summarized in Table 7 suggests that the cotwin is usually discordant for the birth defect, though sometimes it is still at an increased risk compared to a singleton. The discordance of the occurrence and severity

Table 7 - Concordance of some birth defects among MZ and DZ twins [4, 10, 12, 18, 19, 22, 49, 57]

<table>
<thead>
<tr>
<th></th>
<th>MZ</th>
<th>DZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleft lip or palate</td>
<td>18–42%</td>
<td>2–5%</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>26–40%</td>
<td>5%</td>
</tr>
<tr>
<td>Congenital hip dislocation</td>
<td>40%</td>
<td>3%</td>
</tr>
<tr>
<td>Talipes equinovarus</td>
<td>23–32%</td>
<td>3%</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>6–8%</td>
<td>3%</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>5–6%</td>
<td>2%</td>
</tr>
<tr>
<td>CHD</td>
<td>10–15%</td>
<td>3–4%</td>
</tr>
</tbody>
</table>
of birth defects among and within twin pairs suggests that genetic background does not entirely explain the causation of common birth defects, even common ones, and that the intrauterine environment most likely plays a major role and should be better investigated.

Twinning and the nature of birth defects

There seems to be an excess of two main groups of birth defects among MZ twins: some are considered ‘midline defects’ and include anencephaly, CLP, and some other defects that form part of the VATER phenotype. These defects have been collectively called ‘early structural defects’ by Schinzel et al [52]. They suggested that there is a causal link between the twinning process and those birth defects found in excess among MZ twins. Experimental evidence was provided by Stockard [55], who showed that both twinning and early birth defects could be produced in developing minnows by altering environmental conditions such as oxygen level and temperature. He proposed that MZ twinning was a teratogenic event capable of inducing selected birth defects. Melnick and Myrianthopoulos [43] suggested that the MZ twinning process alters the genetic clock of the embryo and that this may cause a disadvantaged state in the two embryos, making them susceptible to the action of subtle environmental agents. This hypothesis has yet to be supported with data.

Opitz [47] suggested that the causal link between MZ twins and early defects could be a cleavage disorder of the midline field. He proposed that the midline is a developmental field in the human embryo with a tendency to weakness. The midline as a developmental field would be the plane of cleavage in MZ twinning and also the plane around which the symmetry of visceral position is determined. Some midline anomalies such as holoprosencephaly and anencephaly are more common among MZ twins, but remarkable exceptions are spina bifida and cleft palate. On the other hand, there could be not one but many mechanisms that together could explain the excess of all the birth defects observed to date among MZ twins. Some of the theories outlined above are not mutually exclusive; moreover, a proportion of defects may be due to additional mechanisms, such as, for instance, the effect of a fetus-in-feto interaction on the development of anencephaly and sacro-coccygeal teratoma.

CONCLUSIONS AND FINAL COMMENTS

Twins are a heterogenous group, in origin, genetic similarity and placentation. There is evidence that these differences are often reflected in specific risks of birth defects and other developmental anomalies and for this reason any meaningful modern twin study should take them into account. One major practical problem for such a study is that the number of enrolled twins should be based on a large sample. For instance, about 100,000 pregnancies have to be monitored to observe 270 monochorionic-diamniotic (MDM) MZ twins, the most common type of MZ twin. Therefore, to observe 100
MDM-MZ twins with esophageal atresia, which affects some 1 in 3,000 births, we have to study about 150,000 such pregnancies or a total of 55 million pregnancies.

Such studies would have a major impact on the understanding, management and follow-up of twin pregnancies, and are likely to shed light on the very nature of many birth defects. Although such large studies have yet to be undertaken, we can nonetheless outline some general preliminary conclusions. For the clinician, it is important to note that in a pregnancy where the cotwin has died in utero, the surviving twin is at risk for some disruptive birth defects. Furthermore, it is also clear that concordance of birth defects in a twin pair is the exception, not the rule, even among MZ twins. Only 40-50% of MZ pairs are concordant for structural birth defects and this varies according to the defect; even when both twins are affected, there are often differences in severity, with one twin affected to a lesser degree.

The geneticist and dysmorphologist may find these data intriguing in that the biology of twinning could be related to birth defects and also to their occurrence in singletons. The discordance rate of birth defects in twin pairs points to a major role played by the intrauterine environment. The specific types of birth defects which seems to be more frequent in twins may be a reflection of the intrinsic risk factor associated with but not limited to twinning. For instance, MZ twins may be at a higher risk for vascular disruption, as one cotwin could be a source of emboli, or pro-coagulative, factors; but these disruptive events could affect a singleton following chorionic villus sampling [41]. MZ twins could be at higher risk for specific birth defects, such as neural tube defects, or patterns of birth defects, such as the VATER phenotype, because of increased liability generated by the twinning process itself; however, this liability could also be present in similarly affected singletons, due to a particular combination of genes or an interaction between genes and the environment. In conclusion, much has yet to be learned from twins, and this knowledge will be of general benefit. A critical approach to twin studies, together with extensive national and international collaboration are the mainstays of future progress in this direction.

REFERENCES

27. Italian Multicentre Birth Defects Survey (IPIMC), unpublished data.

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