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# Causal Hypothesis for Some Congenital Anomalies

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Congenital anomalies are a major cause of fetal and neonatal death and of childhood morbidity. Chromosomal and other genetic abnormalities, environmental teratogens and some nutritional deficiencies account for some congenital anomalies but the majority are of unknown etiology. The hypothesis is here proposed that a significant proportion of congenital anomalies and cerebral palsy of unknown etiology are attributable to a monozygotic multiple conception with monochorionic placentation and that these anomalies, even in singletons, may be explained by early, unrecognized or unrecorded loss of one conceptus in a monochorionic monozygotic conception. The pathological mechanism is hemodynamic instability with episodes of acute feto–fetal transfusion that produce ischemic organ impairment in either or both twins. The resultant clinical abnormality will depend on range of severity (fetal death, infant death, congenital anomaly, normal infant), site or combination of sites (which organ[s] present[s] with the congenital anomaly) and timing (early, middle or late in gestation as shown by variation in brain pathology that is observed).

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Congenital anomalies are a major cause of fetal and neonatal death and comprise a significant component of childhood morbidity. National stillbirth and death registrations for 2001 and 2002 in England and Wales showed that the *International Classification of Disease and Related Health Problems* (10th revision), category Q, congenital malformations, deformations and chromosomal abnormalities, was the main cause in 11.6%, and was among 10.6% of ‘Other’ causes of fetal death (Office for National Statistics, 2004). Thus, in more than one fifth of cases, a congenital anomaly was the main or subsidiary cause of fetal death. To this must be added the contribution to neonatal death where congenital anomalies comprised 20.1% of the main cause and a further 17.4% among the ‘Other’ causes of death, almost two fifths of all neonatal deaths (Office for National Statistics, 2004). Also, about 1% of legal abortions are carried out because of a congenital anomaly.

Chromosomal and other genetic abnormalities, environmental teratogens and some nutritional defi-

ciencies such as folic acid account for some congenital anomalies but the majority are of unknown etiology.

## Hypothesis

It is postulated that a significant proportion of congenital anomalies of unknown etiology are attributable to a monozygotic (MZ) multiple conception with monochorionic (MC) placentation and that these anomalies, even in singletons, may be explained by early, unrecognized or unrecorded loss of one conceptus in an MZ, MC multiple conception.

There are two processes whereby MZ division of a fertilized ovum may predispose to the development of a congenital anomaly. It may result from the type of placentation that occurs with a MZ, MC pregnancy or from an abnormality in the division of the zygote.

## Anomalies Attributable to the Type of Placentation

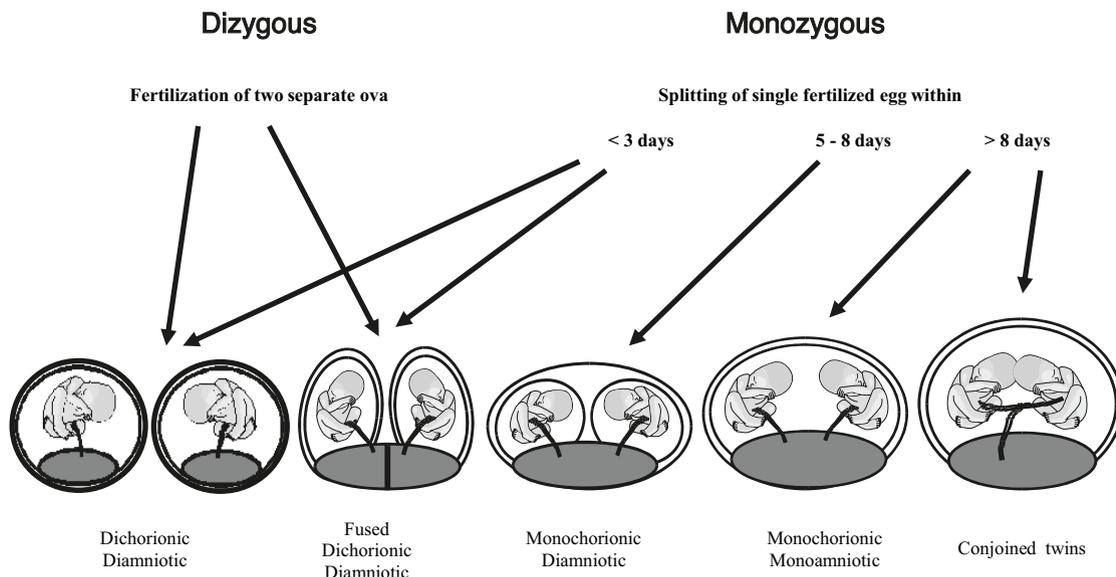
MZ twins arise from the division of the zygote and both twins possess the same genetic make-up. The division may occur at various times in the development of the zygote and the postconceptional age at which the division occurs affects the form of placentation that develops. Early separation of an embryonic blastomere leads to dichorionic (DC), diamniotic (DA) placentation in which the placentas may be separate or completely or partially fused. Crucial to this form of placentation, which is also a feature of all dizygotic (DZ) twins, is that placental vascular anastomoses are rare (Hagahari et al., 2003; Lage et al., 1989). Later splitting of the blastomere leads to monochorionic, diamniotic (MC:DA) or monochorionic, monoamniotic (MC:MA) twins in which placental vascular anastomoses are frequent. Incomplete separation of the fetuses with conjoined twins that are MA:MC is the result of even later splitting.

The different types of placentation are illustrated in Figure 1.

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**Figure 1**

Zygoty and placentation in twins.

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The placental vascular anastomoses that are limited to MC placentation give rise to the acute and chronic fetofetal transfusion syndromes (FFTS). The anastomoses may vary in number and type, that is, arterioarterial, venovenous or arteriovenous or a combination of these, and the variation affects the clinical outcome (Machin et al., 1996). The flow patterns across these anastomoses may be either balanced or imbalanced with adverse clinical outcomes predominantly being with the latter. The effects of chronic FFTS are well-recognized clinical entities with hypovolemia, anemia and oligohydramnios in the donor and hypovolemia, polycythemia and hydramnios in the recipient twin.

The hypothesis that is proposed links the congenital anomaly with one or more episodes of acute FFTS.

#### Mechanisms of Fetal Damage In MC Twins

There are numerous case reports in which fetal death of a twin has been associated with a variety of congenital anomalies in the co-twin. Where zygosity and chorionicity were reported, the cases were almost always from a MC gestation. Cerebral abnormalities such as microcephaly and cerebral atrophy (Fusi & Gordon, 1990; Ishimatsu et al., 1994), polymicrogyria (Baker et al., 1996; Bordarier & Robain, 1992; Larroche et al., 1994; Weig et al., 1995), hydranencephaly and multicystic encephalopathy (Hoyme et al., 1981; Jung et al., 1984) predominate in these reports. These cerebral impairments generally present clinically as cerebral palsy or learning disability (Durkin et al., 1976; Melnick, 1977; Pharoah & Adi, 2000.).

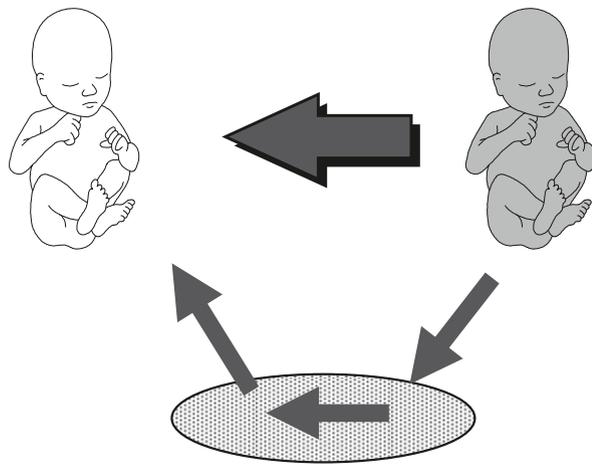
Reports of congenital anomalies of other organs include bowel atresias (Anderson et al., 1990; Hoyme et al., 1981; Saier et al., 1975), renal cortical necrosis and renal agenesis (Benirschke, 1961; Moore et al.,

1969), cardiac valve stenosis (Baker et al., 1982) and acardia, found only in MC twins.

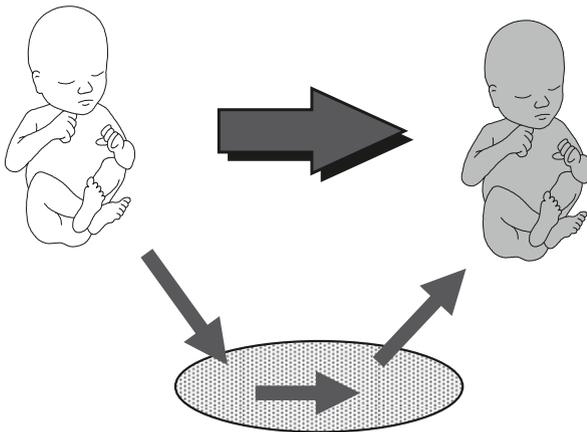
Many of these reported anomalies have been in the surviving co-twin of a fetal death and are compatible with an episode of ischemic damage occurring at some time during intrauterine development. Three possible mechanisms of fetal damage have been proposed and are illustrated in Figure 2.

In the earliest reports, the ischemic damage was attributed to the transfer of thrombotic material leading to disseminated intravascular coagulation or thromboemboli from the dead to the surviving twin (Bejar et al., 1990; Benirschke, 1961; Moore et al., 1969). However, neither thromboembolism nor disseminated intravascular coagulation has often been demonstrated in these cases. Subsequently an alternative mechanism was proposed that the fetal death of one twin created a low resistance vascular sump leading to an acute fetofetal transfusion and a sudden decrease in blood pressure in the surviving twin with consequent ischemic damage (Fusi & Gordon, 1990; Fusi et al., 1991). Both mechanisms require the fetal demise of one twin. A third proposed mechanism is hemodynamic instability with episodes of acute fetofetal transfusion causing the fetal death of one and organ damage in the other twin (Gonen, 1991; Grafe, 1993; Larroche et al., 1994). This mechanism is consonant with the fetal demise of one or both twins or with the survival of both twins. When one or both twins survive, either or both may exhibit organ damage presenting as a congenital anomaly.

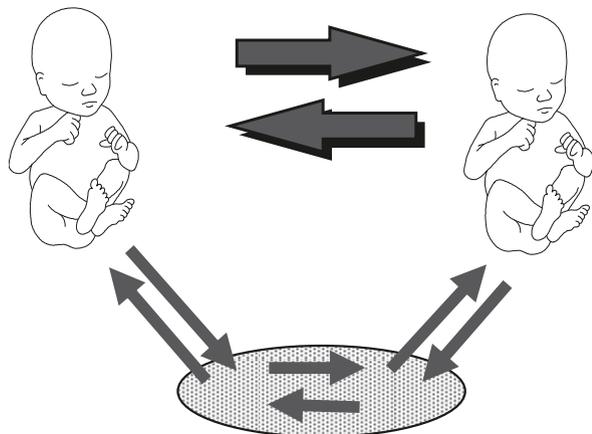
The abnormalities that may be attributed to hemodynamic instability with episodes of acute fetofetal transfusion leading to ischemic organ damage in MC



a) Embolic theory: Thromboplastin-like material or emboli are transferred through an open placental anastomosis to the survivor.



b) Ischemic theory: Blood is shunted into the low resistance circulation of the dead fetus.



c) Hemodynamic instability theory: Bidirectional shunting leads to ischemic damage affecting either or both fetuses.

**Figure 2**

Possible mechanisms of fetal damage in monozygotic twins.

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twins may be considered in the context of three categories of outcome.

**Category 1: Severity of Embryonic Organ Impairment in MC Conceptions**

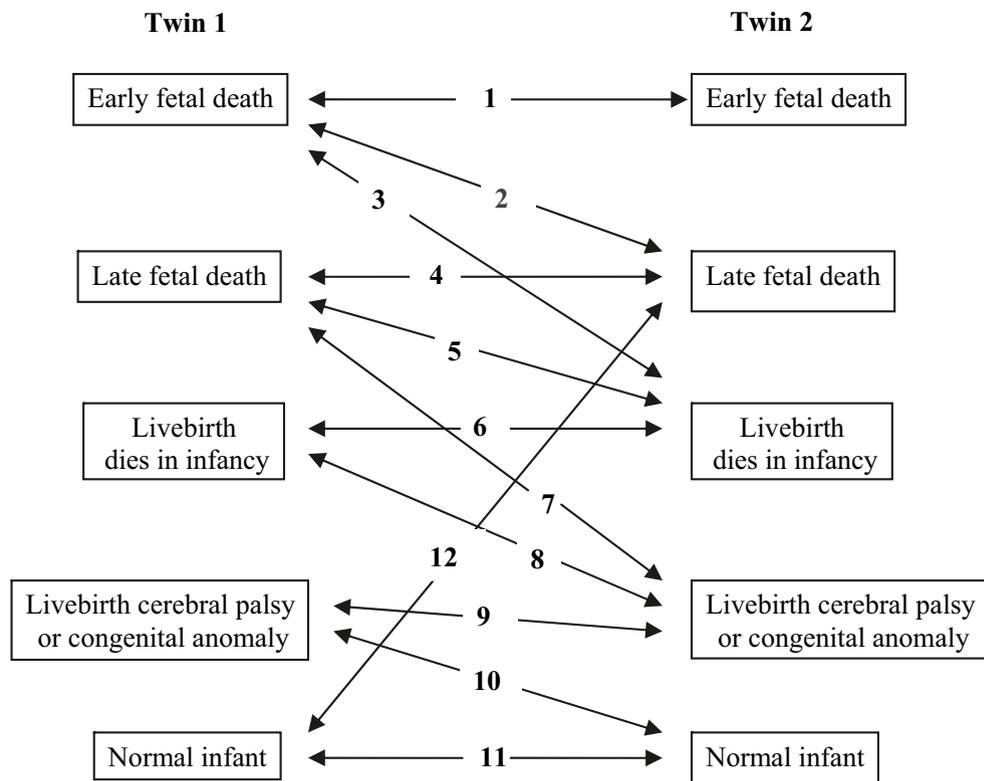
The severity of impairment may range from early or late fetal death, a live birth that dies in infancy, a live birth with congenital anomaly (including cerebral impairment presenting as cerebral palsy or other neurological disability) through to a normal child. The range applies to both twins so that any combination of severity outcomes may be observed. Figure 3 illustrates some of the possible outcomes, all of which may be observed irrespective of chorionicity but can be predicted to occur much more frequently in MC than in DC twins because of the added complications of hemodynamic imbalance.

The early fetal death of both twins (Outcome 1) will present as a spontaneous abortion, and the early fetal death of one twin and late fetal death of the co-twin will present as a singleton late fetal death (Outcome 2). Outcome 3, the early fetal death of one twin with infant death of the co-twin, will present as a singleton infant that dies in infancy. Such singleton infant deaths may be unexplained but postmortem examination would reveal significant cerebral or other congenital anomaly. Quantitative data comparing the relative risk of MC with DC twins for these three outcomes are not available although there are data that suggest MC twins are at significantly increased risk (Benson et al., 1993; Sebire et al., 1997). One study reported that eight of nine MC:DA twin gestations where one twin ‘vanished’ in the first trimester subsequently aborted the co-twin within 3 weeks (Outcome 1; Malinowski et al., 2005.)

National birth registration data for England and Wales do not allow separation of twin maternities into MZ and DZ groups. A proxy for this is comparison of same-sex with opposite-sex twins. Opposite-sex twins must be DZ but same-sex twins comprise MZ and DZ twins in approximately equal proportions. Table 1 is drawn from an analysis of England and Wales birth registration data for 1993 to 2003 for 63,336 same-sex and 31,682 opposite-sex twin pairs.

There are highly significant increased relative risks for same-sex compared with opposite-sex twins for Outcome 4 (two fetal deaths), Outcome 5 (one fetal death/one infant death), Outcome 6 (two live births, both dying in infancy), Outcome 7 (one fetal death and cerebral palsy in surviving co-twin) and Outcome 8 (two live births, one dying in infancy and surviving co-twin with cerebral palsy; Pharoah, 2002). If, as is probable, it is the subset of MC with MZ within same-sex twins that account for the increased risk, the relative risk associated with MC will have been grossly underestimated.

The hypothesis has been proposed that cerebral palsy in an apparently singleton child may be attributed to unrecorded or unrecognized first trimester fetal death of a co-twin as a ‘vanishing’ twin or second

**Figure 3**

Combinations of severity outcome in twins.

trimester death as a fetus papyraceous as shown by Outcome 3 (Pharoah & Cooke, 1997). It is now hypothesized that other congenital anomalies, in apparently singleton children, have the same etiopathogenesis as prenatally acquired cerebral palsy and that such cerebral palsy should be categorized as a congenital anomaly. Quantitative data on the prevalence of congenital anomalies in same- and opposite-sex twins for Outcomes 7, 8 and 9 are not available to confirm or refute the hypothesis. Consideration should be given for congenital anomaly registers to record additional information that will allow such analyses to be made.

Outcome 9 presents clinically as both twins having cerebral palsy, one having cerebral palsy and the co-twin with a congenital anomaly or both twins having a congenital anomaly for which they may be concordant but are more often discordant.

Although MC twins are at much greater risk than DC twins for a variety of adverse consequences, it is pertinent to emphasize that normality of both twins (Figure 1; Outcome 11) is the most likely outcome in MC and DC conceptions.

#### **Category 2: Spatial Distribution of Embryonic Organ Impairment in MC Conceptions**

The second outcome category is a spatial one in that one or more organs may be impaired. Cerebral impair-

ment manifested as cerebral palsy or learning difficulty is more prevalent than any other congenital anomaly, possibly because the brain is of significantly greater volume than other organs during fetal development and therefore is at greater risk of damage from twin–twin hemodynamic instability. Alternatively, the brain may be at greater risk because of its complexity so that even a slight perturbation of its structure may lead to abnormal function. Not only may the embryological development of one or more organs be affected, but also variation in the severity of the impairment could lead to a range of congenital anomalies.

Although MZ show greater concordance for congenital anomalies than DZ twins, as a general rule both MZ and DZ twins are more likely to be discordant (Little & Bryant, 1988). Among MZ twins, concordance for congenital anomalies in general is greater than for specific anomalies (Myrianthopoulos, 1975). Illustrative of this, discordance for specific anomalies is one twin suffering from a cardiac valve stenosis and the co-twin from a gut atresia. MZ twins are almost always discordant for specific anomalies. This provides strong evidence that the majority are not genetically determined (Knox & Lancashire, 1991). An ischemic pathogenic mechanism affecting either twin is consistent with MZ twins being discordant for congenital anomalies though having a higher concordance than DZ twins.

**Table 1**

Relative Risks in Same-Sex : Opposite-Sex Twins

Outcome	Same-sex : opposite-sex Relative risk (95% CI)
Outcome 4 Two fetal deaths	Relative risk 7.9 (5.4–11.5) $p < .0000001$
Outcome 12 One fetal death & one live birth	Relative risk 1.4 (1.3–1.5) $p < .0000001$
Outcome 5 One fetal death & infant death of co-twin live birth	Relative risk of infant death in the live birth 1.9 (1.4–2.6) $p < .0001$ Infant mortality in same-sex 163/1000 Infant mortality in opposite-sex 84/1000
Outcome 6 Two live births, both die in infancy	Relative risk 1.4 (1.2–1.6) $p < .000001$
Outcome 7 One late fetal death & one survivor Cerebral palsy prevalence in survivor	Cerebral palsy prevalence in survivor Same-sex 102/1000 Opposite-sex 38/1000 Relative risk 2.7
Outcome 8 Two live births: one infant death, cerebral palsy in survivor	Cerebral palsy prevalence in survivor Same-sex 129/1000 Opposite-sex 71/1000 Relative risk 1.8
Outcome 10 Two live births, both survive	Cerebral palsy prevalence in survivors Same-sex 8.1/1000 Opposite-sex 4.8/1000 Relative risk 1.7

Note: Mortality data from England and Wales birth registrations 1993–2003.  
Cerebral palsy data from national survey of twins 1993–1995 (Pharoah, 2002;  
Pharoah & Adi, 2002).

Variation in the severity and spatial distribution of organ damage may be illustrated by the congenital cardiac anomalies. The cardiac valve stenoses exemplify the least severe impairment. Single valve atresia and coarctation of the aorta, multiple valve atresia presenting as hypoplastic left or right heart represent severer grades and acardia, found only in MC twins, is the extreme end of the spectrum of severity.

Anomalies affecting more than one organ also are illustrative of spatial variation in organ impairment. Esophageal atresia and, more rarely, tracheal atresia may occur in isolation but are more commonly associated with a tracheo-esophageal fistula (TOF). TOF may also be one component in a nonrandom association of several anomalies under the acronym VATER (Vertebral defects, Anal atresia, Tracheo-Esophageal fistula and Radial-ray limb anomaly and renal dysplasia) and subsequently extended to become VACTERL by the addition of Cardiac and all Limb anomalies to the constellation. It is unusual for all the anomalies to be observed in one infant, and the rarity of the syndrome

has engendered collaborative efforts between congenital anomaly registries to examine whether there is clustering of subsets of the anomaly (Botto et al., 1997; Källén et al., 2001). The data suggest that there are distinct subsets and it was surmised that there is pathogenic heterogeneity within the association (Botto et al., 1997). It is here proposed that at least some subsets of the VACTERL spectrum could be attributable to the effects of hemodynamic instability in an MC conception in which one fetus suffers early demise.

### Category 3: Timing of Embryonic Organic Impairment in MC Conceptions

The pathological abnormalities attributable to episodes of intertwin hemodynamic instability can be expected to vary according to the stage of development at which an organ is compromised. This is exemplified by the variation in cerebral abnormalities that have been described in association with fetal death of a co-twin. Clinically the impairment usually present as cerebral palsy with a variable degree of cognitive disability or by cognitive disability in isolation. However, pathological abnormalities that have been described include anencephaly, holoprosencephaly, schizencephaly, hydranencephaly, porencephaly and multicystic encephalomalacia (Scheller & Nelson, 1992).

Cerebral impairment presenting as a neuronal migration defect has been reported in association with fetal death before the 12th week (Baker et al., 1996) and between the 16th and 18th weeks of gestation (Van Bogaert et al., 1996). Hydranencephaly, porencephaly and multicystic encephalopathy have usually been reported with third or late second trimester demise of the co-twin (Jung et al., 1984; Reisman & Pathak, 1966).

### Anomalies Attributable to Zygote Division

Cell division may result in chromosomal disjunction or loss of a complete or part of a chromosome. When this occurs in a germ cell, fertilization results in trisomy, monosomy or a variety of chromosomal deletion syndromes. Congenital anomalies that are attributable to these chromosomal abnormalities predate fertilization and are not relevant to the hypothesis under consideration here. However, division of the zygote may be associated with disturbances of morphological laterality. Normally the heart and spleen are on the left, the liver on the right, and so on. There may be perfect reversal of laterality that presents as situs inversus usually with no functional impairment. There are lesser degrees of reversal of situs most commonly affecting the heart leading to such anomalies as right or left atrial isomerism with two right or left atrial appendages and partial anomalous venous drainage. These disturbances of morphological laterality comprise a significant proportion of congenital heart defects, are more common in MZ than in DZ twins or singletons (Burn, 1991) and are particularly common in conjoined twins where the abnormality is influenced by the site of union of the

twins (Levin et al., 1996). Other organs may be affected as in the asplenia/polysplenia syndrome. Laterality abnormalities are associated with twinning and the hypothesis now proposed is that, when these abnormalities are observed in singletons, there has been very early loss of a co-twin. As some cardiac anomalies are due to disturbances in laterality associated with division of the zygote, the probability is enhanced that there has been early loss of a co-twin in which the cardiac anomaly was lethal.

If abnormalities of laterality are attributable to twinning, then such cases may also be at increased risk of ischemic damage from hemodynamic instability. They are subject to a 'double jeopardy'. Several anomalies of laterality have associated congenital anomalies that are not attributable to a laterality abnormality. Asplenia/polysplenia frequently coexists with cardiac valve atresias and stenoses and biliary atresia (Rose et al., 1975), and situs inversus coexistent with mitral stenosis and esophageal atresia has been reported (Morini et al., 2001; Owen, 1911). Herein is the double jeopardy. The laterality abnormality is associated with zygote division and the atresias and stenoses are the consequence of hemodynamic instability.

#### Hypothesis Inconsistency

The hypothesis needs to explain the presence of congenital anomalies in twins that are of different sex. An anomalous situation may exist concerning the registration of gender in a fetus of indeterminate sex as in a fetus papyraceous. In England and Wales, parents may be allowed choice in the sex that is registered and in these cases it does not follow that twins of different registered sex are from a DZ conception. Registration procedures for stillbirths of indeterminate sex need to be clarified for all national statistics.

Also, early loss of one conceptus from a triplet pregnancy (a vanishing triplet) would be consistent with one of the remaining twins being MZ:MC. Over 40% of conceptions with three sacs or embryos and over 50% with four or more embryos result in fewer fetuses than expected (Landy & Keith, 2005).

Placental vascular anastomoses may occur early in a DC pregnancy and have been associated with twin-twin transfusion problems (Lage et al., 1989). Although rare, it may account for some cases of congenital anomaly in a DZ conception.

#### Testing the Hypothesis

The earlier that sonographic assessment is made, the greater the proportion of twins that become singletons (Doublie & Benson, 1998). Generally, maternal care in spontaneous conceptions involves sonography late in the first trimester. To test the hypothesis, routine, very early sonography (as soon as the woman considers pregnancy a possibility) will be needed. This will require transvaginal rather than transabdominal examination; nevertheless, a multicentre study to provide adequate testing of the hypothesis is feasible and should be considered.

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