Erratum, Chapter 25

Multiple Pregnancies

25

In a remarkable paper that correlates prenatal events and discordance of twins with postnatal outcome, Price (1950) emphasized the importance of "prenatal biases." He was much concerned with the influence of placentation upon twin development, an aspect that had not often been considered in twin studies. Similar ideas have more recently been echoed by Phillips (1993) who emphasized the influence of the proximity of twin placentas on their ability to support fetal growth. But it was Galton (1875), cousin of Charles Darwin, and after whom the Galton Institute of Genetics in London is named, who was probably the first to suggest that twins, if properly studied, would yield information that might allow us to discriminate between the effects of heredity and those of the environment. It was his famous "Nature vs. Nurture" concept. The extensive studies conducted by Friedrich Schatz at about the same time, suggested that prenatal influences among twins found reflection in the ultimate outcome of the twins. He was instrumental in clarifying that placental study is essential for this understanding. His extensive work is annotated in a bibliographic oddity (Schatz 1900). It summarized all of his papers and citations therein. Some of his numerous contributions were partially translated for the book on twin placentation by Strong and Corney (1967). A concise review of the biologic aspects of the human twinning process was published by Benirschke and Kim (1973), and the new volume on "Twinning and Twins" by MacGillivray and his colleagues (1988) summarizes most relevant aspects of this interesting phenomenon of nature. Baldwin (1994) has produced a remarkable volume that contains all relevant aspects of placentation of multiple pregnancies, and it is well illustrated. Finally, Gall (1996) has summarized all practical aspects of multiple gestations, especially the clinical manifestations and therapy. Several cases of hydatidiform mole in twin gestations have been reported (e.g., Chu et al. 2004). These are discussed in more detail in the Chap. 22.

No doubt, the complexity of human twinning cannot be understood without knowledge of the placentation of twins. Moreover, despite all the benefits reaped from animal studies, the placentation of most relevant species is often very dissimilar from that of humans. Thus, conclusions drawn from animal multiple pregnancies must be interpreted with great care. In recent years, ultrasonographic studies have added materially to our knowledge of prenatal events in twinning and its placentation. Of interest, for instance, are the remarkable observations by Arabin et al. (1996) of extensive intertwin physical interactions. They were observed to occur earlier in monochorionic twins than in those with a dichorionic twin placenta.

25.1 Zygosity

There are "fraternal" (better named dizygotic, DZ) and "identical" (monozygotic, MZ) twins. In higher multiple births, these may be admixed. That such different classes of twins exist derives from several observations. Fraternal twins may be of different or like sex. A hypothesis is herein helpful: if all twins were DZ, then one would expect a similar sex ratio to be found as that for singletons, i.e., approximately 50% MF, 25% MM, and 25% FF. This is not the case. When large statistics of infants' sex at birth are examined, it is found that there is an excess of like-sex twins. This excess is presumed to result from the number of MZ (identical) twins. By subtracting these from the total number of twins, an estimate is had for the distribution of MZ and DZ twins in a population. This is the so-called Weinberg rule (1901). (Hrubec and Robinette 1984, pointed out that the basis for this rule had previously been published by Bertillon 1874). Weinberg's "differential method" can be stated with the following formula:

$$\text{MZ twins} = \text{All twins} - \frac{\text{Unlike sex twins}}{2pq}$$

(p = frequency of male births and q = frequency of female births in a population).

Weinberg's formula should be taken as providing estimates, with considerable errors if it were taken literally.

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This is particularly understandable when one considers the frequencies of different classes of twins as they exist at the time of conception; for there is much evidence that MZ twins have a higher prenatal death rate than do DZ twins. The Weinberg method cannot correct for losses of only one of twins in a gestation, information that is also usually not recorded in birth statistics. It is, therefore, not surprising that the method has often been criticized (e.g., Renkonen 1967; and reply by Cannings 1969; James 1971, 1984; Keith 1974). Nevertheless, it is a unique and valuable tool to assess the approximate frequency of DZ vs. MZ twins in a population. Moreover, a recent prospective study that attempted to validate the method has found that the results agree well with findings from placentation and known zygosity of twins (Vlietinck et al. 1988). An interesting observation by James (1971) is that, among DZ twins, there is an excess of like-sex pairs. This observation is based on small samples of twins whose zygosity was ascertained by blood grouping. It has so far remained unexplained, but some additional data (James 1977a) show an even more marked excess of females among monoamnionic, monochorionic (MoMo) twins, and perhaps in twins with acardiacs. More light has been shed on this phenomenon by the large study of Derom et al. (1988). These authors provided data from the Belgian prospective twin study which included zygosity diagnosis and placental assessment. Not only was the proportion of males reduced in MZ twins (irrespective of chorion status), but also there was a marked reduction of male MoMo twins from what might be expected if this form of twinning occurred at random. The sex proportion of all MZ twins was 0.487, that of MoMo 0.231, while the DZ twins had a proportion of 0.518. Although no large data sets are yet available, they cited evidence that conjoined twins at term are more commonly females, while those of abortuses may be more often males. Of the two possibilities to explain this unexpected observation, greater frequency of late twinning in female conceptuses, and greater abortion rate of male MoMo conceptuses, they favored the former. They referred to the suggestion made by Burn et al. (1986) that "unequal lyonization" of X-chromosomes may be a cause of late twinning and that feature is, of course, unique to females. But Goodship et al. (1996) found no support for this hypothesis when they examined X-inactivation patterns of umbilical cords of various types of twins. Monteiro et al. (1998a, b) have studied this a little further by comparing X-inactivation patterns of lymphocytes and buccal cells of MC-MZ and DC-MZ twins (see also Puck 1998). They assumed from earlier studies that lyonization occurs when there are 10–20 cells in the embryo and deduced from modeling that "MC-MZ twinning occurs three or four rounds of replication *after* X inactivation, whereas DC-MZ twinning event occurs earlier, before or around the time of X inactivation." The apparent excess of female acardiacs is possibly further confirmation (James 1977b) of this phenomenon. The largest prospective survey of twins comes from Belgium (Loos et al. 1999) which encompassed 5,089 twins, 158 triplets, and 14 quadruplets or higher multiples. In this survey, zygosity was established by sex, placentation, and genetic markers in over 95%. Dizygotic twins had the same sex proportions as singletons, while MZ twins had an excess of females.

Considerations of the MZ twinning rates come from Allen and Hrubec (1987) who proposed that a slight suggestion exists of a relationship of the MZ twinning rate to maternal age, as is very certain for DZ twins. These "constants," of DZ to MZ twin frequencies, identified from various statistical considerations, however, are still considered to be arbitrary, and they also appear to differ among various populations.

Other reasons for considering that a proportion of twins are "identical," or monozygotic, come from the numerous reports on genetic "identity," let alone the physical similarity exhibited by some twins. Twin research has traditionally involved ascertainment of zygosity by assessment of likeness. Dermatoglyphics (Newman 1931a; Brismar 1968; Allen 1968; Herrlin et al. 1970; Reed et al. 1975) and blood grouping (Robertson 1969; Selvin 1970) are some of many parameters that have been employed. But these methods have not always been decisive in assigning the zygosity for an individual set of twins, although their general reliability is high. For that reason, methods such as mixed leukocyte stimulation (Jarvik et al. 1969), skin exchange graft survival (Stranc 1966), and repeated blood group study (Osborne 1958) have been advocated. Analysis of banded chromosomes, C-bands and Q-bands, has also been used to ascertain monozygosity (Neurath et al. 1972; McCracken et al. 1978; Morton et al. 1981; Pedrosa et al. 1983). Until recently, this has been the most reliable methodology. These methods established mostly probabilities of twins' zygosity, and they were often somewhat imprecise. The mathematical aspects of phenotypic likeness studies have been treated by Meulepas et al. (1988). New methods have now been developed that are more decisive. How important they can be is manifest from the report by St. Clair et al. (1998). Unlike appearing twins, thought to be dizygotic, had successful intertwin renal transplant because of mushroom poisoning to one twin. DNA fingerprinting found them later to be monozygotic, whereupon the immunosuppressive therapy was successfully discontinued.

The new techniques for the direct comparison of DNA variants have much to be recommended as primary tools. They determine the restriction fragment length polymorphism (RFLP) of twins, and cogent reasons for routinely employing this methodology have been advanced, i.a., by Machin (1994). These methods of comparing fragments of DNA are quick; can be executed on placental tissue, blood, and other tissues; and are decisive (Derom et al. 1985; Hill and Jeffreys 1985). Importantly, the quantities of tissue needed for this study can

be quite small when combined with polymerase chain reaction (PCR). More recently, the use of microsatellites has proven to be useful and rapid in the definitive differential diagnosis of MZ vs. DZ twins (Erdmann et al. 1993; Becker et al. 1997). Thus, antenatal samples may readily be processed by this and related modern techniques for accurate determination of twin zygosity (Kovacs et al. 1988), and they have been decisively used to identify the genetic relationships between twins and triplets (Motomura et al. 1987; Azuma et al. 1989). It is of further interest that this method can also be used to identify DNA patterns of macerated stillborn fetuses (Derom et al. 1991). In fact, Machin and Bamforth (1996) have used placental DNA to identify the relationships among triplets. Neuman and her colleagues (1990) have proved with RFLPs the dizygosity of aborted tubal twins and suggested that the alleged common monozygosity of ectopic twins may be in error. Norton et al. (1997) advocated the use of DNA diagnostic study of discordant multiple gestational products when chorionic status is indeterminate or not helpful. There are, however, reasons to perhaps abandon the term "identical"; these reasons have been discussed in some detail by Hall (1996) and include irregular splitting, differential lyonization, imprinting differences, placental sharing, etc. They must, at least, be well understood before judgments are made.

The least decisive method for the identification of the zygosity of twins, the likeness assessment, however, is also the most widely practiced. It is the easiest method to execute, and it correctly asserts that physical characteristics are more alike in MZ twins than they are in DZ twins (e.g., tooth morphology: Lundström 1963; skin color: Collins et al. 1966; cardiac findings: Preis and Srubarova 1966; immunoglobulin levels: Sowards and Monif 1972; cholesterol levels: Corey et al. 1975; etc.). A fairly reliable accuracy of zygosity diagnosis is said to be achieved with other simple tests, including the use of only questionnaires (Cederlöf et al. 1961; Nichols and Bilbro 1966). These oversimplifications have, however, also led to many misconceptions. Moreover, they have confused the neonatologist who cares for often markedly discordant twins in the neonatal period. He/she has to have better guidelines for the care of neonatal twins than are generally available to clinicians.

It is now certain that MZ twins are frequently discordant in development; some of this discordance can be secondary to unique placental vascular relations between twins (Schatz 1885; van Verschuer 1927; Price 1950); others have their cause in abnormal placentation. Still others may be the result of "unequal splitting" of the embryonic cells mass. Discordance for congenital anomalies is higher in MZ twins than in DZ twins, a feature which has been critically analyzed by Boklage (1987a), by Mastroiacovo and Botto (1994), and most recently by Hall (1996). There are also other fascinating problems to be resolved; for instance, Zaw and Stone (2002) reported caudal regression syndrome in a set of monozygotic but dichorionic twins. Is that due to growth disparity of the twins or to the possibility that only one of the twins was exposed to the abnormalities of glucose imbalance of the MZ twins at the time of putative exposure? Some of such questions can potentially be resolved by the twin methodology, and Hobbs et al. (2002) have drawn attention to this in their review of the genetic aspects of congenital anomalies. Twins, in general, have also been found to have higher hematocrits and somewhat elevated levels of nucleated red cell counts, irrespective of prenatal hypoxia or IUGR (Sheffer-Mimouni et al. 2004). Triplets share this feature, according to Suslak et al. (1987). Melnick and Myrianthopoulos (1979) found that the twofold increase of anomalies in MZ twins cannot be validly ascribed to the monochorionic placental status that is so prevalent in MZ twins. An exception to this, of course, are acardiacs and the destructive results from prenatal disseminated intravascular coagulation (DIC) or acute blood loss, which may depend in their origin from the monochorionic status of their twin placenta. These authors suggested as a possible explanation that the "impetus" for MZ twinning may be similar to that which is the cause of the developmental anomalies. In recent years, Steinman (2001a, b, c and 2002a, b; Steinman and Valderrama 2001) has proposed that the possible reason for MZ twinning is the deficiency of cellular adhesion between embryonic cells, mediated perhaps by calcium-dependent adhesion molecules. Some support for this hypothesis is afforded by the occurrence of MZ twins among ART-derived multiples since the blastocysts are often cultured in EDTA-containing, chelating media for several days. The relative frequency of anomalies in MZ twins (6–9%, with 80% discordance) has important implications with respect to prenatal diagnosis of early embryos (Jarmulowicz 1989). It has been suggested that, with the new methodology of polymerase chain reaction of DNA amplification, single blastomeres might be sexed and that they could then be genetically defined in the future. This is the currently common practice of "prenatal genetic diagnosis" (PGD) from single blastomeres, a practice that prevents implantation of chromosomally anomalous or otherwise defective embryos. It is unknown at this time whether such loss of blastomeres could result in anomalies and whether the discordant anomalies of MZ twins are perhaps caused by an unequal splitting of the morula. Also, monozygotic twins with discordance of organ laterality in ciliary dyskinesia (Kartagener syndrome) have important connotations for an explanation of this disorder (Noone et al. 1999). Similarly, the concordance of truncus arteriosus in MZ twins has implications for that anomaly (Mas et al. 1999). These and similar considerations are important questions for future research. Similarly, the monochorionic twins with significant phenotypic differences described by Gringras (1999) cannot presently be explained, but they need to be borne in mind when speaking

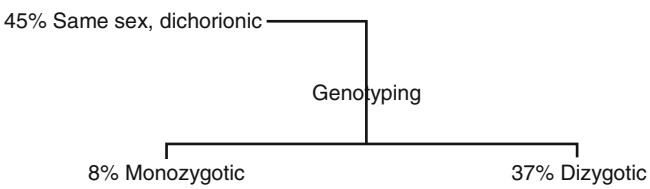
of "identical twins." The PCR fingerprints of these twins were identical.

Twin studies, as advocated by Galton (1875), endeavor to discern between genetic and environmental influences on fetal development. To be successful, they require accurate zygosity determination of the probands. Walker (1957) stated this requirement emphatically. Moreover, it has been found that if the linkage of genetic traits is not taken into consideration in the zygosity assignment, the probability of monozygosity is overestimated (Sorensen and Fenger 1974). Kempthorne and Osborne (1961) and Allen and Hrubec (1979) have developed models to undertake such analyses. Allen (1965) proposed excellent guidelines for the design of twin studies which should be consulted. Kruyer et al. (1994) used this sort of knowledge in ascertainment when the full implementation of the fragile X syndrome mutation is attained – postzygotically, as it turns out. Finally, Kato et al. (2005) have suggested that genetic or epigenetic causes of discordance among MZ twins may exist that are just now being recognized.

25.2 The Placenta in the Study of Zygosity

In order to derive any benefit from placental studies for twin research, it is, first of all, mandatory that the umbilical cords be labeled in the order as the twins are delivered for positive identification of the infants. This is best done by placing one or more ties or clamps around the placental cut ends of the cords. Examination of twin placentas (and those of higher multiple births) may then contribute to the determination of zygosity and an understanding of abnormal events. It is also mandatory that a placental record be made. This is needed for an understanding of possible discordant development of twins and for our understanding of many other pathological features that twins present. The proposition that **all** monochorionic placentas belong to MZ twins (but that **not all** MZ twins have monochorial placentas) was first clearly stated in the seminal contribution of Curtius (1930). He then called for a detailed reexamination of the understanding of placentation in humans. In general, this proposition has been amply confirmed, for instance, in the placental study of 182 like-sexed live-born twins by Ramos-Arroyo et al. (1988). But there are also a few well-proven exceptions that will be discussed below. The correlation of prematurity, twin development (growth and growth restriction), and placental causes for disturbances has been evaluated in contributions by Bleker and his colleagues (1997, 1979, 1988, 1995). Not surprisingly, it was found that monochorial twins were delivered earlier and that they had a higher mortality than dichorionic twins. Abnormal cord insertion occurred more commonly in multiple gestations and was related to smaller fetal weights. They expressed the notion that placental weight importantly influences and often restricts fetal growth in multiple pregnancies. Min et al. (2000) compared the weights of a larger number of twins (according to chorionicity and sex as well) with those of singletons and provided an excellent reference table. They concluded that "well-grown twins and singletons do not differ as much as previously believed." Cooperstock et al. (2000) demonstrated that significant growth differences (40% before 32 weeks) among twins constitute a risk factor for premature birth.

In principle, there are two types of twin placentation: monochorionic and dichorionic. In higher multiple births, these may be admixed, or one or the other types may be present. Monochorionic placentas, so we believe, virtually **always** come from MZ (identical) twins. The reason for this assumption is that no really verified monochorial human placenta has been associated with twins of unlike sex (there are only the rarest exceptions). Furthermore, when genetic markers are studied in monochorionic twins, they are always identical (Corney et al. 1968; the rare exceptions are discussed below). Dichorionic placentas, however, may be associated with both DZ and MZ twins; most are associated with DZ twins. A decisive study of this topic is that of Cameron (1968). He examined the placentas of 668 twin pairs and determined their zygosity with studies of blood groups and placental enzymes. From the fetal sex and the structure of the placental membranes alone, the zygosity could be ascribed accurately in 55%. Genotyping was necessary in the remaining 45%. His analysis gave the following results:



Of his 668 pairs, 80% had diamnionic, dichorionic (DiDi) placentas, and of these pairs, 90% were DZ. There were 20% monochorionic (and therefore monozygotic) twins. With the improved methodology of modern sonographic equipment, it is now usually possible to make the diagnosis of chorionic status before birth; however, discussion continues as to the sonographic accuracy and the criteria to be employed at specific gestational ages. Irrespective of numerous papers urging that this diagnosis of chorionicity be made at birth in all multiple deliveries, Cleary-Goldman et al. (2004) found in their survey that this means of assessing some twins' zygosity is unknown to many obstetricians.

The sonographic appearance of the "diving membranes" is now reasonably securely established by competent ultrasonographic studies. The development of the techniques employed and references to the findings made after 1985 are competently summarized by Tutschek et al. (1998). Thus, D'Alton and Dudley (1989) made the correct diagnosis in 68 of 69 prospectively studied cases using ultrasound and assessing the layers

of the dividing membranes. Winn et al. (1989) suggested sonographic criteria for assessing the width of "dividing membranes." When amniocentesis was done for genetic reasons, the thickness of this dividing membrane was measured in 32 patients. The cutoff point was 2 mm. An accuracy of 82% was said to be achieved by this means. This method may be helpful in the future management of twin gestations. Finberg (1992) found that the "twin peak sign" was diagnostic of dichorionic twinning. He showed that a triangular projection of membranes can be seen above the placental surface in dichorionic twins or triplets; Wood et al. (1996) agreed with that in their study. Monteagudo and her colleagues (1994) asserted from their large experience that transvaginal sonography before 14 weeks' gestation easily establishes the nature of the partitioning layers in multiple pregnancies. Sepulveda et al. (1996) nearly always succeeded sonographically to make a correct diagnosis by analysis of the so-called Ipsilon zone (the Y-shaped area of conjunction of sacs in triplets). Vayssière et al. (1996) succeeded to a high degree of accuracy by counting layers of the dividing membranes in the second and third trimesters, while Stagiannis et al. (1995) asserted that the method has a high intra- and interobserver variability. At least once, in a pregnancy with discordant twin growth and absent twin peak sign, monochorionicity was established by the injection of Levovist, a microbubble contrast enhancement agent. After injection into one twin's intrahepatic vein, the contrast agent later appeared in the other twin's heart (Denbow et al. 1997), thus confirming vascular anastomoses and, thereby, monochorionic status. Malinowski (1997) was able to reliably differentiate the twin membrane layers by transvaginal sonography as follows: DiDi – at 4 weeks; DiMo – at 5 weeks; and MoMo vs. DiMo – at 7 weeks' gestation.

Monochorionic twin placentas virtually always present as single disks. It is most unusual for monochorionic twin placentas to possess separate placental masses, and often, they are then connected with small bridges. Nevertheless, Altshuler and Hyde (1993) have described such an exceptional case in which two completely separate disks were connected by a thin bridge. Underneath the chorion of this bridge was atrophied villous tissue. Rare observations of two disks in monochorionic twins have also been made in conjoined twins (see below). Monochorionic twin placentas fall into two categories: (1) the monoamnionic, monochorionic (MoMo) twin placentas in which the twins are in the same sac and (2) the diamnionic, monochorionic (DiMo) placenta. The MoMo placenta is the least common. It is also associated with the highest perinatal mortality of twins because of cord entanglement. The higher mortality and complication rate for monozygotic twins has been critically examined by Kovacs et al. (1989). Multiple births not only have higher perinatal mortality but they also have greater morbidity. Because of the inordinate contribution to adverse outcomes, Powers and Kiely (1994) provided USA-based population figures that suggested "…to lower the rates of adverse outcomes in twin pregnancies should become a major public health priority." Heyborne et al. (2005) have shown that much improved perinatal survival can be expected when mothers with known MoMo twins undergo early hospitalization for surveillance. Tooke et al. (2010) have added a recent case.

Dichorionic (DiDi) twin placentas may be fused into one mass (DiDi fused), or they may be separated (DiDi separate) organs (Benirschke 1958). From a practical consideration of the analysis of the placentation of individual twins, it is important to first examine these membrane relations. It is most reliably done by making a cross section of the "dividing membranes," i.e., the partition between the two sacs. By excising and rolling a square of these dividing membranes, the two types can then be differentiated (Fig. 25.1). As an alternative method, one may take for histological study a section from the site where the membranes insert on the placental surface, two "T sections," are seen in Fig. 25.2. This method has been particularly well illustrated by Allen and Turner (1971). Either of these methods for taking sections preserves a permanent record. For the experienced placentologist, it is just as effective to make the diagnosis of DiMo vs. DiDi twin placentation by macroscopic inspection.

The dividing membranes of DiMo placentas are usually translucent (Fig. 25.3). They are thin and not opaque, and there are no blood vessel remnants within them. When one separates the two amnions and comes to their insertion on the placental surface, one may continue to strip the amnions off a DiMo placenta, away from the chorionic plate (Fig. 25.4). In addition, the fetal surface does not show a ridge of fibrin, present as a slightly raised white ridge that is present in DiDi placentas. Bleisch (1964) emphasized this point effectively. DiDi membrane partitions are considerably more opaque (Fig. 25.5). They have remnants of villi and vessels in their four layers, and when, by separating the two layers of each placental component, one comes to the chorionic plate, further dissection is impossible (Fig. 25.6). If one attempts to further cleave them, the surface of the placenta is disrupted.

As already stated, the advancements in sonographic equipment have made it possible to distinguish the thickness of the dividing membranes long before birth (Barss et al. 1985; Mahony et al. 1985; Hertzberg et al. 1987; Finberg 1992). This diagnostic modality is particularly helpful in the diagnosis of MoMo twins who are at risk of cord entanglement. Belfort and his colleagues (1993) demonstrated, by color flow Doppler sonography, such cord entanglement in three sets of MoMo twins. They identified obstruction of flow in the umbilical vein by this means and made the point that this diagnosis can lead to improved outcome of these problematic gestations. It is the practice in our hospital now to hospitalize such patients for possible rapid intervention when problems arise.

The other important point to be made is that monochorionic twin placentas usually have blood vessel connections between the fetal circulations; they are not generally present in dichorionic twin placentas. These anastomoses are

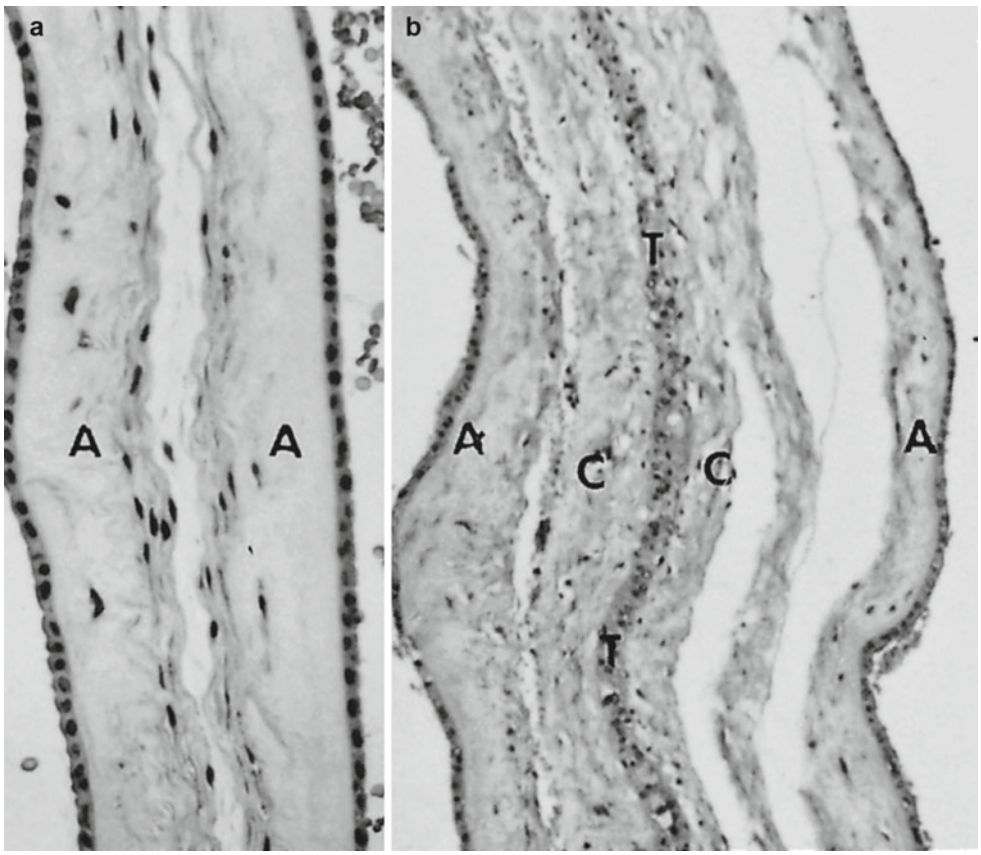


Fig. 25.1 (**a**) Diamnionic (monochorionic) "dividing membranes" of identical (MZ) twins. There is always a space between the two amnions. The amnion consists of epithelial cells and connective tissue. (**b**) Diamnionic, dichorionic "dividing membranes." The right amnion is dislodged from the underlying chorion, a frequent artifact. The central trophoblastic remnants have fused. *A* amnion, *C* chorion, *T* trophoblast. H&E, ×100

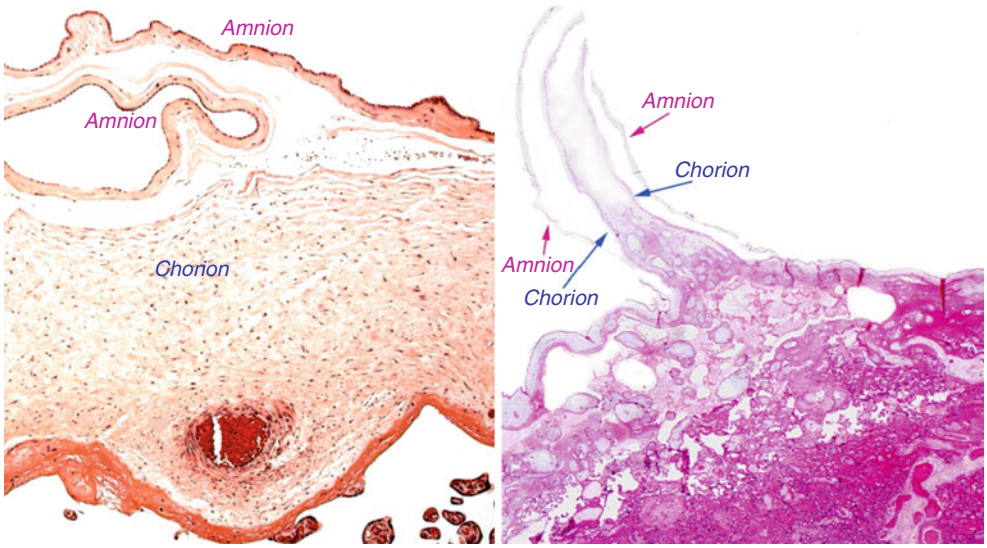


Fig. 25.2 (*Left*) T-section of dividing membranes of monochorionic, diamnionic twins. Note the contiguity of the chorion over the surface of the placenta at the bottom and the separation of amnions. (*Right*) T-section of diamnionic, dichorionic twin placenta. There are atrophic villi and trophoblastic remnants extending between the two chorionic membranes. H&E, ×40

discussed in greater detail later in this chapter. Note also that not all authorities have concurred with the ease of distinction between DiMo and DiDi placentas just elaborated. Thus, the famous gemellologist H.H. Newman (1931a) believed that one could easily mistake a DiMo for a fused DiDi placenta. This is certainly not the case in experienced hands, but it points to the desirability of examining histological sections for affirmation. Moreover, it must be recognized that blood group studies in twins have the problem that fetal blood is commonly admixed because of the frequent blood vessel anastomoses in the monochorionic group. It then follows that, if DZ twins were associated with a monochorionic placenta in which anastomoses existed, their different blood antigens would permanently mingle. Only a highly sophisti-

Fig. 25.3 Diamnionic, monochorionic twin placenta. The "dividing membranes" are held up to disclose their transparency (See Fig. 25.5 for contrast with DiDi placenta)

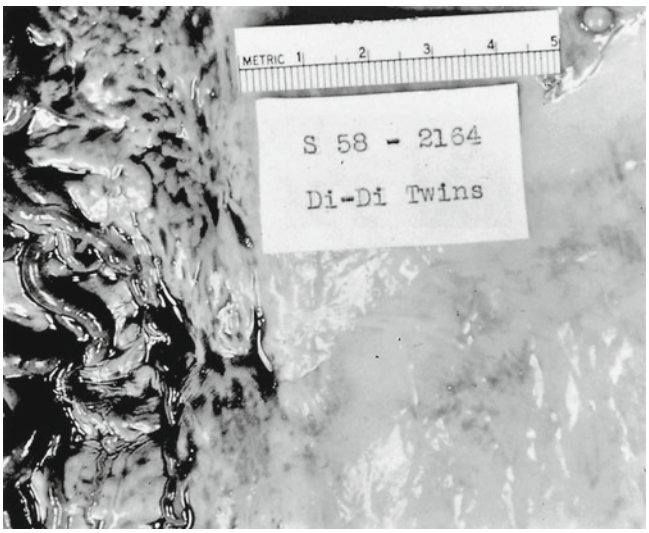


Fig. 25.5 Dividing membranes of diamnionic, dichorionic twins are characteristically opaque. They are only rarely translucent

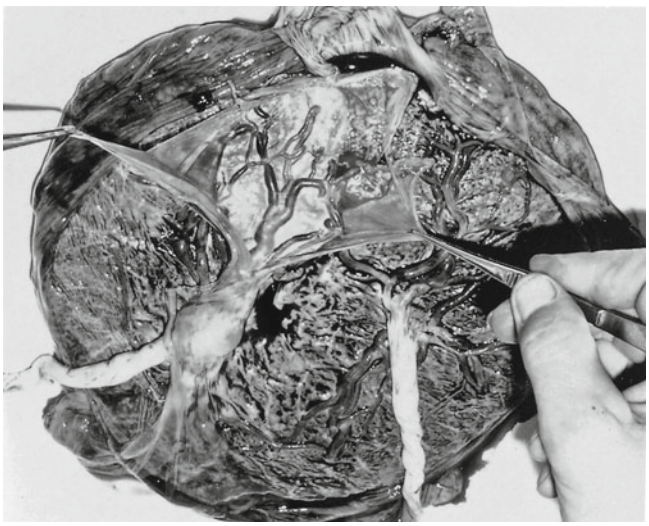


Fig. 25.4 Diamnionic, monochorionic twin placenta. The "dividing membranes" are being separated; at their base, they are easily peeled off the chorionic surface. The vascular communications between the two fetal vascular beds are thus disclosed

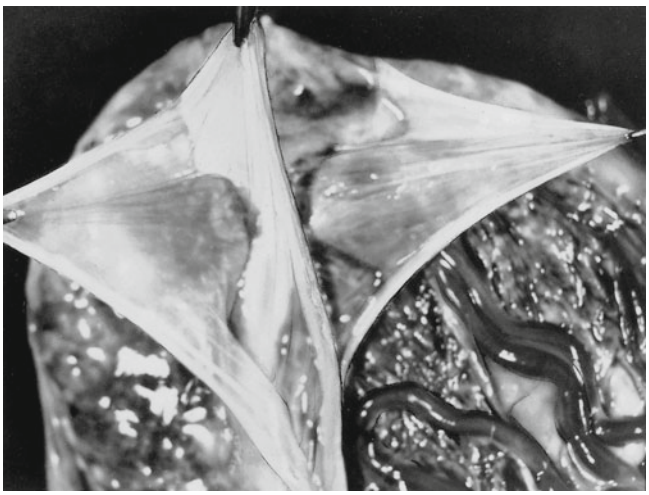


Fig. 25.6 Diamnionic, dichorionic twin placenta. The two amnions are being peeled off the central two chorionic leaves. The latter cannot be completely stripped off the placental mass without disrupting it

cated analysis of their blood groups would ascertain the presence of "blood chimerism." The unusually high frequency (±8%) of blood chimerism reported by van Dijk et al. (1996) remains puzzling and needs verification before it can be accepted as proven. On the other hand, Quintero et al. (2003a) reported a well-studied case of a DiMo twin placenta with discordant sex and unsuccessfully treated twin-to-twin transfusion syndrome, clearly a great exception. More, the genital development of the twins was normal despite the blood chimerism, unlike that found in Artiodactyla (freemartins) and similar to what is found to be so in marmosets (v.i.). Miura and Niikawa (2005) reported six dizygotic but monochorionic twin pairs after ART. Moreover, they discussed the absence of genital abnormalities in spite of blood chimerism and the possibility of psychological trauma when such XX/XY chimerism is found. Assaf et al. (2010) described another set of boy/girl twins with laser-treated TTTS whose "recipient" had significantly higher levels of blood transfer.

In this connection, it is important to mention that Mortimer (1987) has challenged the concept that monochorionic placentas are diagnostic of MZ twins on the basis of blood studies. Cord blood grouping studies were conducted on 12 sets

Table 25.1 Distribution of placental types in twins

Source	DiDi (%)	DiMo (%)	MoMo (% or ?)
Szendi (1938)	66	34	0
Vermelin and Ribon (1949)	45 (like sex) 32 (unlike sex)	23	
Benirschke (1961)	68.5	30	1.5
Potter (1963)	76	21	3?
Cameron (1968)	80	20	
Corney et al. (1968)	41 (like sex) 37 (unlike sex)	21.8	
Fujikura and Froehlich (1971)	73	24	2.4
Nylander (1970)	76 (Aberdeen) 92 (Yoruba-Nigeria)	19 5	5? 3?
Derom et al. (1988)	72	27	0.9
Barss (1988)	74.2	24.2	1.7

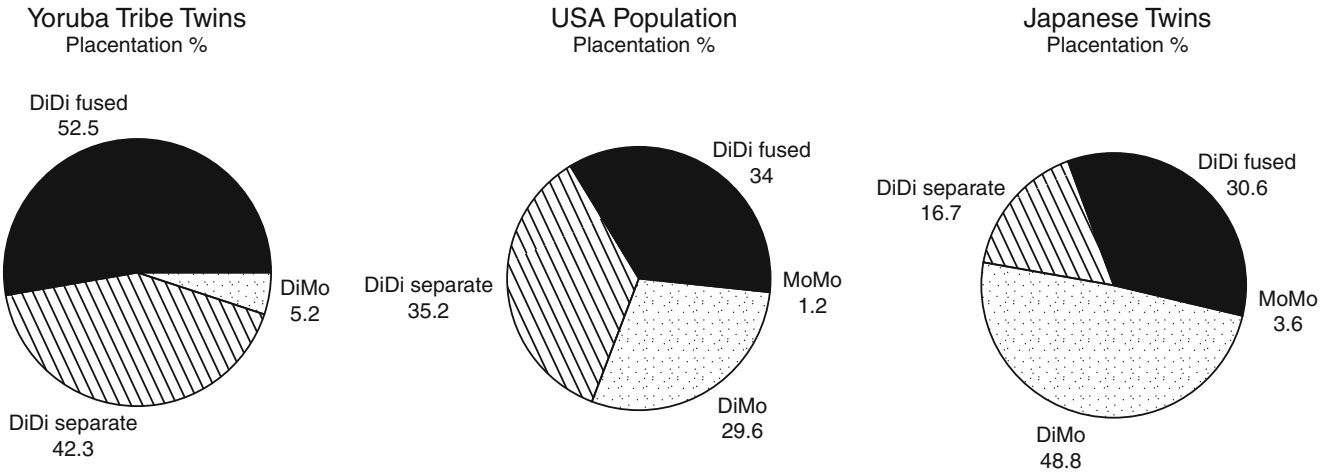


Fig. 25.7 Twin placentation in three racial populations. The figures for the Yoruba (*left*) are from MacGillivray et al. (1975); those for the US population come from Benirschke and Driscoll (1967); those for the Japanese population come from Sekiya and Hafez (1977)

of monochorionic twins for 16 red blood cell antigens. In three sets, there were discrepancies between the antigens, despite the presence of artery-to-artery and vein-to-vein anastomoses. These discrepancies always involved single and minor blood groups. How such antigenic difference can come about is difficult to understand, as the anastomoses should have guaranteed complete mixing, as is the case in the few blood chimeras to be considered later. In our view, this study is insufficient evidence for Mortimer's proposition that 25% of the monochorionic twins studied were dizygotic. If this were so, there should be many more boy/girl twins found with monochorionic placentas, and it is not the case. Only two, perhaps three, such examples can be cited, and they were not well studied. The use of the DNA methods (with DNA to be obtained from solid tissues!) discussed earlier will dispel any doubt in the future if twins with such apparent discrepancies come to light.

After it was recognized that monochorionic placentation is useful for the identification of at least two-thirds of MZ twins, several larger series of twin placentas were published. They are summarized in Table 25.1. Note that marked differences exist in the distribution of the different twin groups in these reports. Thus, the frequency of monochorial (MZ) twins is much lower in Nigeria where the incidence of twinning is especially high, owing to the high frequency of DZ twins in the Yoruba tribe. Knox and Morley (1960) found Western Nigerian Yoruba twin frequency as high as 5.3%, with 91% being DZ. The converse is true of some Oriental populations. Sekiya and Hafez (1977) determined the type of placentation in 84 sets of Japanese twins. They found that 40 were dichorionic [26 fused (30.6%), 14 separated (16.75%)]; 41 were DiMo (48.8%), and 3 were MoMo (3.6%) (Fig. 25.7).

The placental relations of DiMo and DiDi twins are easiest to identify in very young pregnancies (Fig. 25.8). The youngest implantation sites of DiDi twins (10–12 days) have been illustrated by Meyer and Meyer (1981). They featured tiny blastocysts that had implanted far away from one another in the uterine fundus. Parenthetically, it may here be mentioned that Ohel et al. (1987) have suggested that, as seen by ultrasonographic "grading" methods (calcifications), the

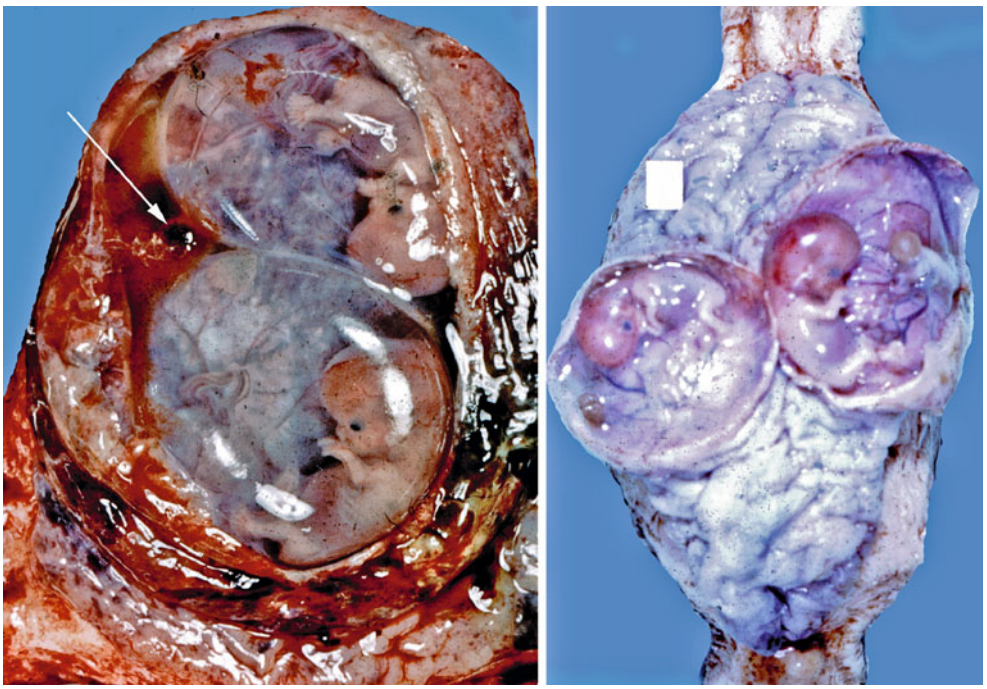


Fig. 25.8 (*Left*) Uterus with diamnionic, monochorionic ("identical," MZ) twins at 8 weeks' gestation. Note the two delicate amnions enclosed in a single chorion. Two yolk sacs are present at the *arrow*. (*Right*) Uterus with diamnionic, dichorionic twin implantation. The uterus has been opened laterally, and the cervical halves are seen at top and bottom. The two separate placental membranes are easily seen. If these placentas later expand, they will certainly collide and fuse

Table 25.2 Cord insertions and other pathological features of 7,090 consecutive placentas of which 143 were multiple births (1985–1986)

	Singletons (%)	Multiple gestations (%)
Marginal insertion of cord	8.9	28.7
Velamentous insertion of cord	1.1	16.1
Meconium staining	14.9	4.9
Succenturiate lobe	7.6	3.7
Immaturity	7.8	37.8
Abruptio placentae	4.9	2.8
Infarcts	20.7	11.2

placentas of twins exhibit advanced maturation compared to age-matched singleton placentas.

Twin placentas differ in many other respects from those of singletons (Table 25.2). The frequency of marginal and velamentous cord insertion will frequently be mentioned here and has great relevance in interpreting birth weights and also mortality. Succenturiate lobes are much more common, perhaps because of focal areas of placental atrophy and, of course, they are more often immature structurally because of early delivery. It was surprising though to note less commonly a finding of meconium staining and villous infarcts, the reason for these differences being less clear.

25.3 Causes of Multiple Births and Incidence

A fundamental difference exists in the respective etiologies of DZ and MZ twins. DZ twins (and many higher multiples) are the result of polyovulation. This may be hereditary; it is also certainly age-related, and it can be induced by the administration of gonadotropins and other hormones. The strongest evidence that hormones (gonadotropins) are responsible for multiple ovulations comes from their therapeutic use in infertility patients. Intentional induction of multiple ovulations with gonadotropins is regularly employed in the livestock industry (e.g., Chupin et al. 1976) and is well studied in laboratory animals and, more recently, during the practice of assisted reproductive therapy (Chap. 27).

Milham (1964), therefore, hypothesized that spontaneous DZ twinning in humans may be explained by a maternal increase in pituitary gonadotropin production. He based this idea on the increase in pituitary size with advancing age, the larger pituitaries possessed by African Americans, and the increase in size of the hypophysis after repeated pregnancies. These features correlate with an increase in DZ twinning rates. Numerous studies have since been undertaken to verify this hypothesis. In humans, there is now good evidence that the recruitment of follicles for ovulation is controlled by follicle-stimulating hormone (FSH) (Vermesh and Kletzky 1987). Marshall (1970) reviewed the findings following ovulation induction by gonadotropic hormones and clomiphene. The administration of clomiphene led to a 6% incidence of twins, and gonadotropin administration was followed by a 5–50% incidence of twins. These variable frequencies were found to be dose-related. Nylander (1973) determined that Nigerian women of the Yoruba tribe, known to have very high rates of DZ twins, also had elevated levels of FSH and luteinizing hormone (LH), when compared with Whites. Moreover, because of the tendency of eating large quantities of yams (estrogen-containing) by Yoruba women, this has

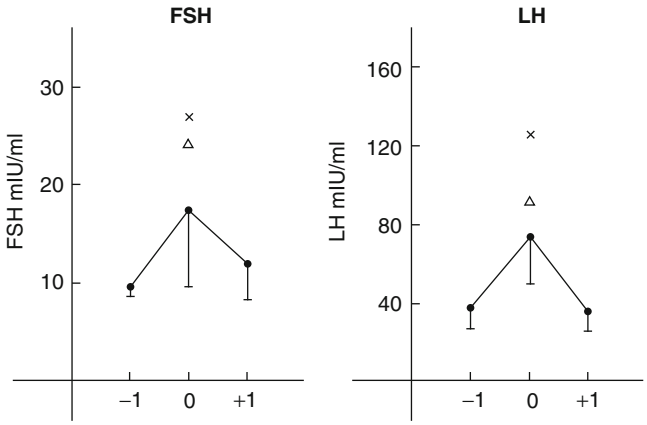


Fig. 25.9 FSH and LH levels in women around the time of ovulation. X peak value in Yoruba tribe women of Africa, Δ peak value in US Whites, *solid line* ten Japanese women (From Soma et al. 1975, with permission)

been speculated to be the responsible factor for the high incidence of DZ twins in this tribe. Soma et al. (1975), noting the lower frequency of DZ twins in Japanese when compared to other populations, measured the FSH and LH levels in ten Japanese women. They found significantly lower values for both hormones than are present in Nigerian women. The values were also lower than those reported for the American populations (Fig. 25.9). Because these two sets of data came from women near the time of expected ovulation, the validity of the results was questioned and the thesis then reexamined. Presumably, recruitment of follicles for the next ovulation takes place around the time of menstruation. For that reason, Martin et al. (1984a, b) undertook a study of various hormonal levels in women during the first 4 days of their menstrual cycles. They compared women who had, at least, one set of DZ twins with those who had no twins. They also found that FSH and LH (less so) were elevated in twin-bearing mothers. Estradiol was also elevated. Then, Gilfillan et al. (1996) studied the hormone profiles in mothers of DZ twins and concluded that those mothers do not have elevated FSH levels and that there is "… an increased tendency … that may be due to a reduced rate of atresia in advanced follicles." In a later study, this group of investigators found no difference in inhibin A and B levels of mother of DZ twins (Gilfillan et al. 2003). Spellacy et al. (1982) attempted to ascertain if the pituitaries of twin-bearing women were more responsive to the injection of gonadotropin-releasing hormone (GnRH). It proved not to be the case. It must be cautioned, however, that Spellacy's studies were undertaken during the luteal phase of the cycle and may thus not reflect the natural effect on FSH production needed for follicle recruitment. Lambalk and Boomsma (1998) determined that in twin-prone women, the elevated FSH levels are "entirely related to an increase in number of FSH pulses." The elevated FSH levels of older women they argue results from a decrease of ovarian inhibin production.

The aforementioned hormone studies support somewhat the notion that the genesis of DZ twins may indeed be the result of excess production of FSH, but they are still not conclusive to explain the heritable tendency for DZ twinning. Milham (1964) had suggested that the higher gonadotropin production he assumed to be the basis for DZ twinning is a racial characteristic of the hypophysis. This idea was challenged by Eriksson (1964) who pointed out that in some countries, the DZ twinning rate has recently declined and that it could not be explained by an assumed lowering of the age of pregnant women and by differences in racial composition. His point was that DZ twinning is a "genetic trait." We believe that the gene responsible for higher FSH levels must now be considered to be the principal agent in familial twinning. The hormonal assays from many sources all point in this direction, but it is not entirely certain as yet. Whether the effect of increased FSH production is the sequel of more pituitary cells or more GnRH production or is also due to greater follicle sensitivity needs to be studied. A further investigation supports the genetic nature of the multiple ovulation events. When women who had delivered DZ twins were followed sonographically, it was found that they had considerably more ovulatory activity than controls (Martin et al. 1991).In addition to inducing twin gestations, hormonal induction of ovulation is often followed by the birth of triplets and higher multiples. Schenker et al. (1981) reviewed this topic in detail, including the complications that arise from such pregnancies. They also made recommendations as to the prevention and management of multiple births. Although it is true that multiple births are generally multizygotic, it has long been noted that, among such multiple offspring, there is often an admixture of DZ and MZ infants. For instance, Atlay and Pennington (1971) reported on quadruplets born after pituitary gonadotropin stimulation; two of the infants were monoamnionic and thus MZ twins. Whether the incidence of twinning rises following the discontinuation of chemical contraception ("the pill") is controversial. Rice-Wray et al. (1971) found no such increase in their study of 516 women, whereas Rothman (1977) and Bracken (1979) found that twinning was about doubled when pregnancy occurred within 1–2 months after cessation of oral contraception. The increase was found to be due to DZ twins in both of these studies. Bracken inferred that it results from pituitary response to oral contraceptives. Interesting discussion followed Bracken's paper (James et al. 1979; Bracken 1979; Honoré 1979) and suggested that after oral contraception, pituitary gonadotropin release may, in fact, lead to DZ twinning. Whether it is also responsible for an increase in embryonic aneuploidy (particularly the occurrence of triploidy as has also been suggested) awaits further study. It has been hinted that currently, a general rise in MZ

twinning rates is occurring and that this is perhaps related to the use of oral contraceptives (Bressers et al. 1987). Possible other environmental agents, however, could not be excluded by these investigators. Thus, advancing maternal age and ART have had significant impacts to explain the rise.

As had been noted by Weinberg (1909), twinning may be familial. Weinberg asserted that DZ twinning is inherited; however, it was believed that hereditary factors played no role for MZ twinning. Hamamy et al. (2004) have now shown in a remarkable family that five generations had apparently MZ twinning (13 pairs in 2,035 members interviewed) inherited by what they assumed to be an autosomal dominant gene. Shapiro et al. (1978) who had already brought some similar albeit smaller pedigrees together also assumed a possible autosomal gene and advanced the view that one might look upon MZ twins as "altered morphogenesis." The situation in DZ twinning tendency differs. Of course, such a possible genetic effect can be manifested only by a woman with the genetic background for twinning, not by the father of twins. He may pass on this gene to his offspring, but only double ovulation in women can **prove** the existence of the gene. It is thus sex-limited. The finding by Bulmer (1960) that increased twinning among relatives of fathers of twins is due to underreporting of singletons does not seem to alter the inheritance of presumably higher FSH levels. These aspects are further elaborated by White and Wyshak (1964).

In our opinion, familial and racial predisposition to DZ twinning may result from enhanced production of FSH. Montgomery et al. (2000, 2001, 2003; Duffy et al. 2001) have searched for possible gene linkage, finding none so far. It may be relevant, however, that McNatty et al. (2001) found an X-chromosomal mutation that leads to multiple ovulation and is dose-dependent, and Galloway et al. (2000) have similar findings in human families. Busjahn et al. (2000) suggested that a gene on chromosome 3 relates to DZ twinning; obviously, more work will be done in future, and a more conclusive result can be anticipated. Others suggested that there may be an altered FSH receptor gene mutation, but that has not been firmly established either. Now, Montgomery et al. (2004) studied families with DZ twinning frequency and identified a deletion mutation in GDF9 (on chromosome 5q31.1), much as had been seen in sheep. The racial relation to DZ twinning is most impressively shown by comparing the frequency in Nigerian women from the Yoruba tribe with Oriental women (Nylander and Corney 1969; Nylander 1971a). Nylander et al. observed that monochorial twins were rare in Nigerian women of the Yoruba tribe and that zygosity determinations indicated a vast preponderance of DZ twins. The frequency of MZ twins was the same as that found in Whites (4.5 per 1,000). In the north of Nigeria, the twinning rate was 21 per 1,000, in the midregion 31 per 1,000, and in the West and East 45 per 1,000. These data contrast with reports from Japan, where the overall twinning rate is 6.1 per 1,000, with a 1.65:1.00 ratio of MZ/DZ twins (Inouye 1957). Similar rates have been reported from Taiwan (Wei and Lin 1967). In Europe, there tends to be a "progressive decrease in the frequency of twins from north to south" (Eriksson 1962).

The known higher frequency of DZ twins in older mothers may then also be due to their enhanced FSH secretion. There is a steady rise in DZ twinning to the maternal age of 35, and, after that age, there is a sharp decline in DZ twinning. Although longitudinal studies of FSH secretion have not been published for individual women, some data exist to indicate that FSH levels rise steadily with maternal age (Albert et al. 1956). This finding supports the notion that the increased DZ twinning frequency observed with advanced maternal age is due to enhanced FSH secretion by older women's pituitaries, but it does not prove it. The FSH levels are, of course, much higher still in postmenopausal women. Longitudinal studies are needed. Lawrence et al. (2004) tested the hypothesis that food fortification with folic acid might affect the twinning rate but found this not to be so.

The interesting question has been raised as to whether the higher gonadotropin secretion of individuals with the genetic trait to produce twins is also manifest in men. For sheep and other domestic animal species, some evidence exists that, in individual races, there are differences in the frequency of DZ twinning (Land et al. 1973). It has also been suggested that the testicular weights from such animals are greater in males that carry the gene for twinning (Land 1973; Islam et al. 1976). In order to study this aspect further, Short (1984) has reported ethnic variations of testicular size in men; he found that Orientals have smaller testes than Europeans. There are no data yet from Yoruba men, but racially different testosterone levels have been reported by Ross et al. (1986). They tend to support the same principle and are viewed as being in support of the marked differences in prostatic cancer (Gittes 1991). These and related aspects were considered in some detail in Diamond's stimulating editorial (1986). The differences of placentation in three well-studied racial groups were depicted in Fig. 25.7, which displays graphically how meaningfully different the placentas of twins are constructed when their zygosity is so variable.

The **cause of MZ twinning** is not fully understood either. Whereas dizygotic twins (and multiples) derive from the fertilization of more than one ovum, monozygotic twins must originate from the spontaneous separation of blastomeres. Although this process occurs in all animal species with approximately the same frequency as that observed in humans, there are two nearly similar species in which this polyembryony occurs with regularity: the two *Dasypus* species of armadillo – *Dasypus novemcinctus* (nine-banded armadillo) and *Dasypus septemcinctus al. hybridus* (seven-banded armadillos, mulita) (Fernandez 1909; Newman and Patterson 1910; Hamlett 1933). The precise understanding of

the mechanism of their polyembryony eludes us. Hamlett (1933) was critical of the statements made by Newman, who had inferred that it was the delayed implantation of armadillos that leads to impoverished nutrition and deficient oxygenation of the blastocyst, and it was thus the cause of polyembryony. It is of additional relevance that other species with delayed implantation do not share this phenomenon of polyembryony. Hamlett advocated that segregation of blastomeres is determined by genetic factors. More recently, Loughry et al. (1998) advanced the notion that this feature resulted from the small implantation site in a unique uterus, but they cautioned that this needs future analysis. They were the first authors, however, to show clearly the monozygosity of the litters by their finding complete identity of DNA microsatellites.

The nine-banded armadillo, ranging from Texas to Uruguay, always has "identical" quadruplets; the mulita may produce 7–12 male or female "identical" offspring. Although the mulita is much smaller, the two species are closely related and possess, for instance, identical chromosomes. The mulita is a common animal in Uruguay and Argentina; it has a single blastocyst (and corpus luteum) in a pregnancy that is also characterized by delayed implantation. Immediately after implantation, the embryonic mass separates into multiple offspring. Whether it is by "fission or budding" was a hotly contended point of the discussions between Newman and Hamlett. In contrast to the monozygotic twinning in other mammals, the production of multiple births of these two armadillo species is so well regulated that anomalies, such as conjoined twins, acardiacs, and most other abnormal events occurring in human MZ twins, have rarely been observed (Hamlett 1933). We deduced that one reason for these discrepancies may be that, in these species, the splitting of blastomeres is a precisely timed event. Also, placental anastomoses do not occur in armadillos (Anderson and Benirschke 1963), possibly because of the different timing of their placentation. Perhaps it is the reason for their relative freedom from placental problems. The most searching inquiry into the causes of MZ twinning comes from a review of Blickstein and Keith (2007). They weighed the armadillo gestation, various prior hypotheses, and also the enhanced MZ twinning rate in ART and superovulation. Despite examining all these factors, they concluded that the true etiology is still elusive.

Other mammals, those that have approximately similar rates of MZ twinning as humans, have no precisely timed monozygotic twinning period. In them and in humans, the splitting of the embryonic mass appears to occur at random during the early embryonic period. It has also been observed that MZ twins commonly occur after surgical transfer of single bovine blastocysts into pseudopregnant cattle recipients (Moyaert et al. 1982; Kraay et al. 1983). Paulson et al. (1988) reported that triplets were born after the transfer of two previously frozen human embryos. Surprisingly, after assisted reproductive help, monochorionic, even monoamnionic multiple pregnancies have repeatedly been reported, by Edwards et al. (1986) and by Salat-Baroux et al. (1994). Massip et al. (1983) observed cinematographically the atypical hatching of a cow blastocyst in vitro and suggested that it may be the mechanism by which dichorionic MZ twins take their origin. They observed partial protrusion of blastomeres from a zona, and after the "hatching" was complete, the two cell masses were connected only by a diminutive bridge. That hatched blastocysts are capable of twinning was demonstrated by surgical division of sheep embryos (Willadsen 1979) as well as in mice (Tsunoda and McLaren 1983), horses (Allen and Pashen 1984), goats (Tsunoda et al. 1985), pigs (Nagashima et al. 1989), and other animals. In many such experiments, implantation led to normal development of these split embryos. Nevertheless, a prospective study by Blickstein et al. (1999) came to different conclusions. They studied the outcome of human in vitro fertilization results with those of single sperm injection fertilization. While the former procedure had a 12 times the expected MZ twinning rate, the latter technique (although presumably more destructive to the zona pellucida) produced no twins. Their conclusion was that it is perhaps the handling of eggs during in vitro fertilization that results in the splitting. Steinman (2001a, b, c and 2002a, b; Steinman and Valderrama 2001) incriminated the adverse role of EDTA (calcium-depleting) in the culture media. The true cause remains elusive, however. Some of these aspects are further treated in the Chap. 27.

It is necessary to recognize that there are many temporal differences in the development of the inner cell mass and the setting aside of the trophectoderm in animals. Thus, when different species are compared, it is difficult to draw precise analogies to human development, especially to placental growth. Thus, the mouse segregates embryo from trophectoderm at the fourth cleavage stage (about 12–16 cells). The peripheral cells develop tight junctions and form the future placenta (Ziomek and Johnson 1982), an event taking place much later in the sheep and cow. In humans, similar to the mouse, the event occurs at about the fifth division of cells. In 1% of cultured mouse embryos, spontaneous separation of blastomeres into MZ twins takes place, analogous to what would be expected of the process that leads to conjoined twins (Hsu and Gonda 1980). Runner (1984) observed two inner cell masses in a mouse blastocyst at the stage of proamnion cavitation, which suggested to him late division of the embryonic mass and development of mirror imagery, which is also more commonly seen in MZ human twins. Experimental fission of quail embryos has also produced conjoined twins (Lutz and Lutz-Ostertag 1963). The production of MZ twins in sea urchins was demonstrated by the

isolation of first-cleavage blastomeres (Driesch 1891). These embryos were rarely normal. Marcus (1979) showed that by shaking fertilized sea urchin eggs to remove their envelope and with subsequent exposure to hypertonic water, he was able to promote separation of blastomeres. Many of these MZ twins were also underdeveloped. It is particularly interesting to note that there were many intertwin morphological differences. Ludwig (1927) had commented on the irregular division of "hereditary material" in MZ twins but did not believe that blastomeres were capable of separating. He thought twinning to be a late event and also expected that MZ twins would often be different.

When pregnant mice were exposed to low doses of vincristine on days 7 and 8, unexpectedly many MZ twins developed, some being monoamnionic (Kaufman and O'Shea 1978). Kaufman and O'Shea cited the few other reports of conjoined twins produced by experimental teratogens. Perhaps best known are the experiments of Witschi (1934), in which he produced twins in the frog by fertilizing eggs that were 3–5 days overripe. Witschi observed the development of several blastopores and gastrulation. Other sporadic observations of MZ animal twins have been cited by Corner (1955). He reviewed the few available specimens of early human MZ twin embryos, which are not dissimilar from those observed in experimental animals. Corner also cited the interesting observation of frequent admixture of MZ and DZ twins, to which we previously alluded.

The results of statistical surveys suggest that multiple ovulation due to hormonal stimulation is not the sole cause of enhanced multiple gestations. Derom et al. (1987) observed that MZ twinning (1.2%) is significantly higher than would be expected from random births (0.45%). Boklage (1987a) has, in fact, gone so far as to ascribe the causes of MZ twinning to factors that differ little from those that induce DZ twins. When all evidence is taken together, it must be said that spontaneous MZ twinning is still a poorly understood phenomenon. Boklage (1981) takes exception with the notion of embryonic "splitting" as the etiology of MZ twinning. He pointed out that the high embryonic mortality that occurred in the early experimental studies makes splitting an unlikely cause of MZ twins. There is no doubt any longer, however, that splitting can take place in mammals, and it can definitely be done experimentally. Boklage also stated that none of the many experimental chimeras that have been produced in mice experimentally had resulted in MZ twins. This, in itself, however, is insufficient proof against "splitting," as it seems to us. Few mice eventuate in MZ twins in the first place, and not many offspring of experimental chimeras have been sufficiently studied to identify their possible monozygotic derivation. The arguments on this topic are not unlike the controversy of "splitting versus budding" of the past, and these are well denominated as being a "skirmish in semantics" by Hamlett (1933). It should also be said that, currently, we have a protocol in place that examines the number of corpora lutea in **all** Cesarean section, including that of twin gestations. Eventually, this should settle this controversy.

To explain MZ twinning, Boklage conceived that forces responsible for organizing a "field" or "gradient" in early embryos may be the reason for the MZ twinning event. He opined that a "weakness in the enforcement of that directive might allow a second such organizing center to induce a second developmental scheme." He was particularly concerned with understanding neural symmetry and with mirroring in twins. McManus (2002) produced an interesting book on the mirroring aspect of twinning and other events of asymmetry.

In our opinion, the armadillo is the best animal from which to gain a better understanding of this puzzling yet frequent event of embryonic duplication. It is to be regretted that they are difficult to breed in captivity and thus make it difficult to accumulate the relevant observations. Other than for the pregnancy outcome, there is no good evidence that heredity in some way controls the MZ twinning event (other than in armadillos). The incidence of MZ twinning is nearly the same throughout the world, and it is not significantly influenced by maternal age or the environment. It appears to be a sporadic event. Because of the nature of the fetal placental membrane relation in human MZ twins, one assumes that MZ twinning can occur at any time during the first 2 weeks of development. It then appears to be randomly distributed.

For lack of a better term and better insight into the etiology of MZ twinning, we have referred to the cause as the "twinning impetus." We make further inference that this impetus affects the developing embryos at random and that, because of this randomness of the timing, the different placental membrane relations shown in Fig. 25.10 come about. We believe this "impetus" to be effective from days 1 to 14 of embryonic development. Our hypothesis further assumes that it is impossible for the "impetus" to split an already formed embryonic cavity such as the yolk sac, chorionic cavity, or amnion. The monozygotic twinning process, then, is a biological continuum during this early period.

The phenomenon was discussed by Gould (1982) in an entertaining thesis on the not so trivial question as to whether conjoined twins are one or two persons. Finally, an interesting result, with experimentally derived MZ mouse twins, has been published by Gärtner and Baunack (1981). They produced MZ twins at the eight-cell stage and compared their growth with DZ twins in the same strain of mice. Despite the fact that they worked with an isogenic strain, the DZ twins differed more from each other in a variety of characteristics than did the MZ twins. The cause of this unexpected finding is not yet understood.

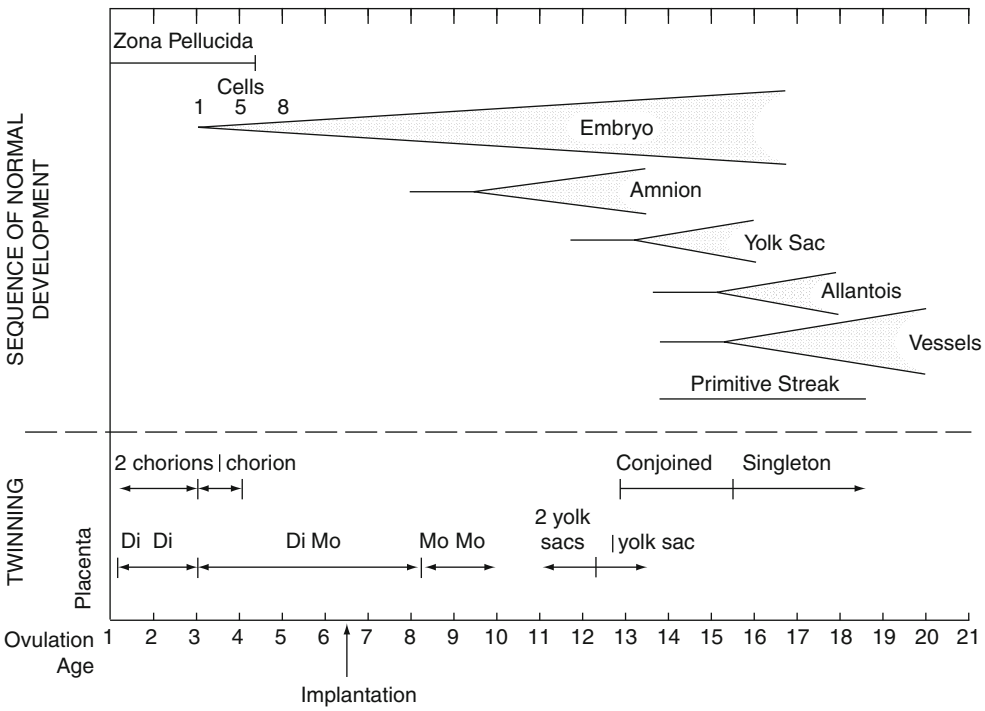


Fig. 25.10 Interpretation of early events in the MZ twinning event. The earliest observed embryonic events of various are depicted in the *upper portion*. The *bottom portion* suggests that certain placental structures result if twinning occurs at certain times. Note that the DiDi/DiMo frequencies correspond roughly to the observed 1:3 ratio. It is also assumed that with later development (after day 8), MZ twinning becomes ever more difficult because of the enlarging embryonic/placental masses. Once the primitive streak is formed, conjoined twins may develop at first. Soon, however, the presumed twinning "impetus" is ineffective

25.4 Third Type of Twin

The possibility of the existence of a "third type of twin" is occasionally considered in discussions of the twinning events. It proposes that MZ twins do not consist solely of "identical" twins, but that "nonidentical" twins, arising from a single ovulation event, make up part of the spectrum. It may amount to some 1% of twins who would usually be classed as DZ twins because of some dissimilarities of their genotypes. This concept envisages that polar body fertilization may occur. Thus, the twins would then come from a single maternal, but two paternal, genomes. They would be intermediate in their genetic configuration between MZ and DZ twins. Such a possibility is supported by the occasional finding of polar bodies that have a similarly large size as the normal oocyte. This is especially so in some bat species. Furthermore, there are some theoretical considerations detailed by Mijsberg (1957) that suggest the existence of "third twins." In fact, the fertilization and further development of polar bodies has been observed. Dixon (1927) has described human polar bodies in mitosis, synchronous with the oocyte mitosis. It is also noteworthy that, in humans and in a variety of animals, binucleated ova are observed. They may produce such twins or even result in the development of chimeras. Binucleated eggs have been described repeatedly in the ovaries of a variety of animals, in women (Kennedy and Donahue 1969) (Fig. 25.11), and in children. Manivel et al. (1988) found binucleated oocytes in 19% and binovular follicles in 52% of their pediatric autopsy material. The fertilization of such abnormal ova has been observed by Zeilmaker and colleagues (1983).

The occurrence of "third twins" would explain the occasional finding of a single corpus luteum associated with fertilizations that were diagnosed to be DZ twins. The concept has been considered in some detail by Elston and Boklage (1978). Later, Boklage (1987b) suggested the term "tertiary oocyte" rather than polar body fertilization and critiqued the acceptance of the Weinberg formula in assigning zygosity, in particular for discordant twins. He also favored the notion that overripe ova may be responsible for some of these abnormal fertilization products. It must be cautioned, however, that mere inspection of ovaries (at operation) is insufficient evidence for the presence of a solitary corpus luteum only. A second corpus luteum may be present and found buried underneath another, as is shown in Fig. 25.12. The macroscopic inspection of the ovary in this case would have been misleading. Further complicating the resolution of the question is that two normal ova may reside in a single antrum (Fig. 25.11). Such a Graafian follicle would result in a single corpus luteum and yet possibly produce fraternal twins. Finally, it can be said that a possible instance of polar body twins, one an acardiac fetus with triploid chromosome constitution and the other diploid, has been studied in detail described by Bieber et al. (1981). On the other hand, employing molecular methodologies, Fisk et al. (1996) were able to rule out polar body fertilization in nine sets of twins with acardiac gestations. This subject is discussed in greater detail in the section on acardiac twins.

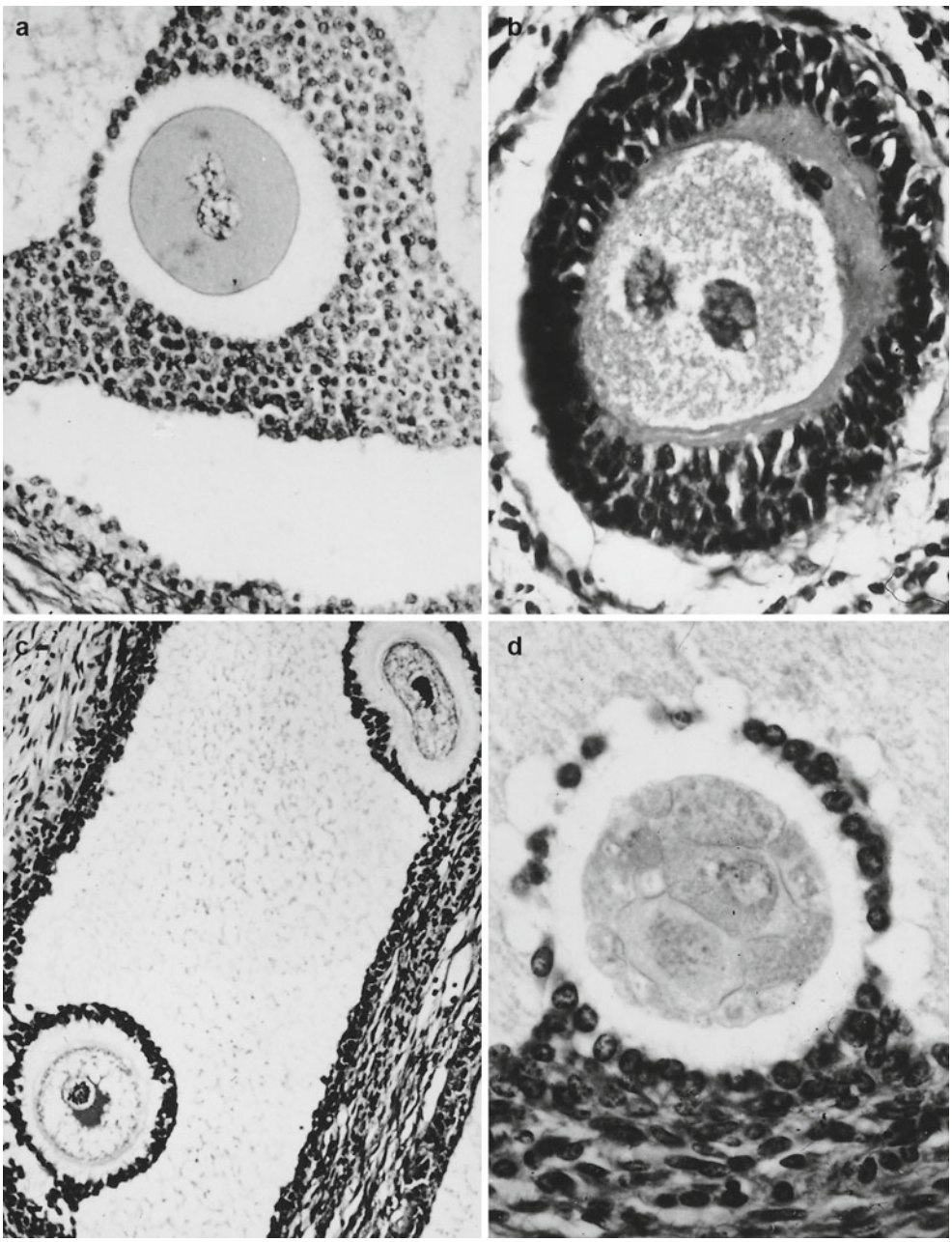


Fig. 25.11 Four Graafian follicles with abnormal ova whose future potential cannot be anticipated. (**a**, **b**) Binucleate ova in Graafian follicles. (**c**) Binovular follicle. (**d**) Segmenting ovum within Graafian follicle. H&E, ×100, ×160, ×80, ×100 (**a**, **b**, **c**, **d**, respectively)

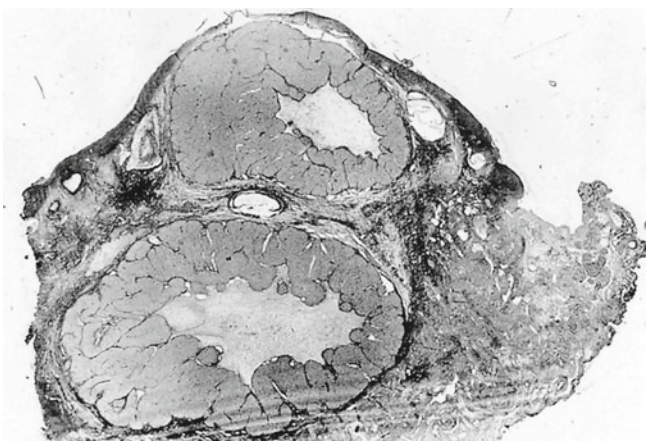


Fig. 25.12 Cross section of an ovary at 8 weeks' gestation with two corpora lutea of pregnancy. One is hidden from external view because of its position, so only one would have been recognized by inspection. This specimen is from the diamnionic, monochorionic (hence assumed to be MZ) twin gestation shown in Fig. 25.8. H&E, ×4

25.5 Twinning Incidence

The incidence of multiple pregnancies has been the topic of numerous investigations. This aspect was particularly well covered by Bulmer (1970) in his classical book on twinning in man. It has also been the topic of several discussions, published in the third issue of the Acta Geneticae Medicae et Gemellologiae (Vol. 36, 1987). The rate for dizygotic twinning in various populations has been summarized by Diamond (1986) whose data are shown below.

Ethnic group	Locality (per 1,000 births)	DZ twinning rate
Asians		
Japanese	Hawaii	2.2
	Japan	2.3
Chinese	Formosa	1.4
	Hawaii	2.1
	Malaya	2.8
	Singapore	4.1
	Hong Kong	6.8
Malays	Hawaii	2.2
	Manila	2.7
	Malaya	5.2
Hawaiians	Hawaii	3.9
Koreans	Korea	5.1
	Korea	5.8
	Korea	7.9
Indians	Bombay	6.8
	Bangalore	7.3
	Calcutta	8.1
Caucasians		
Europeans	Spain	5.9
	France	7.1
	Switzerland	8.1
	Holland	8.1
	West Germany	8.2
	Norway	8.3
	Sweden	8.6
	Britain	8.9
African Blacks		
Bantu	Johannesburg	16.0
	Leopoldville	19.0
Yoruba	Ibadan	40.0
	Ilesha	49.0

These data impressively show that DZ twinning has a profound racial variation. In contrast, the MZ twinning rate "…is nearly constant at about three and a half per thousand in all races" (Bulmer 1970). Eriksson (1962) has drawn attention to the decline of twinning rates from north to south in Europe, which is due to variations of DZ twinning rates. The twinning rates and outcomes for a large US population have been analyzed by Myrianthopoulos (1970a, b). He reviewed the data of the US multicenter "Collaborative Study" which analyzed 56,249 pregnancies with known outcome. It contained 615 twins (1 per 91.5 births). The differences in the ethnic background of that US population and its relation to multiple pregnancies can be seen in the following data from his report:

Group	Twins (no.)	Population (no.)	DZ twins (no./births)
Whites	259	25,991	1/100.3
Blacks	331	26,080	1/78.8
Puerto Ricans	25	4,178	1/167.1

The zygosity of 508 of these twins was examined as best as then possible, but a large number of twins remained unclassified. The results were as follows:

MZ = 29.6%
DZ = 51.4%
?Z = 19%

The profound influence of maternal age is well documented in these reports. The incidence of DZ twinning rises until, at 35 years maternal age, there is an abrupt fall in the incidence. A greater frequency of twins in the US Black population had also been noted in the large database summarized by Guttmacher (1953). He reported on the frequency of triplets and higher multiple births at a time that preceded the use of fertility drugs. Over a 22-year period, viable twin births occurred in 1 per 92.4 (Whites) and 1 per 73.8 (Blacks); triplets occurred in 1 per 9,828 (Whites) and 1 per 5,631 (Blacks).

The occurrence of higher multiple births, such as triplets, quadruplets, has commonly been estimated by the "Hellin-Zeleny" hypothesis: If twins occur with $1/N$, then triplets occur with $(1/N)^2$ and quadruplets with $(1/N)^3$. This method is merely an approximation and is subject to maternal age, medical therapy, race, and other factors.

Multiple pregnancies showed a progressive decline from 1938 to 1949; more recent declines in the twinning rate have been studied by a number of investigators. Akesson et al. (1970) showed that the incidence of twinning in Sweden fell from 1.4% in 1871 to 1.1% in 1960. This change was due to fluctuations in the number of DZ twins born. Changes in maternal age were considered, but they were not deemed to be the cause of this decline. Reports from the United States, Canada, Australia, and other countries have been similar (Elwood 1973; James 1973). The decrease in twin births in Holland was believed to be secondary to a decrease in maternal age at conception (Hoogendoorn 1973). James (1975) suggested that either the decline may relate to exogenous agents or that it is secondary to voluntary birth control. That the latter effect may have some significance is borne out by

the apparent cessation of the DZ twinning decline in Canada (Elwood 1983) and Hungary (Métneki and Czeizel 1983); but James (1983) was not convinced. Allen (1987) provided data to show that there was no decline in US twin births from 1964 to 1983. Imaizumi (1998) has summarized the twinning and triplet rates for 16 countries from 1972 to 1996 and indicated that most countries have a slightly **rising** rate of multiples. In recent years, however, there has been a remarkable increase in multiple gestations, and much of it appears to be the result of assisted reproductive technologies (ART). It is the case also in other "developed" countries; in the USA, the frequency of multiple is now 1:30 births perhaps as a result of this practice (Martin et al. 2003). Interestingly, only certain regions and populations are so affected but the results are startling. Thus, a review by the March of Dimes (MOD) Foundation (2003) states that "… fewer than 1% of live births result from IVF, they account for about one-third of all twin births and more than 40% of triplets or higher-order births in the US." There have been many discussions as to the value and nature of ART (see Chap. 27); because superovulation so often leads to an uncontrolled number of fertilized eggs (and the frequent need for fetal "reduction"); Vidaeff et al. (2000) thus suggested that blastocyst transfer by ART may be more appropriate for infertile couples. Gleicher et al. (2000) examined the risk of higher numbers of conceptuses by superovulation and suggested that smaller amount of gonadotropins needs to be employed than was then used. But this still does not really control the process, which is what is hoped for. The practice of ART is also changing over time; it consists of in vitro fertilization, intracytoplasmic sperm injection (ICSI), blastocyst development by culture in vitro for up to 7 days (see Sills et al. 2003; also many different culture media are used), and transfer of a variable number of blastocysts to the recipient uterus. Rijnders and Jansen (1998a, b) described that not all fertilized ova developed normally in vitro which, in part at least, may be responsible for some of the abnormal outcomes that are observed, especially in implantation and placental development. The ova to be fertilized are obtained following superovulation by hormonal means. Additionally, there are other modalities employed such as transfer into a surrogate uterus, employment of donated sperm and eggs, and other practices are under development. Small wonder then that the outcome varies as to the number of embryos resulting, often depending, on how many blastocysts are transferred, "sacrifice" (reduction) of one or more embryos depending on the numbers conceived, and frequently abnormal placentation. Daniel et al. (1999) even found that singleton placentas of pregnancies conceived by ART are abnormal (slightly larger and thicker, abnormal cord insertion). The highest numbers of successfully transferred embryos we have seen are sextuplets delivered from a compound placenta at 28 weeks' gestation. Most remarkable has been the frequency of the development of more than the number of transferred blastocysts by the "splitting" of one or more blastocysts (Rijnders et al. 1998a, b; Behr et al. 2000; Lancaster 2004). Platt et al. (2001) estimated that 15.7% of ART twins are monozygotic and that monochorionic twins are more problematic is well demonstrated by Dubé et al. (2002). Sills et al. (2000) impressively discussed the possible mechanisms by which monochorionic placentas can develop in such manipulations, perhaps by alteration of the zona pellucida, a concept to be discussed more fully below. Daniel et al. (2000) found among the twin pregnancies so conceived that they were more commonly undertaken in older mothers, that they more often were prematurely delivered, and that they were associated with PIH and various other complications of pregnancy. Later, they (2001) described the abnormality of placental development in such nonreduced twin gestations; they found mostly DiDi placentas that were thinner, more infarcted and had anomalous cord insertions. The economic impact and other aspects are discussed by Nkemayim et al. (2000) who also presented suggestions for limitation of blastocysts transferred that is now lawful in several European countries (see also Ozturk and Templeton 2002 who suggest limiting transfer to two blastocysts). Templeton (2004), Nunley (2004), and an Editorial in Lancet (2003) have all addressed the problems attending ART and the social implications faced by its practitioners. Jain et al. (2004a) have summarized these trends of transferring fewer ova in recent years, concomitant with a greater survival of the ART gestations. Most recently, Thurin et al. (2004) have compared single- vs. double-embryo transfer in women younger than 36 years in order to reduce the number of multiples. Blickstein (2005) reviewed in detail the frequencies of MZ splitting in ART and its various forms of embryo culture and comes to the conclusion that exact genetic diagnosis of such multiples is necessary (see also Chap. 27). Finally, it must be mentioned that the neonatal outcome is often suboptimal, aside from their prematurity and number. Some of these concerns have been reviewed by Schieve et al. (2002) and Strömberg et al. (2002). The latter paper led to intensive discussion (Akande and Murphy 2002; Leviton et al. 2002; Davies and Norman 2002).

The incidence of DZ twinning has also been shown to have a seasonal relation. Timonen and Carpen (1968), who observed this phenomenon in the Finnish population, deduced that this results from the continuous light stimulation which induces enhanced gonadotropin release. The peak of twin births occurred during early spring and summer. Elwood (1978) found the peak for a Canadian population to be in October, whereas Edwards (1938) had reported two peaks for conceptions (February and August) in a British population. The effect was more pronounced with twins than with singletons. Harlap et al. (1985) raised the possibility that an increase in DZ twins results from the development of overripe ova.

25.6 Superfetation and Superfecundation

Twins may have different fathers through the process known as **superfecundation** (two ova are fertilized by spermatozoa from different fathers). That the concept is valid was proved by finding HLA antigen differences in the twins studied by Terasaki et al. (1978). In the accompanying editorial, Ryan (1978) referred to other cases and to its occurrence in "test-tube babies." Another report, with one white and one black twin, was forthcoming from Harris (1982). This report is most remarkable because the fertilizations apparently occurred 1 week apart. Verma et al. (1992) proved superfecundation by two different fathers with cytogenetic markers but were refused DNA fingerprinting. Harris (1982) also referred to a case of **superfetation** with twins of apparently different gestational ages (34 and 37 weeks). Rhine and Nance (1976) described the pedigree of a relevant family. They suggested that superfetation was the basis for the repeated dissimilarities of twins. They assumed it to be inherited as a dominant trait and expressed through a putative placental inability to suppress new ovulation after conception.

25.7 Vascular Anatomy of Twin Placentas

One of the most important observations to be made in the study of twin placentas is the accurate determination of the nature of fetal surface blood vessels. Their relation to one another is perhaps the single most important determinant for the outcome of many twin pregnancies. These aspects were first clearly demonstrated by Friedrich Schatz, whose numerous contributions have been summarized in English by Strong and Corney (1967). Price (1950) considered the various vascular anastomoses of monochorionic twin placentas to be the most important determinants for the frequently discordant development of MZ twins. This notion dates back more than a 100 years, and many observers since have reached similar conclusions that anastomoses have a profound influence on outcome. The mechanism, however, how anastomoses are established in the developing placenta is still poorly understood, and especially mysterious is how it is possible that arteriovenous communications develop. From the fact that, in lasered TTTS placentas mostly superficial infarcts are found, we infer (KB) that the basic structure for TTTS is constructed very early, as the villous cotyledons are being formed and the capillaries develop. It has recently been published that vascular communications in mouse models employ yolk sac–derived macrophages to establish connections between the terminal "filopodia" of sprouting capillaries (Fantin et al. 2010; Schmidt and Carmeliet 2010). Perhaps a similar method is used in the early establishment of arteriovenous anastomoses in the cotyledons. This is a critical point in our understanding, and it is a difficult one to investigate now.

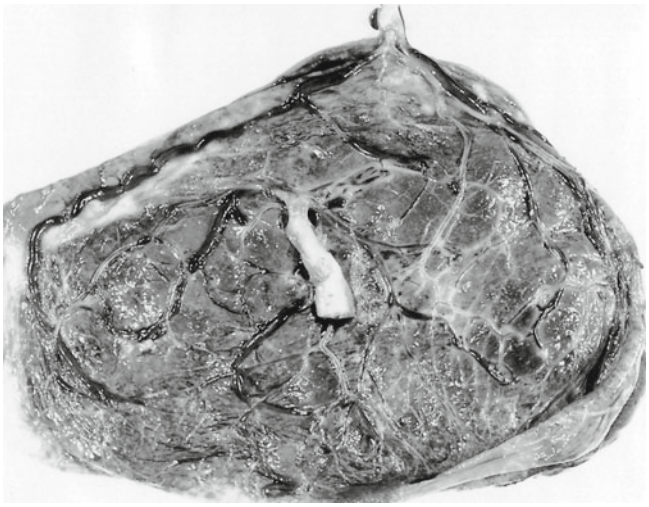


Fig. 25.13 Diamnionic, monochorionic twin placenta (26 weeks' gestation) with velamentous insertion of one cord. This twin had a much smaller portion of placental tissue and died

The demonstration of anastomoses is relatively simple. Once the anatomy of the placental vascular architecture is learned, injection studies are rarely necessary; they aid, however, in delineating the patterns for the novice and should be performed routinely. A simple method for the detection of anastomoses has been described by Coen and Sutherland (1970). They used milk for injection because it is so readily available and demonstrative, but other liquids are equally useful. For the purposes of injection, it is best to cut the umbilical cords near their placental surface, so as to reduce vascular resistance. One should also have stripped the amnion from the chorionic surface, which exposes the fetal surface vessels well (Fig. 25.13). The general examination of the placenta should have been completed, of course, but samples for histological study should be taken only after the injection has been done. For optimal results, several tools are desirable, and they are depicted in Fig. 25.14. It must be admitted, however, that a simple syringe and water are usually adequate. One must inspect the surface of the placenta carefully, follow major vessels to their ends, and determine, visually at first, which vessels are likely to have communications between the two fetal circulations (Fig. 25.13). In the normal placenta, the fetal arteries terminate in the periphery, dip into the villous tissue, and emerge nearby as veins, which then course back toward the same umbilical cord. The arteries are recognized as those vessels that cross over veins, particularly those of a larger caliber. A 1:1 relation is usually found in the final vascular ramifications: one artery to one vein. Bajoria et al. (1995) demonstrated that the likelihood of the presence of the typical twin-to-twin transfusion syndrome (TTTS) is greater the fewer anastomoses are present. Parenthetically, it may be mentioned that TTTS has also been referred to as TAPS (twin anemia-polycythemia sequence, Lopriore et al. 2010).

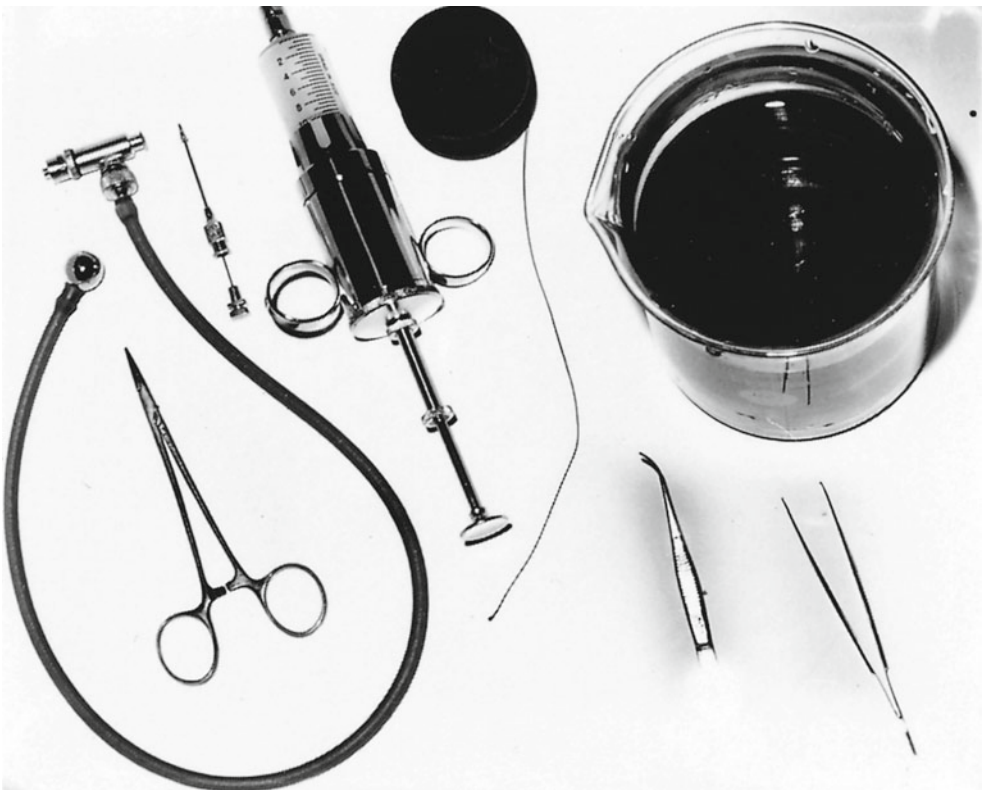


Fig. 25.14 Ideal set of tools to inject twin placentas: syringe with beaded needle, string to tie needle in place, colored liquid (e.g., milk), clamps, and forceps

When no returning vein can be identified to accompany a peripheral arterial branch in a twin placenta, an artery-to-vein (A-V) communication may exist, from one twin to the other. This area then becomes important for the exploration of a so-called deep anastomosis. These A-V anastomoses perfuse a "common" (or shared) cotyledon and form the basis for the transfusion syndrome, discussed below. They are common and constitute the "third circulation" of twin placentas. Most frequent are artery-to-artery anastomoses (A-A shunts); vein-to-vein (V-V) communications are the least frequent types of anastomoses, findings already made by Schatz in (1882) and more extensively in 1884. He believed that A-A anastomoses are more common because of the higher blood pressure existing in arteries; therefore V-V anastomoses are rare, and they were thought to obliterate more commonly before birth.

To document the presence of a direct A-A or V-V anastomosis, it is often sufficient to stroke blood back and forth through a major shunt. If one wishes to demonstrate it conclusively, injection of milk, colored water, or similar solution is feasible. To do so, one inserts a needle near the point of presumed anastomosis and then gently injects the liquid, which usually readily passes to the other side of the twin placenta (Figs. 25.14, 25.15, and 25.16). The injection of as little as 5–10 mL of fluid is usually sufficient. Note from the figure that it may help to have a needle with a bead and to tie it into the vessels to allow more pressure to be exerted during injection. Usually, grasping the end of the needle in the vessel with the thumb and index finger of the other hand is sufficient to allow injection of fluid with some pressure. It is also important to recognize that one should not attempt to inject the entire placental bed from the vessels near the cord insertion. This measure requires so much volume of injection fluid that pressures are generally insufficient to demonstrate finer anastomoses (Fig. 25.17). Moreover, the villous tissue of twin placentas is often damaged during delivery and the placenta then leaks when injected from the umbilical cord. This frequent disruption can make adequate demonstration of anastomoses difficult.

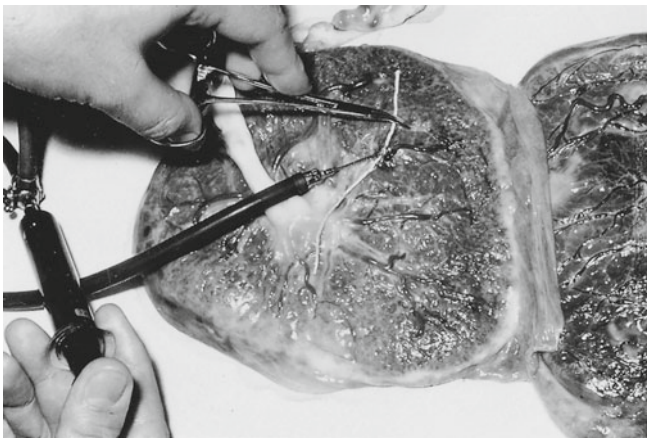


Fig. 25.15 Injection of DiDi twin placenta. A potential anastomotic area has been isolated, the amnion is stripped, and a needle is inserted and tied in place

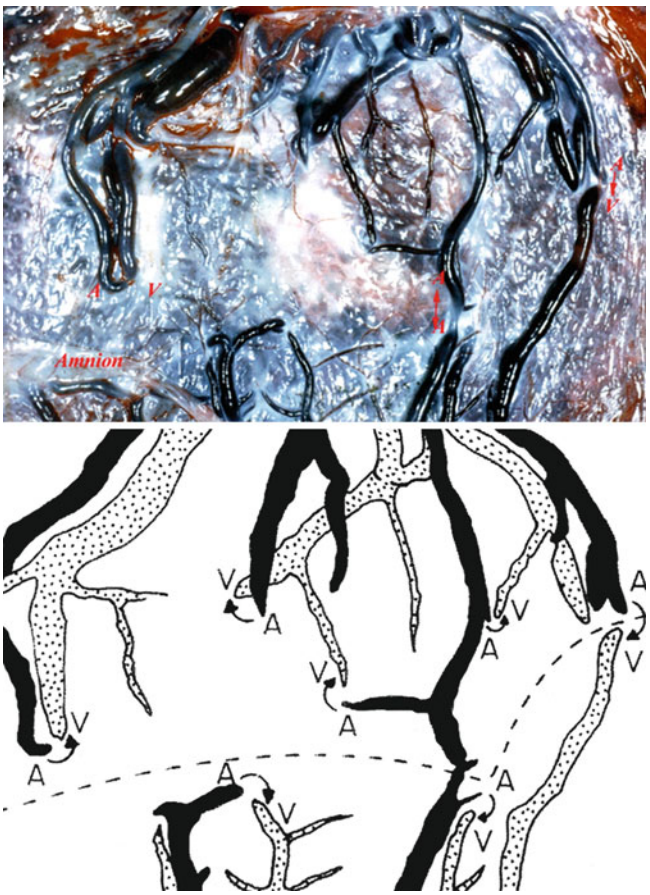


Fig. 25.16 Vascular equator of a DiMo twin placenta to show *A-A* and *A-V* anastomoses, as well as the normal cotyledonary supply. The diagram below is self-explanatory

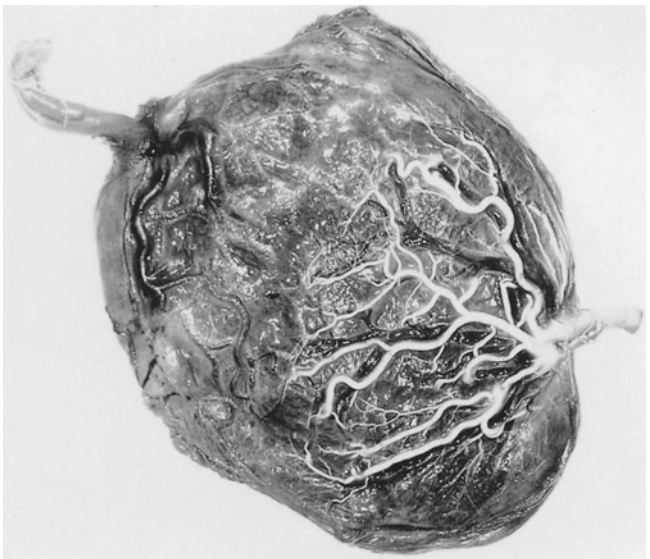


Fig. 25.17 DiMo twin placenta with amnion stripped off; the right side has been injected with barium sulfate through one umbilical artery. There are no anastomoses. Both cords have a marginal insertion; arteries cross over veins. This method failed to disclose two small A-V shunts (*bottom*) because of the lack of sufficient pressure exerted when the entire tree is filled (Courtesy of Dr. S. Romney, New York)

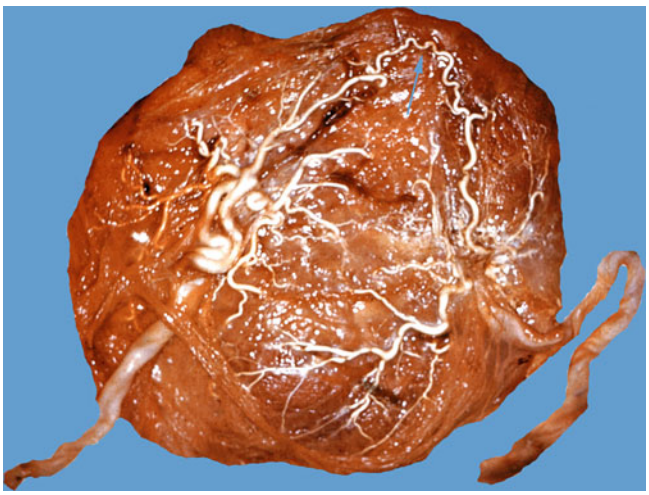


Fig. 25.18 DiMo twin placenta with single large A-A anastomosis at *top left*. It has also been injected with barium. Finer A-V districts have not been filled. The small blue *arrow* points to the AA anastomosis

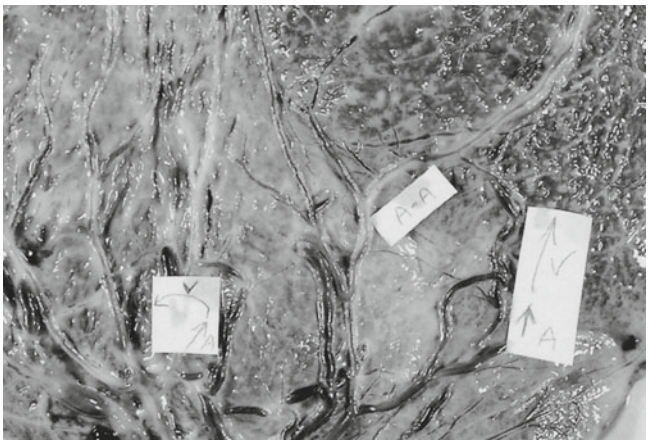


Fig. 25.19 DiMo twin placenta, vascular equator. The amnions have been removed, and the various types of anastomosis are delineated on pieces of paper

The identification of A-V shunts is usually the most difficult. It is best to inspect the surface carefully to identify possible areas of A-V shunts and then inject them successively. It is immaterial here whether one fills them from the arterial or the venous end. When the fluid is injected slowly under some pressure, one sees an area of placenta distend and increase in thickness. After a short while, the fluid emerges from the other side, and it can then be traced to a larger vessel where its nature (artery or vein) can be ascertained. The delineation, direction, and number of these shunts are especially important if one wishes to understand the basis for the transfusion syndrome. Finally, it is recommended that a drawing of the entire vascular relation is made for the record at the end of the procedure. Figures 25.18 and 25.19 show various types of anastomoses in two monochorionic twin placentas at their "vascular equators."

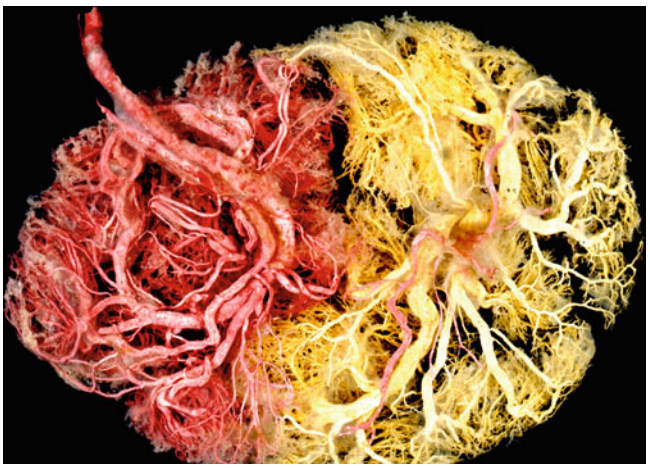


Fig. 25.20 DiMo twin placenta that has been injected with colored plastics and then made into a corrosion cast. A pink vessel, injected from the *left* one half, can be seen over the yellow-injected vessels on the *right*. The possible presence of "shared cotyledons" is impossible to identify

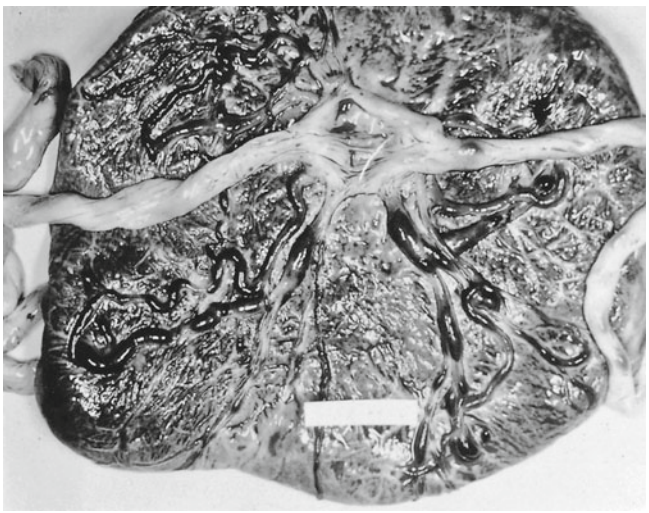


Fig. 25.21 MoMo twin placenta with amnions removed. The cords insert next to each other, adjacent to major anastomoses

If one wishes to make injections of the placental vasculature with plastics for later corrosion, special procedures are necessary. The placenta must be intact. It must first be washed out with warm dextran to open all vessels and to remove the fetal blood. Saline has been found to be less satisfactory (Robertson and Neer 1983). After the specimen has been flushed, one can then achieve gradual filling with plastics solutions in different colors and with ever-increasing strengths (see Torretta and Cobellis 1966). A diamnionic, monochorionic twin placenta, thus prepared, is shown in Fig. 25.20. As will be seen, there is slight filling of a (pink) arterial branch over the yellow-injected placenta, but only exhaustive examination of such a specimen allows one to identify the possible presence of shared cotyledons. By and large, these preparations are more beautiful than they are useful. Only experienced observers such as Hyrtl (1870) have profited from their preparation.

One might suspect that the proximity of cord insertions in twin placentas may influence the frequency and type of anastomoses, but that has not been our experience. Although it is true that in placentas with cords next to each other, as depicted, for instance, in Figs. 25.21, 25.26, and 25.38, large communications often exist whose injection is scarcely needed; they cannot be assumed a priori. Many MoMo placentas have no communications, irrespective of their cords' proximity. This point was well made in the study by Wenner (1956). He was surprised to find no anastomoses in the placental vascular ramifications of a thoracopagus. The demonstration of anastomoses is most difficult when one fetus has died before birth. It is thus often impossible to demonstrate vascular connections in DiMo placentas with a fetus papyraceus and also when the placenta has been fixed in formalin beforehand.

Despite numerous injection attempts, we have never seen anastomoses between blood vessels of dichorionic twin placentas. That they may exist in rare cases is not doubted. The finding of rare blood chimeras (*v. i.*) and occasional reports of such connections by competent observers (Fig. 25.22) (Cameron 1968: his Fig. 5) make them a reality of great interest. In contrast, anastomoses occur frequently in the DZ twins of some other species, such as marmoset monkeys and cattle. This aspect is discussed further below.

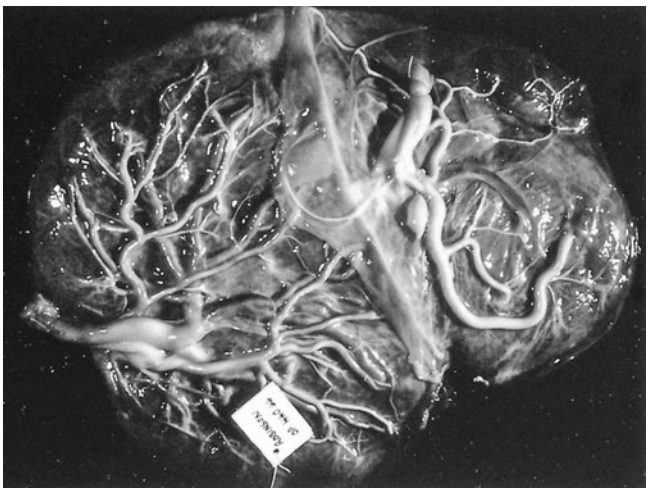


Fig. 25.22 DiDi twin placenta with minute anastomosis coursing over the dividing membranes. The associated like-sex twins were MZ (From his Fig. 5, Cameron (1968), with permission)

The observed frequency of intertwin blood vessel anastomoses in human MZ twins is difficult to assess because of the differences in techniques employed for their demonstration. We previously reported the following relationships of anastomoses in 60 injected monochorionic twin placentas (Benirschke and Driscoll 1967).

Type of anastomosis	Total found #	Infant survival #
A-A (one or more)	17	12
A-A + A-V	17	14
A-A + V-V	5	3
V-V	3	2
A-V	7	3
A-V + V-A	2	1
None	9	6

Similar findings have been published by others. Robertson and Neer (1983) reported on 278 twin placentas (of 23,810 births, incidence 1/86, 7 triplets). They used dextran and heparin for injection, cannulated the vessels, and injected 100 mL over 30 min. The vessels were then infused with warmed solutions of dyes in colloid suspension. India ink did not work well. Nineteen placentas were damaged and excluded; 97 placentas were separate masses. Of 162 successfully injected fused placentas, 96 (59%) were DiDi; the remainder were monochorionic. Of 56 monochorionic twin placentas studied, all but one had demonstrable anastomoses. The one placenta without anastomoses had an infarcted area that had produced a separation between the two halves. There may have been a communication in the past, as obliteration of such anastomoses is not uncommon. In one dichorionic placenta, the injection material exchanged between the two sides through a tiny villous district. The long-term outcome of these twins is not known, as is true for Cameron's case (Fig. 25.22). These twins had identical blood groups, even though the pair was dichorionic. As we indicated above, identical blood groups should be **expected** when vascular shunts exist in the placenta of twins. Four cases of the typical transfusion syndrome were found in the study by Robertson and Neer (1983).

The topic of DZ twins having a monochorionic placenta and vascular intertwin anastomoses is somewhat controversial. Scipiades and Burg (1930) first described anastomoses in two boy/girl twin placentas. Lassen (1931) and Tüscher (1936) each added a rare case of MZ dichorial twins with fine anastomoses. It must be emphasized, however, that some of these cases are not well supported by pictorial or other conclusive evidence. Even Lassen (1931), who performed stereoradiography on a placenta, was not absolutely certain of the connections he demonstrated. The technique of stereoradiography is not very satisfactory, as the findings in seven placentas from DZ twins with anastomoses have shown (Pérez et al. 1947). Szendi (1938) admitted this lack clearly in his discussion of the stereoscopic analysis in 4 of 20 dichorial placentas with putative anastomoses. Bleisch (1964) found arterial anastomoses in all 18 monochorionic, but in none of 42 dichorionic, twin placentas. He also succinctly explained why one should not accept the diagnosis of MoMo placentation in the boy/girl twin placenta reported by Pickering (1946). Wenner (1956) reemphasized Schatz' point of the rarity of V-V anastomoses. He found only three such cases among the perhaps 100 placentas that were studied. He suggested that this type of connection may have lethal consequences because "one fetus aspirates blood through these anastomoses from the other," a point to which we return later. In a later study, Bleisch (1965) found that all of his 75 monochorionic twin placentas had anastomoses. In all but one case the anastomoses were grossly identifiable, and the sizes of anastomoses were partially related to the distance of the cord insertions. He was unable to identify any specific reasons for the directions of flow, but death of one twin was associated with thrombosis. Only one V-V anastomosis was found, and Bleisch hypothesized first that the possibility exists for large blood shifts through large anastomoses, particularly given different intrauterine pressures, a point that is especially relevant when intrauterine demise of one monochorionic twin occurs. No connections were found between the circulations of dichorionic twins, but see below with cases in which chimerism was demonstrated.

Twin placentas have other vascular peculiarities. Bhargava et al. (1971) made a detailed study of the vessels in the chorionic plate of 166 placentas from twins and triplets. They found many more placentas with arterial and venous tortuosities, "arteriovenous dissociations," and reversal of arteriovenous relations when they compared twin placentas with 167 singleton placentas. Their conclusion was that these vascular abnormalities are determined "mainly under the influence of the functional demands of the corresponding foetus." Identification of these anomalies may enhance our understanding of prenatal development.

The frequency of abnormal insertion of the umbilical cords in multiple gestations is particularly important, as was demonstrated in Table 12.3 (Chap. 12). Kobak and Cohen (1939) described the incidence of velamentous insertion of one cord as being nine times higher in twins (routinely in triplets, according to De Lee, as quoted by these authors) than the 1% or so found in singleton placentas. Similar results were reported by Englert et al. (1987), when they observed abnormal placental shapes and cord insertions in multiple pregnancies after in vitro fertilization, and Lopriore et al. (2007) found that its frequency was similar in DiMo twins with the transfusion syndrome. Eberle et al. (1993), who investigated the placental pathology of weight-discordant twins, found that discordant placental lesions were correlated more with dichorionic than monochorionic twins rather than this discordance being correlated with placental weight. Feldman et al. (2002) found that velamentous cord insertion in triplets correlated significantly with fetal growth restriction. Likewise, in the searching review of placental lesions with abnormal growth in twins, Redline et al. (2001) found that peripheral cord insertion and, less significantly so, avascular villi and evidence of reduced maternal perfusion to be associated. Further, Benirschke and Masliah (2001) have reviewed the issue of discordant placental development in DiMo and DiDi placentas and considered the "competition for space" as one possible reason for the differences occurring in the placental development of multiples conceived by ART. Abnormal cord

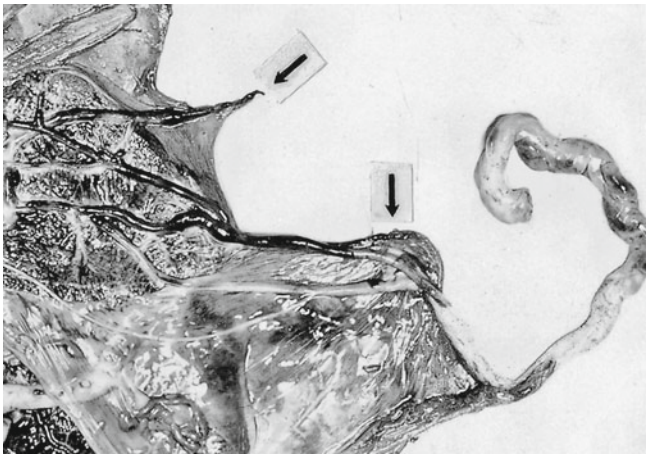


Fig. 25.23 DiDi twin placenta with velamentous insertion of the cord from twin B. He exsanguinated within 3 min after rupture of the second sac. There was disruption of the velamentous vessels (*arrows*)

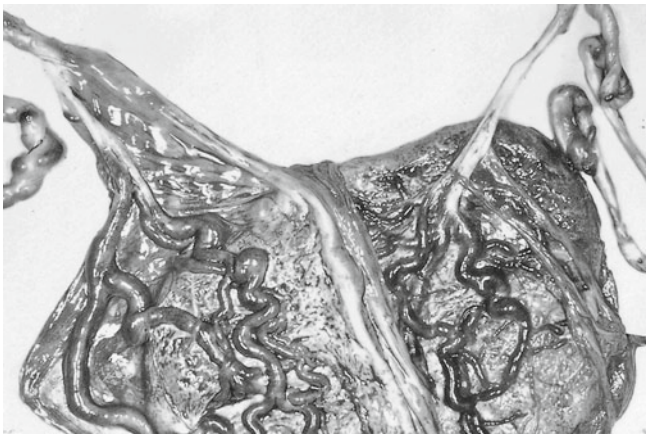


Fig. 25.25 A DiDi fused twin placenta with velamentous cord insertion of the left cord. Its fetal vessels are markedly dilated and course over the membranes at left. Note that the major vessels of these twins do not approach the dividing membranes

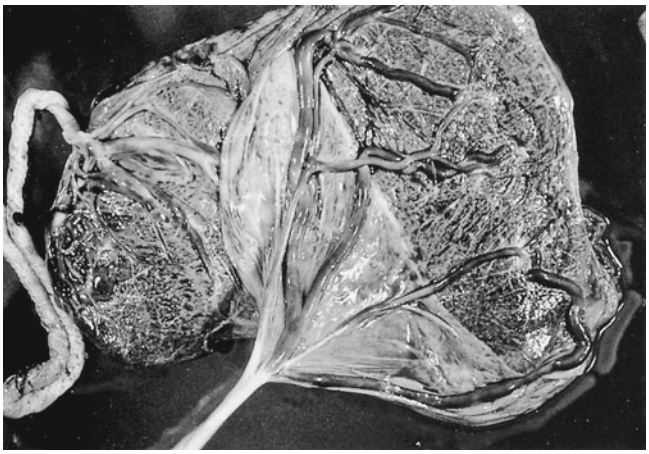


Fig. 25.24 A DiDi fused twin placenta with large vessels of twin A coursing over the dividing membranes. Twin A has a single umbilical artery. These twins delivered at 34 weeks' gestation. The superficial chorionic veins of twin B (*right*) were nearly completely thrombosed. The infants survived

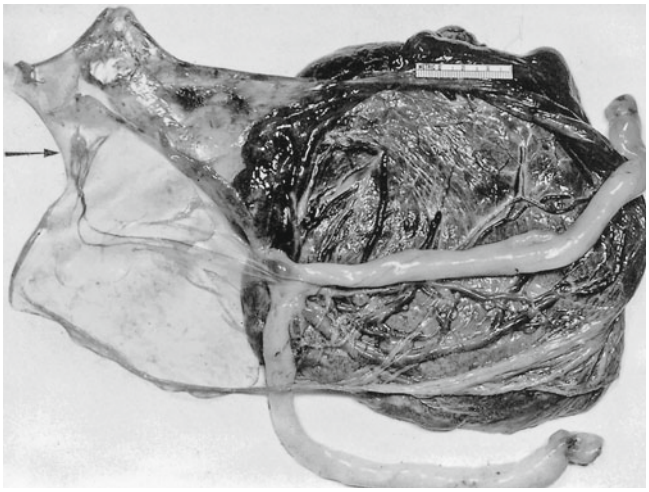


Fig. 25.26 Immature DiMo twin placenta whose translucency of the dividing membranes is apparent. The cords seem to arise at the same spot but are nevertheless in separate amnionic compartments. Note the remains of a single yolk sac (*arrow*), whence omphalomesenteric vessels course toward the cords

insertions are of concern to the perinatologist because of the possibly greater frequency of vasa previa in twins. Kobak and Cohen (1939) described the stillbirth of a twin following vaginal bleeding that had resulted from disrupted vasa previa. Two similar cases of DiMo placentas and vasa previa were described by Whitehouse and Kohler (1960). Three of their six reported infants died from exsanguination. When this problem is anticipated, Kleihauer stains of the vaginal blood disclose the presence of fetal blood. We have seen several similar cases. In one, the fetal blood loss was recognized, and immediate neonatal transfusion with 100 mL of maternal blood saved the infant. A similar case has been described by Duenhoelter (1989). In another case we saw, vasa previa were present in the dividing membranes of DiDi twins. They ruptured, and fatal exsanguination occurred within 3 min of the second sac's rupture (Figs. 25.23, 25.24, and 25.25). Because there are often large anastomoses between DiMo twins, rapid exsanguination of the second twin may also occur when vasa previa are ruptured in the first twin. It can also occur through an untied umbilical cord after delivery of the first twin. This potential exsanguination of a second twin is allegedly the reason for routine clamping of the placental end of the umbilical cord, lest an undiagnosed twin bleed from the cut end of the firstborn. Velamentous vessels of twins may thrombose before birth, or they may atrophy. Rarely are they of vitelline origin and then of no importance (Fig. 25.26). Antoine et al. (1982) grossly underestimated the reported frequency of vasa previa in twin placentas, when they cited only eight cases. They described a case in which sinusoidal fetal heart rate patterns initiated appropriate fetal studies, e.g., amnioscopy and examination of the blood. Despite these efforts, both DiMo twins exsanguinated. Ramos-Arroyo et al. (1988) have also found that

abnormal cord insertion was higher in twin gestations. Velamentous or marginal cords were found in 27.4% of monochorionic placentas, compared with 13.8% in dichorionic organs. They considered this as evidence in favor of trophotropism (see Chap. 7). Conversely, Gavriil et al. (1993), who studied the placentas of in vitro fertilization, interpreted the more frequently eccentric insertion in twins as resulting from "oblique orientation of the blastocyst at the nidation" but provide no further explanation why this should happen. The excess frequency of velamentous cords in DiMo twin placentas has significant correlation with the transfusion syndrome. Fries et al. (1993) found that one-third of DiMo twin placentas had such abnormal cord insertions and that 64% were involved with transfusion syndrome cases and delivered significantly earlier. They thus sought an etiological role for this abnormal insertion. It may also be considered that velamentous insertion is so common in this syndrome because normal placental development failed to take place. Bruner et al. (1995) found a similarly high frequency of velamentous cord insertions of the donor twins, and Mari et al. (1995) also felt that it may have an etiologic role in causing the imbalance that leads to the transfusion syndrome. We believe this to be possible because of the constant slight drainage of blood that occurs from the placenta with the velamentous cord into the other twin. Therefore, this placenta with reduced pressure (? or fewer cells) may not have grown as avidly and centrifugally as it should have. The primacy of the vascular component in villous capillary development was addressed by Giles et al. (1993). These authors studied sonographically abnormal umbilical artery waveforms (systolic/diastolic – S/D ratios) in twins and correlated these with villous vasculature. They found that "microvascular disease" of villi (reduction) correlates with growth restriction and abnormal S/Ds. Velamentous cord insertion was found as frequently as in 45% of monochorionic twin placentas by Machin (1997). He opined that it was an added risk factor of the twinning phenomenon and found growth discrepancies more commonly in central/velamentous cord insertions of monochorionic twins. Also, A-V anastomoses were more common in this situation.

There is a wide spectrum of vascular relations in twin placentas. How do they come about, and what is so different in other species? In marmosets, the assuredly DZ twins always have placental anastomoses; in artiodactyla (especially *Bos* but also *Sus*, *Ovis*, *Bubalus*, and others), DZ twins often have fused placentas, and blood traverses from one fetus to the other. In marmosets it leads invariably to blood chimerism, but other than for an occasional fetus papyraceus, the anastomoses cause no known complications. With artiodactyla, however, in addition to the blood chimerism, the female twin becomes a freemartin when she is connected to a male's placental circulation. This is not the case in humans, where dichorionic twins rarely have anastomoses, but where they have clearly occurred because of blood chimerism being detected. Heterosexual blood chimerism is rare and it is not associated with sterility, i.e., freemartinism in women (see Quintero et al. 2003a).

The reason for the differences must be found in the early embryological development of the embryo and placenta. In marmosets, fusion of chorions occurs very early (Benirschke and Layton 1969), but in human DZ twins no such fusion of chorionic circulations occurs. Here, the placentas may become intimately fused, but they do not develop interplacental vascular anastomoses. Indeed, despite numerous suggestions to the contrary, villi do not fuse in the human placenta, however closely they may become approximated. When sections of India-ink–injected, intimately fused dichorionic twin placentas are prepared, one observes that the villi may intermingle, but they do not connect with one another. No blood vessels traverse from the villi of one fraternal twin to those of the co-twin.

To understand the vascular commonality of monochorionic twin placentas, it is easiest with a review of their early embryology (Fig. 25.10). We suggest with this diagram that, in human placental development, the single chorionic sac has long since formed when vessels develop from the yolk sac or in situ, on about the 13th day. Enders (2002) provided some pictorial support for this by his observation of the apparent "splitting" of a 15 day rhesus monkey embryo. One must envisage that these primitive vascular precursors sprout all over the inner surface of the primitive chorionic membrane and, when the fetal heart gradually begins to pump, these fine vascular precursors begin to fill with blood. The vessels undoubtedly link with one another at this early time. The type of anastomosis that ultimately develops is probably a matter of chance. Whether the vessels become arteries or veins is determined by the direction of blood flow and its pressure. Some of the anastomoses are kept open, and others atrophy, depending on the velocity of flow. It may also be presumed that MZ twins often derive from embryonic splits with unequal cell numbers; it is therefore possible that one heart beats sooner or stronger, and that this influences the direction of flow in the anastomoses.

25.8 Monoamnionic Monochorionic Twin Placenta

The MoMo twin placenta is the least common type. It occurs in approximately one or two of 100 sets of twins in the US population but has had a nearly 40% perinatal mortality. Barss (1988) found that fetal demise occurred mostly before 24 weeks, when enough room for fetal motions and entanglement was still available in utero; Carr et al. (1990) found that after 30 weeks, no further deaths occurred. Similarly, Tessen and Zlatnik (1991) who reviewed 21 sets of MoMo twins found that fetal death did not occur after 32 weeks. Double survival used to be so uncommon that many papers were published with a title such as "MoMo twins with double survival." The classical paper on MoMo

twins is that by Quigley (1935) who believed the condition to occur only once in 60,000 pregnancies. Quigley found only one case report in the preceding 12 years. Altogether, perhaps 110 cases had been reported at the time of his review. More recent papers give an incidence of 1:10,000 to 16,000 pregnancies. Quigley found double survival in only 15.6% and an overall fetal mortality of 68%.

Most commonly, fetal death is due to entangling of umbilical cords because of fetal movements. This knotting of cords is unpredictable and is often found in very young pregnancies, with abortion ensuing. It can now be visualized sonographically before birth, and management of such cases is changing. Thus, Belfort et al. (1993) identified not only cord entanglement but also venous obstruction by color Doppler flow study. This diagnosis led to successful interruption of an otherwise endangered pregnancy. Similarly, Deutsch et al. (2007) did an immediate Cesarean section at 32 weeks when decelerations occurred and knotting was diagnosed sonographically; the neonates did well. More surprising is the case described by Krause and Goh (1998). Their twins had clearly entangled cords with compromise of the circulation, but a monochorionic placenta with diamnionic membranes was found. There must have been a window in the dividing membranes of this DiMo twin placenta for the entanglement to have occurred. Shahabi et al. (1997) were unable to save one twin despite making the diagnosis at 20 weeks; such cases are the reason why in our hospital such twins are hospitalized early in order to be able to intervene quickly when flow compromise is diagnosed. Tabsh (1990b) suggested that the diagnosis of monoamnionic twin placentation is easily made at amniocentesis by injection of indigo carmine, and the sonographic demonstrations by Belfort and his colleagues (1993) indicated that this new modality is superior to previous studies. They found cord entanglement and venous obstruction with Doppler flow studies that led to better management of their three pregnancies. Abuhamad and his colleagues (1995) reported similar findings in two MoMo twin pregnancies. Rodis et al. (1997) studied 13 MoMo twin pregnancies with 26 liveborns (2 died neonatally for other reasons) and deduced that their early diagnosis and appropriate management improved perinatal survival. Cord entanglement was noted in eight of their twins, and two sets had the transfusion syndrome. These authors found 96 publications on the topic, with 202 sets of MoMo twins. Other complications occur in MoMo pregnancies, such as prenatal coagulation, exsanguination through placental anastomoses, or bleeding from one twin into the other through anastomoses, and congenital malformations. Westover et al. (1994) found rare nuchal cords by Doppler imaging in MoMo twins that allowed appropriate management at delivery. Quintero et al. (1997) successfully ligated one of the umbilical cords in MoMo twin pregnancies when one twin was diagnosed as being nonviable.

Other obstetricians have also hoped, as did Belfort et al. (1993), that through early prenatal diagnosis (Dunnihoo and Harris 1966; Sutter et al. 1986), the chances of MoMo twin survival can be improved, as was recently shown also by Quinn et al. (2011). Rodis et al. (1987) managed three sets of twins successfully despite their severely knotted cords; they also made suggestions for management. These authors identified one of these twins as having the typical transfusion syndrome, as did Cordero et al. (2006). Driscoll (1970, personal communication) has also seen the transfusion syndrome in MoMo twins. To find the transfusion syndrome in MoMo twins is otherwise uncommon (Wharton et al. 1968; Hack et al. 2008).

Table 25.3 presents a summary of some of the relevant literature on MoMo twin survival. Of 229 sets of MoMo twins, only 304 infants (66%) survived. The causes of death were predominantly cord entanglement [with stillbirth (Figs. 25.27 and 25.35) or neonatal death], prematurity, and congenital anomalies. The aim of prenatal surveillance is to prevent that the knots or entanglements of the cords become fatal. It is not known when knots first form, but because it requires considerable fetal mobility to produce knots, they are frequently found already early in pregnancy, when more fluid exists (e.g., Fig. 25.27). On the other hand, it must be noted that term neonatal MoMo twins can have extensive knotting without compromise of the umbilical circulation. One presumes that space limitations in the uterine cavity prevented the formation of new knots with advancing gestation, which may also be the reason why such knotting is uncommon in triplets. Only knots that are already present from an earlier gestation may have the potential to compromise the fetus.

C.Y. Lee et al. (1988, Management of monoamniotic twins diagnosed by ultrasound, personal communication, Flint) endeavored to ascertain the best mode of pregnancy management when MoMo placentation is diagnosed sonographically. They surveyed perinatologists and ascertained 59 pregnancies with an overall perinatal mortality of 34.8%. A much higher mortality was found when the diagnosis was made before 25 weeks' gestation than later. Although entangling of cords was an important cause of late deaths, there was an astonishing frequency of transfusion syndrome fatalities during earlier gestation. Frequent nonstress tests were recommended as the principal strategy for supervising these gestations.

The proximity of cord insertion is apparently not the principal determinant of knotting. We have seen extensive knotting in cords that were inserted at opposite margins of the placenta and no knots in some placentas whose cords arose next to one another (Fig. 25.21). When a cord is obstructed for long periods, it may become very thin (Fig. 25.28), a condition described in several papers (Table 25.3). But the long-standing obstruction that can occur when MoMo twins' cords entangle is often evidenced by thromboses in placental surface veins (Fig. 25.29). Even when these twins survive, defects may have been caused by such hypoxic states. One complication of MoMo twinning is that the accoucheur may inadvertently cut the wrong umbilical cord during delivery. Donald (1964) described such a case, and a similar set of

Table 25.3 Reports of monoamnionic twin pregnancies (incomplete)

Source	Year	Sets of MoMo twins	No. of survivors	Remarks
Quigley	1935	1	1	Review of 109 cases
Litt and Strauss	1935	1	0	Knots, one anencephalic
Parks and Epstein	1940	1	2	Knot, no anastomoses
Coulton et al.	1947	2	4	No entangling
Wilson	1955	5	4	Anencephaly, CHD, knots, tangles, anastomoses, fold
Whitehouse	1955	1	1	1 Papyraceus, knots, anastomoses
Craig	1957	1	2	Entangling, 166 cases cited
Librach and Terrin	1957	3	6	One knotted
Walters and Whitehead	1957	2	2	Both knotted
Sinykin	1958	1	3	First triplets, entangling
Pickhardt and Breen	1958	1	2	No knots, anastomoses
Semmens	1958	1	0	(1) Anemia, RDS (2) CHD. No knots
Green et al.	1960	1	2	Knot, entangling
Zuckerman and Brzezinski	1960	2	1	2 sets macerated, knots; other knots; 1 lived, 1 macerated
Tafeen et al.	1960	3	4	2 knotted
Raphael	1961	5	5	2 anomalies, 4 knot/entangling
Wensinger and Daly	1962	3	5	3 knots/entangling
Timmons and de Alvarez	1963	4	4	3 knots; 1 CNS damage; onefold
Goplerud	1964	1	2	No knots/entangling
Benirschke and Driscoll	1967	3	3	Knots
Dunnihoo and Harris	1966	1	2	No knots
Simonsen	1966	2	2	1 knots
Wharton et al.	1968	18	24	1 CHD, 1 palsy, anastomoses
Larson et al.	1969a	1	0	Forked cord
Larson et al.	1969b	1	1	Both anomalies; no knots
Moestrup	1970	2	2	1 SUA (third case); no knots
Israelstam	1973	1	0	Knotting
Chapman	1974	3	2	Knotting
Mauer et al.	1974	1	1	Both discordant anomalies
Averback and Wigglesworth	1977	1	1	No knots
Litschgi and Stucki	1980	1	1	Macerated, entangling
McLeod and McCoy	1981	1	2	Cord of No. 2 around neck of No. 1, cut during delivery, both velamentous, IUD
Colburn and Pasquale	1982	1	2	Entangling
Colgan and Luk	1982	1	1	Torsion and thrombi of cord
Berry et al.	1984	1	1	SUA, severe anomalies; knots
Lumme and Saarikoski	1986	23	13	4 anomalies; knots, entangling
Sutter et al.	1986	1	2	Knots
Rodis et al.	1987	3	6	3 knotted
Barss	1988	5	9	Knots in 1; transfusion syndrome; anomaly; twinning in 1/87 pregnancies, after 20 weeks
Lee et al.	1988	59	77	Review of prenatally diagnosed MoMo twins 1991–2128
Tessen and Zlatnik				Controlled study; no deaths after 32 weeks
Tabsh	1990a	2	4	Method for diagnosis in utero
Deutsch et al.	2007	1	2	Sonography; knotting
Cordero et al.	2006	36	68	TTTS, congenital heart, VATER, body stalk
Total		229 (458 twins) 100%	304 survivors (66%)	154 dead (34%)

RDS respiratory distress syndrome, *CHD* congenital heart disease, *IUD* intrauterine death, *CNS* central nervous syndrome

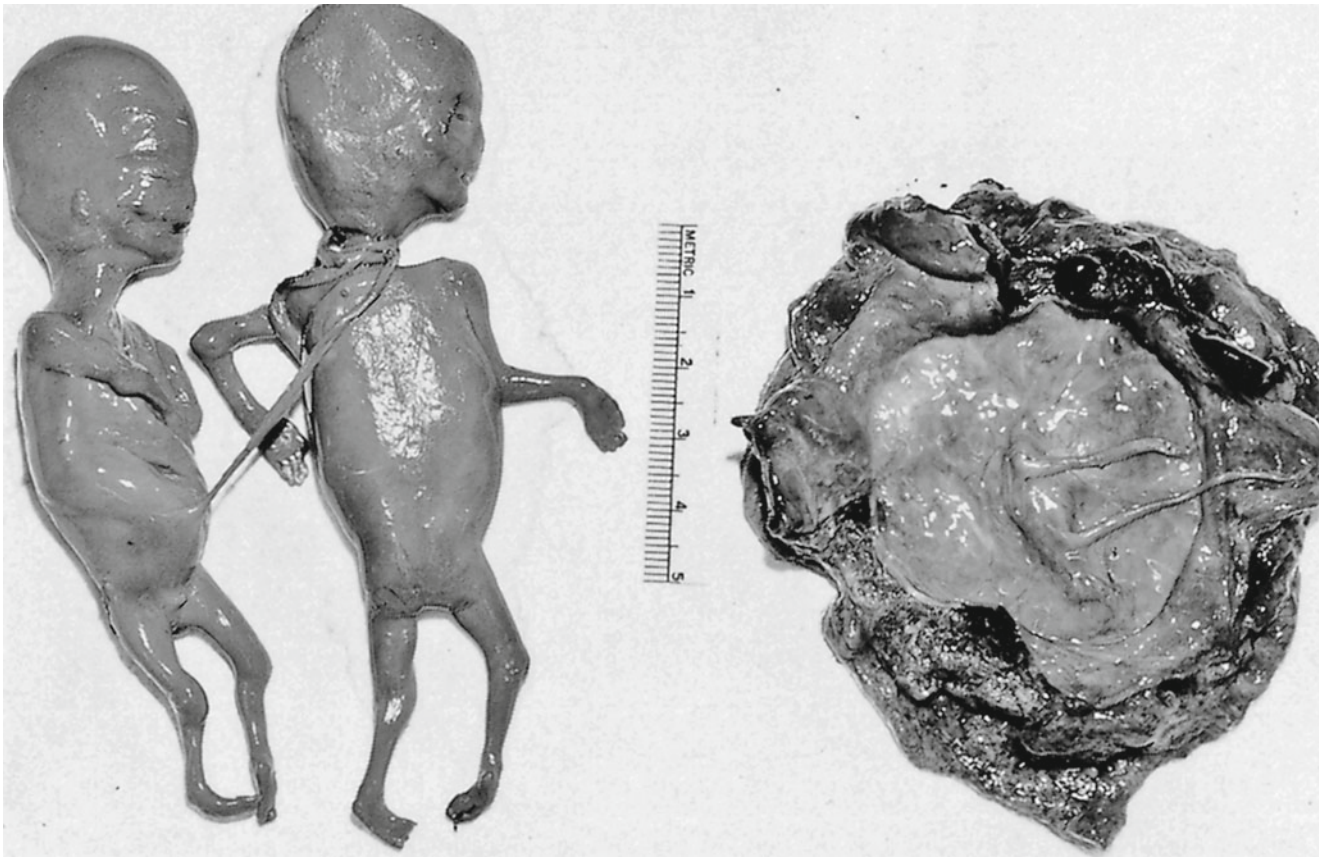


Fig. 25.27 Macerated monoamnionic twins (12 weeks) with extensive knotting and entangling of cords. Fetal movements must have been extensive at an early embryonic age

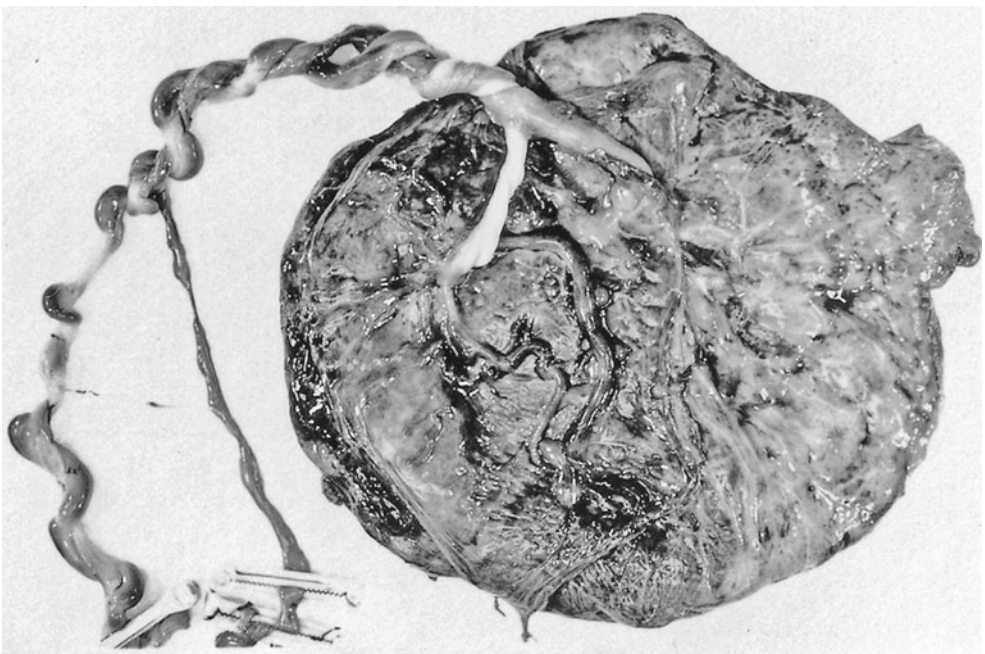


Fig. 25.28 MoMo twins at 38 weeks' gestation with fetal death of one at 23 weeks (20 cm CR, 400 g macerated). Survivor is alive and well. Note the entangling and knotting of cords, the thin cord of the dead twin, and the extensive infarction of the right placental half. Anastomoses cannot be demonstrated this late after fetal death

MoMo twins was observed by McLeod and McCoy (1981). When the first twin could not be delivered because the cord was extensively entwined about the infant's neck, the cord was severed. Only after the fetus was fully extracted was it realized that a mistake had been made. After rapid delivery of the second twin, both twins survived.

The placental surface of MoMo twin placentas usually has a continuous sheet of amnion without folds between the

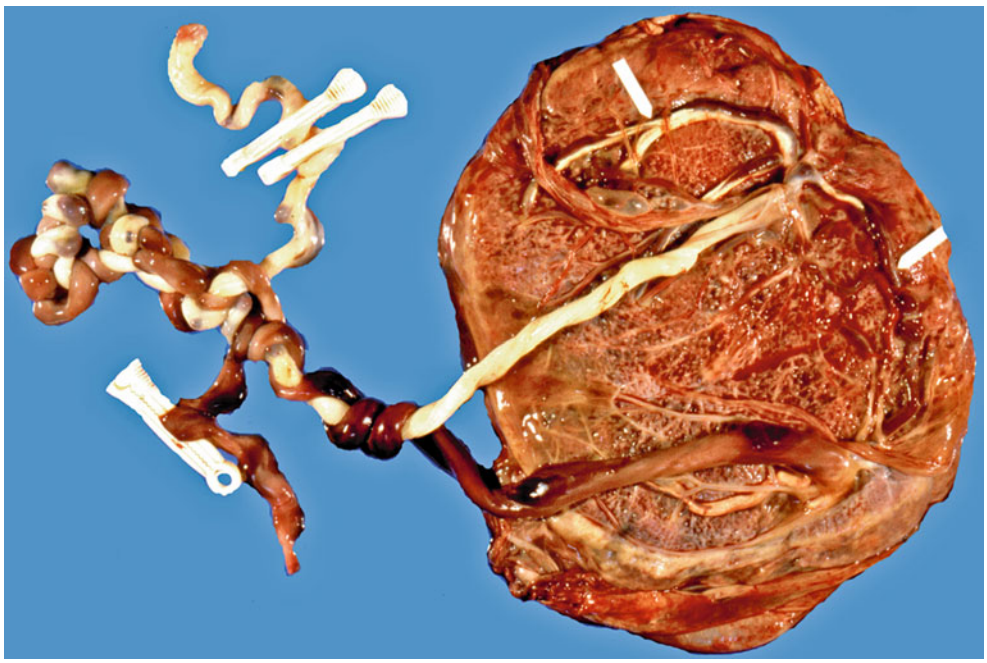


Fig. 25.29 Monoamnionic twin pregnancy with extensive entangling of umbilical cords. One (*dark*) twin was stillborn, the other died with extensive areas of cerebral necrosis. Note the calcified veins in the live-born twin (*top*) and more recent thrombi (*right*, at *white arrow*)

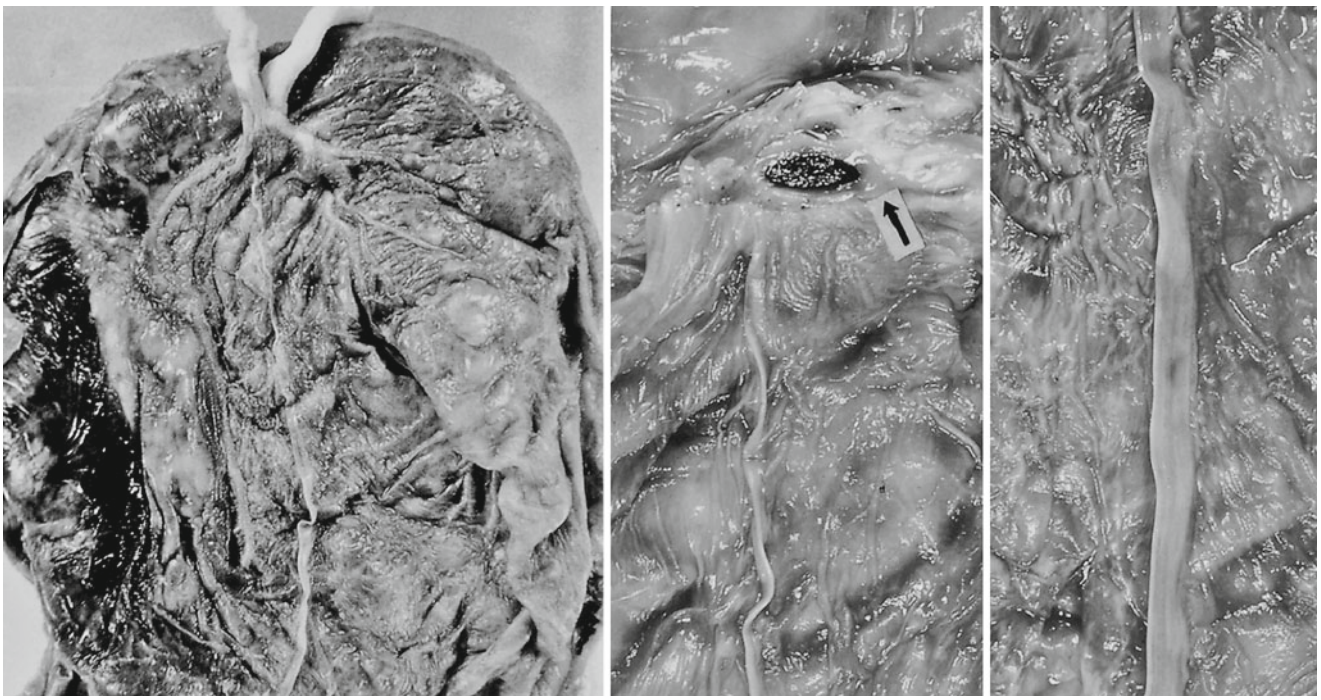


Fig. 25.30 MoMo twin placenta, one twin had Klippel–Feil syndrome. The two cords arise from same spot, where vessels merge (*arrow*). Thin plica, composed of two amnions, extends from cord insertion to the margin. It is presumably the remains of an early attempt at formation of two amnionic cavities, interrupted by the twinning event

cord insertions. There have, however, been four observations of the existence of folds. Timmons and de Alvarez (1963), in their report of four cases of MoMo twins, found "…a short fold of what was thought to be membrane … present in the midportion of the fetal surface but [it] did not extend between the origins of the umbilical cords." Another plica ("fringe") was described in one of the five MoMo twins reported by Wilson (1955). It inserted between the two cords of a set of MoMo macerated twins born with a surviving DZ triplet. A similar case has been described by Wolf (1920), and another is shown in Figs. 25.30 and 25.31. One of these twins died during the neonatal period with the Klippel-Feil anomaly. The cords arose from a single point and had six vessels that merged into three (*arrow* in Fig. 25.30) at their base. A thin, falciform plica extended from the cords to the margin of the placenta. The tip of this

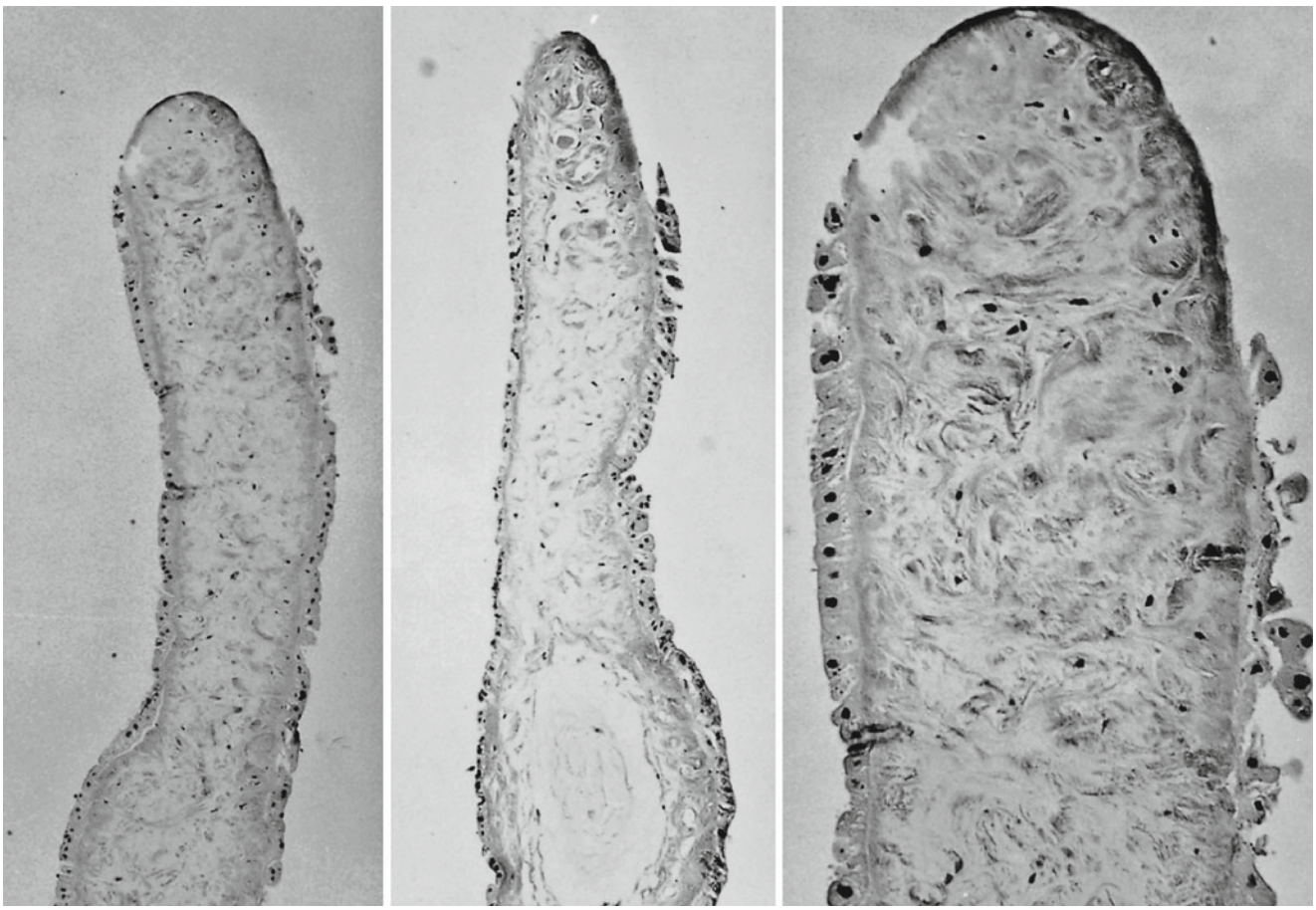


Fig. 25.31 Sections through the tip of the plica shown in Fig. 25.30. Note the degeneration of amnionic epithelium and the scarring of underlying connective tissue. H&E, ×260

plica, which consisted of two fused amnions, showed degenerative changes and scarring (Fig. 25.31). It is possible that disruption of the dividing membranes of two former amnionic cavities had occurred. It is also possible that the twinning took place just about at the time (7 days) when the amnion is first set aside, thus preventing the formation of two complete amnionic sacs. It is difficult to conceive that an apparently single cavity could form from the spontaneous breakdown of the dividing membranes in a DiDi placenta, although this was assumed by Pickering (1946) in his description of boy/girl twins with a MoMo placenta. Nylander and Osunkoya (1970) also described "…heterosexual twins with monochorionic placenta." They depicted a ridge with DiDi configuration present in one part and a DiMo relation in another portion of the placenta. Another unexplained case of monochorial placenta with fraternal twins was recorded by van Verschuer (1925). He relied on the placental diagnosis of an assistant, and the dizygosity was based only on some physical differences (e.g., hair color). Gilbert and his colleagues (1991) not only identified several new cases of twins with rupture of dividing membrane occurring in utero ("pseudomonoamniotic" according to Megory et al. 1991), they also highlighted the morbidity

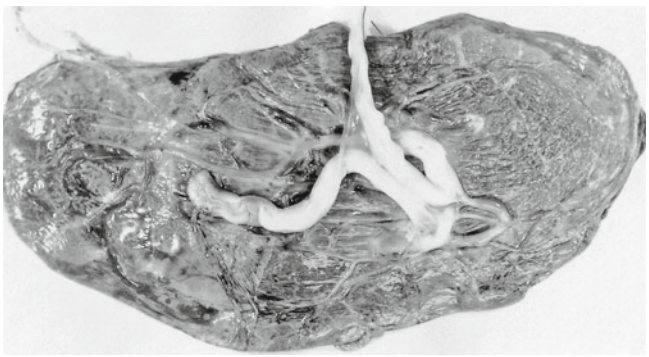


Fig. 25.32 MoMo twin placenta at term with extensive interfetal vascular anastomoses. The nearly commonly arising cords are bound within an amnionic fold. This stage presumably arises shortly after the placenta shown in Figs. 25.31 and 25.32

that may ensue, such as entangling of extremities in bands and entangling of cords. Diamnionic placentas can also be transformed into MoMo organs by amniocentesis and funipuncture (Magyar et al. 1991; Feldman et al. 1998) and spontaneously, perhaps by fetal activity. In tracing the history of MoMo twinning one step further, one may postulate that the placenta of Fig. 25.32 was determined shortly after that which yielded the plica. Here the two cords, arising

nearly one from the other, are bound together by a delicate amnionic membrane.

We have observed a placenta from a set of MoMo twins with unusual findings that are relevant to the understanding of prenatal injury. One of the twins had cerebral atrophy that was attributed to the entwining of the umbilical cords. There was focal amnion necrosis, but this was confined to the regions directly above the fetal surface blood vessels; elsewhere, the amnion was intact. This finding and the observation that the nodules of amnion nodosum are generally absent on cord and free membranes and that they occur primarily in amnion between the surface vessels leads us to speculate that the amnion maintenance depends on the oxygen supplied from different sources. Oxygen tension in amnionic fluid is low (Jauniaux et al. 2003), and it is possible that it is augmented by oxygen from fetal surface vessels, the decidua capsularis, and also from the vessels in the umbilical cord. Further evidence for this surmise is that partial necrosis of thrombosed vessel walls can be seen in some cases with occluded cord vessels (see Chap. 12). Thus, in the present case with cord entanglement, we hypothesize that the entanglement led to reduced flow of one twin's vasculature (hence the cerebral atrophy of that twin) and the necrosis of the surface vasculature's amnion.

Direct anastomoses of fetal blood vessels appear to occur even more commonly in MoMo placentas than in DiMo twin placentas when injection studies are made (Bajoria 1998), this perhaps being the reason for the rarity of the twin transfusion syndrome in MoMo twins (see also Katz et al. 2009). Umur et al. (2003a) came to the same conclusions in their review of 24 MoMo vs. 200 DiMo twin placentations. The proximity of the cord insertion may be one determinant, as the cords are more often centrally located. Of great importance also is that, when large intertwin communications exist, the cell and blood traffic between the two fetuses may have greater influence on the fetal well-being. The example depicted in Fig. 25.33 features the placenta of a macerated MoMo twin and a co-twin who expired soon after birth (Benirschke 1961). This case has aroused much legal interest subsequent to its occurrence. The initially surviving infant died within 62 h. Bilateral renal cortical necrosis, cerebral liquefaction, and other degenerative changes, including thrombi and focal mineralization (Fig. 25.34) were present. These findings are descriptive of the sequelae from disseminated intravascular coagulation (DIC). We then postulated that thromboplastin from the macerating twin had entered the survivor's blood stream via interplacental anastomoses prior to birth and had thus initiated DIC. The development of DIC, as resulting from thromboplastins liberated by the dead twin, now seems to us to be far-fetched, because the fetus is dead and cannot contribute much to the survivor's circulation. But there have been several other reports of neonatal deaths with findings of DIC (Table 25.4). During the past few years, we have been consulted with many similar cases, where the medicolegal question arose as to possible preventive Cesarean section after the death of one twin. Many of the descriptions in the literature are also similar to the case here shown, but conclusive proof of prenatal DIC with definitive coagulation studies has been difficult to obtain. In a case of macerated MoMo twin with a term live-born co-twin, Bulla et al. (1987) found neonatal platelet counts of 67,000/mm^3 that later rose to 300,000/mm^3. The infant died on day 10 with bilateral renal, splenic, and central nervous system (CNS) necroses. Patten et al. (1989b), who examined five co-twins with one fetus having died prenatally and who used the term twin embolization syndrome (TES), identified "active consumptive thrombocytopenia" in one of their cases with renal and CNS defects. Microcephaly and various other CNS abnormalities, in addition to intestinal, peritoneal, and renal destructive lesions, were the focus of their observations. They urged prenatal sonographic studies of such pregnancies. As to the evidence of consumptive coagulopathy, diligent study of some other cases ruled out their existence

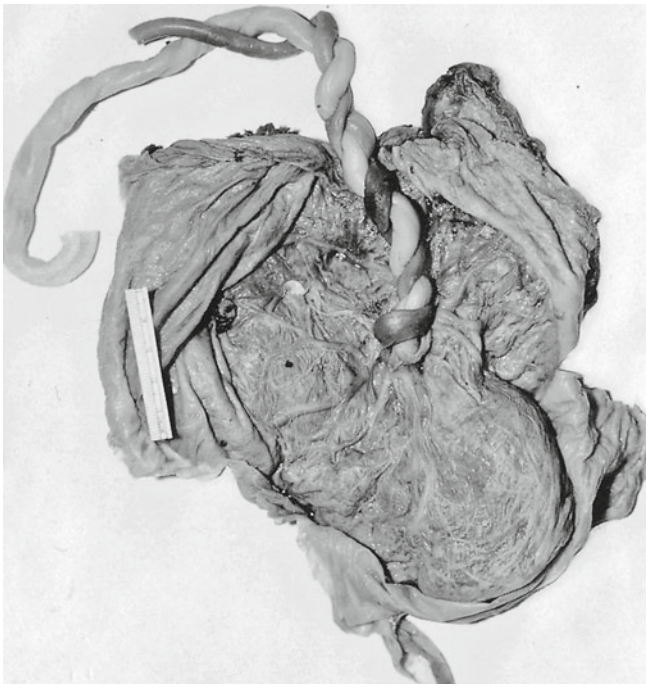
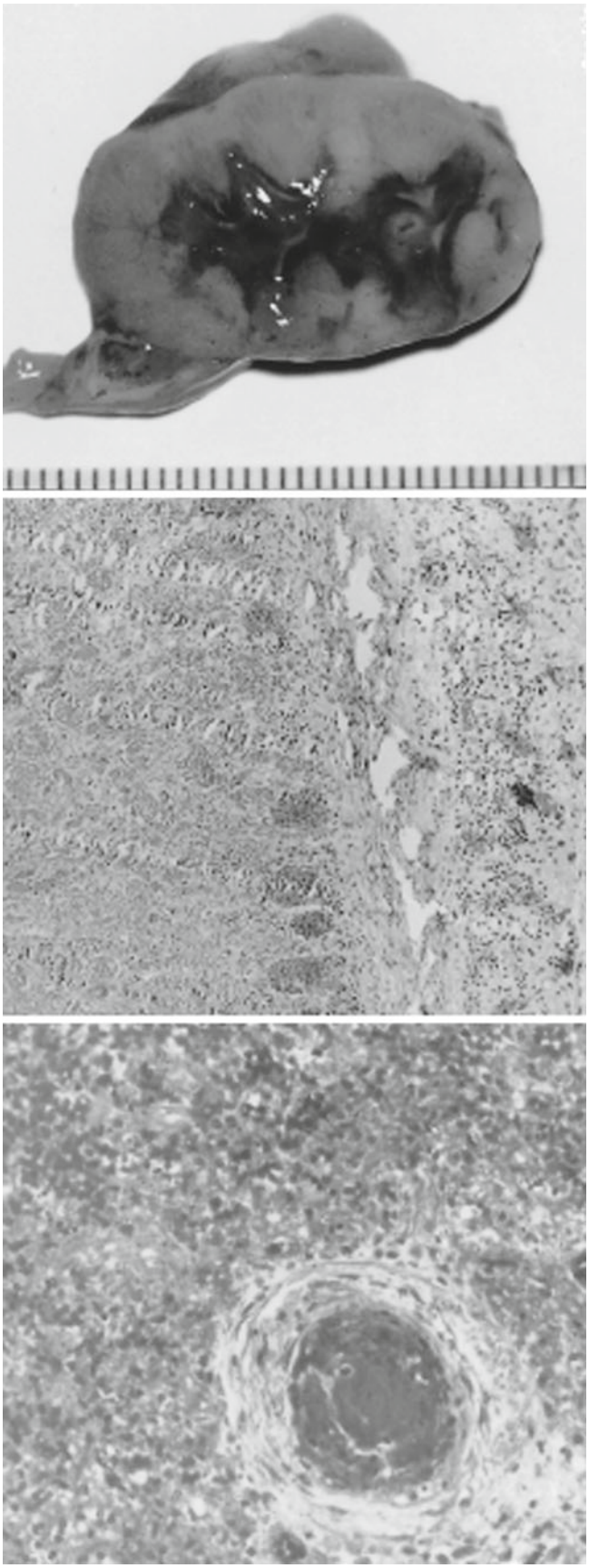


Fig. 25.33 MoMo twin placenta with one macerated fetus (*dark cord*). The survivor, who had disseminated intravascular coagulation, died at age 62 h (see Fig. 25.34) (From Benirschke (1961), with permission)



when fetal demise of one twin had occurred (Hanna and Hill 1984). Okamura et al. (1994) did funipuncture in seven surviving twins following the demise of the co-twin. Coagulation parameters were not abnormal, although three infants suffered cerebral abnormalities. This was seen as strong evidence for the primacy of acute anemia due to presumed acute hypotension (shunting through anastomoses) as the cause of the cerebral destruction rather than DIC or embolization. This is further discussed subsequently and was eloquently shown to be correct by prenatal blood sampling (Nicolini et al. 1998).

This is a complex issue of great importance. Many investigators have tried to answer the many questions that arise from these observations. Litschgi and Stucki (1980) reviewed their twin material and found that in 13 cases of 191 twin pregnancies (6.8%; 0.07% of all births), a macerated fetus was delivered with a live twin. They found one MoMo, seven DiMo, and five DiDi cases and suggested that immediate delivery is not advisable when one twin has died. In view of the distribution of deaths in relation to ultimate delivery, they recommended that all such pregnancies be terminated by 39 weeks. This aspect is discussed further in the section on fetus papyraceus, as this pathological feature is not limited to MoMo placentation but affects all monochorial twins. Since the probability of thromboplastin infusion from a dead twin is actually highly unlikely (because its circulation has stopped), alternative explanations have been sought. They are completely summarized in a large paper by Liu et al. (1992) and will be further discussed later in this chapter. Specifically, they suggested that acute hypotensive events occur in the surviving twin immediately after one twin dies because of the common placental vasculature. Jou et al. (1993) even observed sonographically the reversal of blood flow in the umbilical cord after fetal death of one twin. Less decisive flow disturbances after demise of one twin were recorded by Malinowski et al. (1996). That such an event may occur is also evident from the detailed postmortem description of the original Siamese twins Chang and Eng Bunker (Kormann 1869). After the death of Chang, Eng complained of chest tightness and expired within 2 h. Large anastomoses were present in their xiphoid connections at autopsy through which exsanguination of Eng

Fig. 25.34 Organs of a premature neonate whose placenta is shown in Fig. 25.33. There were bilateral renal cortical necrosis and widespread thrombosis when this infant died at 62 h (*upper right*). The kidney had diffuse, yellow, cortical infarction (*upper left*). Microscopic appearance of renal cortical necrosis (*upper right*). Splenic thrombus (*bottom*)

Table 25.4 Summary of twins with prenatal damage perhaps due to vascular transport of coagulation products or acute blood loss

Source	Year	Placenta	Remarks
Benirschke	1961	MoMo	Macerated twin; survivor with renal cortical necrosis, porencephaly; presumed DIC (Figs. 25.33 and 25.34)
Figure 25.35	1959	MoMo	Macerated twin, thrombi in umbilical vessels; survivor died with extensive cerebral palsy
Figures 25.39 and 25.40	1986	MoMo	32 weeks; stillborn 1,800 g, survivor 2,400 g died with hydrops (? due to cord tangles); AQA, AV anastomoses, arthrogryposis, CNS atrophy
Figure 25.41	1986	DiMo	Fetus papyraceus, velamentous cord; survivor has porencephaly; **mother** had DIC after delivery; transfusion syndrome
Timmons and de Alvarez	1963	MoMo	Case 4 had cerebral palsy from "embarrassed circulation"
Rosenquist	1963	DiMo	Adrenal, pulmonary, renal calcifications in donor of transfusion syndrome
Moree et al.	1969	DiMo	(1) Singleton with velamentous cord and DIC (2) Monochorionic, macerated; survivor developed DIC and died; blood studies were normal (3) DiMo, one macerated stillborn, other had anemia and bilateral cortical necrosis but survived
Dimmick et al.	1971	DiMo	Velamentous cord, CNS, and renal necroses, unable to identify anastomoses; secondary to cord insertion
Thomas	1974	Tri?Di	Male had IVH and coagulation disorder; one female macerated, the other had mild coagulation disorder
Durkin et al.	1976		Review of eight cases of monochorionic at highest risk
Mannino et al.	1977	DiMo	Fetus papyraceus with aplasia cutis in survivor; review
Melnik	1977	?	Macerated twin; CNS damage in survivor who died with CNS necrosis; review of collaborative study and risk assessment
Yoshioka et al.	1979	?	MZ three sets of twins had porencephaly and macerated stillborn; thrombosis of cerebral artery; authors considered emboli as cause
Jung et al.	1984	?	Review of hydranencephaly and porencephaly with macerated stillborn; 11% had twins, most were macerated
Barth and van der Harten	1985	DiMo	Term with macerated twin (death at 13–16 weeks); gastroschisis, CNS damage
Nakayama et al.	1986	DiMo	Macerated fetus with infarcts of CNS, kidney, spleen, liver; reviewed 14 twins, only the monochorionics had a poor prognosis
Hughes and Miskin	1986	DiMo?	Fetal death at 20 weeks, following which prenatally diagnosed CNS cysts developed, microcephaly, renal dysplasia
Yoshida and Soma	1986	DiMo	Review: macerated with cerebral palsy in survivor; skin defects in male; macerated female co-twin
Szymonowicz et al.	1986	DiMo?	Six cases with survivors having CNS deficits; other infarcts; review of total literature (53 cases)
Bulla et al.	1987	MoMo	Renal and CNS necroses; other was a macerated fetus AA and VV anastomoses
Leidig et al.	1988	?	Two of four cases with IVH were twins
Jones	1988	?	Hydranencephaly; 30-cm fetus papyraceus
Patten et al.	1989b	DiMo	Five cases with various brain, kidney, and intestinal defects
Fisher and Siongco	1989	DiMo	Massive porenecephaly; renal and splenic infarcts
Cherouny et al.	1989	MoMo	Twenty cases; one MoMo twin developed brain cysts, prenatal evaluation was reassuring
Anderson et al.	1990	DiMo	Four cases, second trimester fetal deaths, CNS lesions, GI lesion in 2
Larroche et al.	1990	DiMo	Fifteen monochorionics, vascular "instability"
Fusi et al.	1991	DiMo	CNS and renal necroses, no coagulation defect, transfusion
Margono et al.	1992	DiMo	Foot necrosis before birth
Liu et al.	1992	DiDi/DiMo/MoMo	Thirty-eight twins, 3 triplets; damage in 19 offspring (72% monochorionics)
Grafe	1993	DiMo	CNS necroses in both twins

presumably occurred, and autopsy indicated exsanguination of Eng into Chang. An important case report has been published by Sherer et al. (1993) that showed the rapid development of the cerebral consequences of such fetal demise. They followed a twin transfusion set of twins with fetal death of one at 23 weeks, followed by spontaneous resolu-

tion of hydrops. They were able to demonstrate sonographically that echogenic changes had become prominent in the brain of the survivor within 48 h already. The authors considered these to be hemorrhages that eventuated into a severely microcephalic anomaly. Death of one MZ twin was observed at 27 weeks by Lander et al. (1993). Doppler sonographic observations within 24 h after the death showed, "…remarkable variability in flow velocity waveforms in the umbilical artery of the surviving fetus. Changes from reversed to normal end-diastolic flow velocities were recorded within 6 min." This mechanism of CNS damage from exsanguination into the other after one twin's death will be discussed further below.

These are simplistic hemodynamic explanations for a very complex dynamic state that exists in utero of ill-defined vascular communications. Since hemodynamic results of these anastomoses have been largely inaccessible to us until the event of Doppler flow studies, relatively little hard information is available at this time, and it is common to oversimplify from our incomplete knowledge. That the situation is much more complex in utero is to be inferred from the case report of Grafe (1993). She described DiMo live-born premature twins, both with antenatal white matter necrosis; they died subsequently. Aside from a velamentous insertion of twin A's umbilical cord, there were artery-to-artery and vein-to-vein anastomoses. We assume that irregular flow back and forth through these anastomoses was responsible for the cerebral destructions. Perhaps such variable blood exchange occurs often in monochorionic twins.

At this point, it is important to understand the possible fates of placental tissue when one twin dies. If there are large interfetal vascular communications, the placental half of the dead fetus may continue to be perfused by the survivor. If, on the other hand, the anastomoses are small, the placenta of the dead fetus gradually atrophies and eventually appears as though infarcted. It is much the same as what happened to placental tissue when experimental fetal removal was practiced in rhesus monkeys. There is gradual atrophy of placenta, with much deposition of intervillous fibrin.

The problem of **maternal** DIC with a dead fetus is often discussed under the heading "dead-fetus syndrome" (Strauss et al. 1978). Although it has been described in some cases where one twin had died in utero (Skelly et al. 1982; Romero et al. 1984), in other patients it did not develop (Wittmann et al. 1986; Cherouny et al. 1989). The reason for the differences is not clear. When Zorlu et al. (1997) examined what happened to maternal coagulation parameters in 25 women with one dead twin, they found that coagulation parameters were temporarily abnormal in two, but rectified by delivery. They felt that, for the mother's health, no undue concern needs to be had. This complex aspect is not treated further in this text.

To explain some cases of prenatal damage observed in twins after the death of the co-twin, it has also been postulated that thrombi in the fetal circulation embolize via the interfetal anastomoses, from the dead to the living twin. While it is true that thrombi from fetal vascular occlusions can embolize to the fetus (Wolf et al. 1985), the lesions usually seen in the survivors of pregnancies with a macerated co-twin, however, are not typical of those caused by emboli. Yoshioka et al. (1979) postulated that the CNS damage of the twins they examined, which had macerated co-twins, resulted from occlusion of large vessels. They believed that emboli from macerated co-twins were the most reasonable explanation for the damage. They cited a case by Clark and Linell (1954) in support of this hypothesis. The erythroblastotic stillborn described by Clark and Linell, whose mother had been treated with cortisone, had an occlusion of the internal carotid artery and cerebral vessels. The authors suggested that, because the thrombus did not look like loose clot, it probably originated from an embolus, and they opined that it represented embolized "placental tissue." This assumption cannot be the case, for there were no villous remains in the clot. Admittedly, it contained erythroblasts, but degenerating placental tissue never embolizes to the fetus. Clots could embolize from venous vessels, which have occasionally been shown to be thrombosed. Such an event is shown in the fetal vessels of Fig. 25.35.

Massive plethora in a macerating twin masqueraded as the recipient of the twin transfusion syndrome in several cases. The actual presence of the twin-twin transfusion syndrome should have been ruled out, however, because the twins were of the same size, had similar-sized hearts, and there were large placental anastomoses. We presumed that the plethoric twin had recently received large quantities of blood from the survivor via large vascular communications in the placenta. This acute transplacental fetus-to-fetus bleeding, with resulting plethora of one twin, was first mentioned by Lehndorff (1961) and was also described by Cameron (1968). Lehndorff correctly hypothesized that marked shifts may occur through large anastomoses during, or even before, delivery. Later, Bleisch (1965) had the same thoughts. This phenomenon is different from the typical "transfusion syndrome," which constitutes a specific entity and is discussed below, and it should not be labeled as such.

All these cases have assumed great importance in the legal realm because cerebral palsy is so common in twins (Durkin et al. 1976; Scheller and Nelson 1992; Gray et al. 2011). Eastman et al. (1962) estimated it to be five times

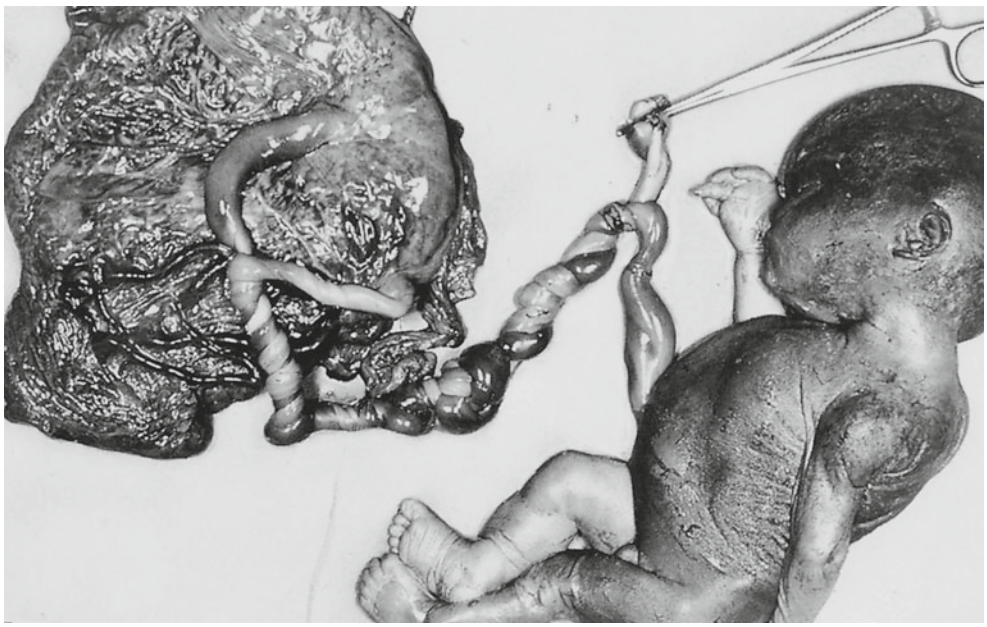


Fig. 25.35 Macerated stillborn MoMo twin with extensive knotting of cords. The surviving infant died 3 months later with extensive brain necroses

more common than in controls and assigned as the chief cause the prematurity of twins and an "unfavorable intrauterine environment." This higher incidence of cerebral palsy (and of "mental deficiency") affects primarily monozygotic twins (Berg and Kirman 1960; Russell 1961). Furthermore, a characteristic type of skin defect that is secondary to prenatal dermal necrosis (aplasia cutis) is also primarily associated with DiMo placentation and fetus papyraceus (Mannino et al. 1977). It is thus challenging to better understand what causes these prenatal insults. Moreover, as stated, there has been much litigation in cases of twins with cerebral palsy. In these legal suits, it is commonly assumed that the obstetrician must be at fault when brain damage occurs in one of twins because, had only a quick Cesarean section been done, this damage would not have occurred – or so it is stated (an important case is explored in great detail by Werth 1998). It must be pointed out in this context that Bejar et al. (1990) have shown that porencephaly may already be present at birth and that it correlates best with one of two circumstances: (1) fetal infection (chorioamnionitis, funisitis) or (2) MZ twins having placental vascular anastomoses. Taylor et al. (2009) surveyed the Australian population of cerebral palsy and found that 3% occurred in twins with one fetus lost. They concluded that this comprises a relatively small risk to the population of cerebral palsy. Ortibus et al. (2009), in their multicenter prospective study, concluded that cerebral palsy was ten-fold higher in "complicated monochorionic twins," such as having TTTS or being artificially conceived. Leviton and Paneth (1990) reviewed the possible causes of CNS white matter necrosis. They, as Larroche et al. (1990), also concluded that circulatory phenomena were important aspects in the causation of cerebral palsy. Fusi and colleagues (1991) found no coagulation disorder but observed "acute twin-twin transfusion" as the cause of brain damage. They were emphatic that intervention would have to take place before fetal death occurred if CNS sequelae were to be prevented. Norman (1980, 1982) made somewhat similar observations on prenatal brain necrosis in DiMo twins. A large retrospective review of brain damage in twins was undertaken in Sweden by Rydhstroem (1995). He found no difference in relation to birth order and like-sex vs. unlike-sex status, but there was an increase of cerebral damage in the heavier of twins. Interestingly, Maier et al. (1995) who assessed degrees of hypoxia in twins found that the smaller twin has higher concentrations of erythropoietin. The principal reason for CNS damage was seen to be the increased prematurity of multiple gestations, with cystic periventricular cystic white matter necrosis following (Allan et al. 1994). The outcome is not significantly different from that of singleton premature infants (Nielsen et al. 1997; Kilpatrick et al. 1996) when matched for gestational age.

For all these reasons, it is of future importance that we delineate more precisely the pathogenesis that leads to this prenatal CNS damage, so that it may be anticipated and prevented, if possible. Hurst and Abbitt (1989) observed that encephalomalacia and intraventricular CNS hemorrhage developed prenatally in a set of twins with the classical transfusion syndrome. In the case described by Hughes and Miskin (1986), bleeding complicated a known twin pregnancy at 20 weeks, and subsequently, one twin became macerated. In the survivor, brain cyst development could be followed sonographically after 30 weeks and was found in the newborn after Cesarean section at 37 weeks. Interestingly, the kidneys of this microcephalic and porencephalic infant had cystic changes, which we assume stemmed from former focal areas of necrosis. Nakayama et al. (1986) studied 14

live-born twins with macerated co-twins. Among the three with neonatal death, CNS, renal, splenic, and liver necroses were found. Several other relevant contributions have been forthcoming (Dudley and D'Alton 1986; Liu et al. 1992), but a consensus as to the best management of monochorionic and monoamnionic twin pregnancies has not yet emerged (Hagay et al. 1985). Melnick (1977) estimated that some 3% of near-term monozygotic twins have a dead co-twin. Furthermore, one-third of the survivors, or possibly 1% of MZ twin births, have severe brain defects as a consequence of putative DIC (Jones 1988).

These considerations are especially important in view of the evolving practice of intentional fetal elimination when discordant anomalies of twins are found, when too many multiples are conceived, during the therapy of the prenatally diagnosed transfusion syndrome, and for prenatally diagnosed genetic disorders (Åberg et al. 1978). In these situations, it must be recognized that there are possible consequences for the second twin when one is eliminated and the status of anastomoses had not ascertained (Wittmann et al. 1986). Yamagishi et al. (1998) reported on discordance of male MZ twins with deletion of a chromosomal band in #22 (22q11.2). They had the TTTS, and one twin (the donor) had tetralogy of Fallot, not the other. Prenatal cardiovascular adjustment to the TTTS was considered to be the reason for the major discordance. Discordance for some diseases may also be the sequel of the twin-to-twin transfusion syndrome. Thus, Lazda (1998) recorded the occurrence of endocardial fibroelastosis in the larger of two recipients of this unequal blood sharing of twins prenatally. Other unusual features may occur. We draw attention to the fetal demise due to hydrops from parvovirus 19 infection in a DiDi twin placenta in which the other fetus survived and did not have the infection (Foster and Allen 2004). Remarkably, the gravida developed DIC 4 weeks after fetal demise.

The possibility of DIC developing in the remaining living twin, after one had died, led Cox et al. (1987) to sample the fetal vasculature of 19 twins. This evolving technique of fetal blood sampling promises much insight into the prenatal vascular relations among twins. It is for these complex reasons that we have summarized relevant case information in twin pregnancies with fetal death in one twin (Table 25.4). Other large tables may be found in Liu et al. (1992) where all relevant literature is also discussed. As will be seen, there is a good possibility that the survivor in cases of prenatal twin death experiences significant acute blood loss through superficial, large interplacental anastomoses. One can envisage that when one twin dies, the other bleeds into this vascular bed, now devoid of counterpressure. Indeed, paradoxical plethora has been seen in discordant twins, in which the smaller (earlier dead) twin is plethoric. Modern studies with Doppler sonography have come closer to an understanding of the redistributional changes of blood in twin placentation

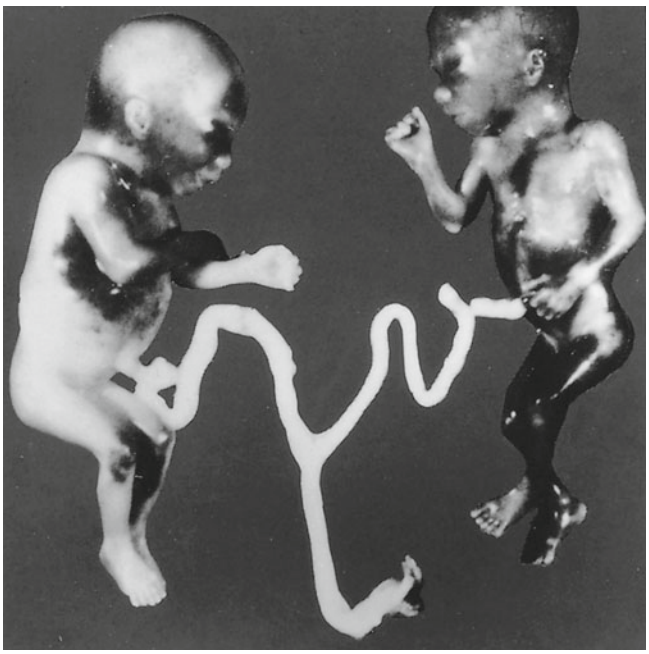


Fig. 25.36 Forked umbilical cord of MoMo twin abortuses at 17 weeks' gestation. The smaller twin (*right*) had a single umbilical artery but no other anomalies (Courtesy of Dr. Marilyn Jones, San Diego)

(Gaziano et al. 1998). The authors found a much more important and more frequent effect of the vascular anastomoses in DiMo placentas than originally anticipated and discuss eloquently the impact of these on cerebral arterial perfusion in the fetus.

In order to accumulate relevant prenatal information of such occurrences, Toubas et al. (1981) studied the fetal response to acute hemorrhage (15%) in the lamb. The arterial blood pressure, pH, and heart rate of the fetus fell significantly, and the cardiac output decreased. The blood flow in the fetus (kidneys, gastrointestinal tract, and lungs) and to the placenta was markedly reduced. Toubas et al. did not report any structural changes of these organs due to the hemorrhage. It will be necessary in future cases of prenatal death of one MZ twin to accumulate information on neonatal hematological parameters. Measurements of hematocrit, deformed red blood cells (schistocytes), split fibrin degradation products, platelet changes, and nucleated red blood cells can provide some of the information needed for better understanding this entity.

MoMo twins presumably arise at approximately days 8–10 of fertilization age and are next to last in the spectrum of the MZ twinning events (Coulton et al. 1947). This type of placenta is also nearly always found with conjoined twins, only one exception having been published (Weston et al. 1990). Monoamnionic twins may have a single or a forked umbilical cord (Fig. 25.36; see also Fraser et al. 1997 who reported live-born twins), or there may be two separate cords. Forked cords are occasionally found also in completely

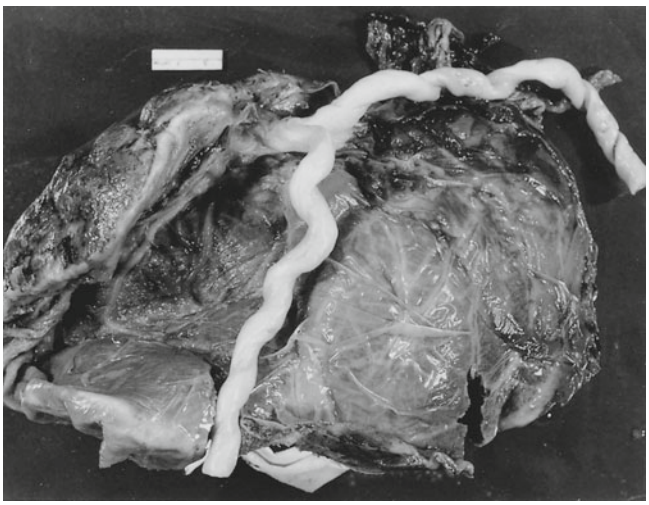


Fig. 25.37 Forked umbilical cord of MoMo twins (Courtesy of Dr. S. Romanski, Los Angeles)

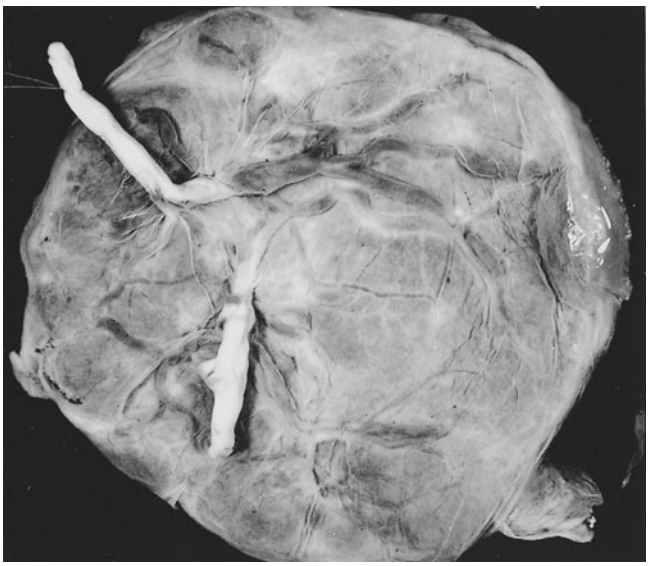


Fig. 25.38 Term MoMo twin placenta. Note the extensive vascular anastomoses on the fetal surface

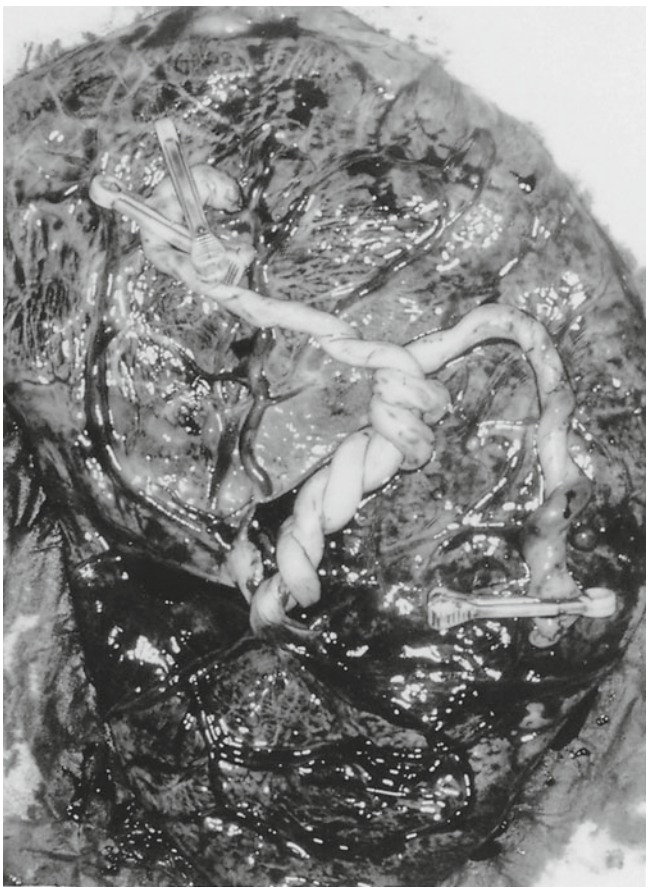


Fig. 25.39 A MoMo twin placenta with entangling of umbilical cords. Twin B (*top left*) died from nonimmune hydrops. At autopsy no cause was found for the hydrops. It was assumed to be the result of interference with venous return from the placenta. Figure 25.40 shows the large anastomoses after the cords have been untangled

separate MoMo twins (Fig. 25.36). In other MoMo twins, the cords originate close to each other on the placental surface, as in the cephalopagous conjoined twins whose placenta is shown in Fig. 25.37. Forked cords have been described by Larson et al. (1969a) in a set of macerated abortuses. MoMo twins often have extensive vascular anastomoses between the fetal circulations, particularly when the cords are in close apposition (Figs. 25.38, 25.39, and 25.40). The impact that the cord position may have on the outcome of the surviving MoMo twin (after fetal death of one) is further documented in Table 25.4. When velamentous insertion of one cord complicates placentation in such cases, growth restriction and fetal death are especially common (Fig. 25.41). Monoamnionic twins, as other MZ twins, may have remarkably different development, as was true of the case described by Larson et al. (1969a). Discordant anomalies are particularly common. Observations on MoMo twins have led to a better understanding of some types of congenital anomaly. Thus, the occurrence of renal agenesis in one of MoMo twins (unilateral agenesis in the other, who survived) was not associated with the Potter syndrome, as expected. Rather, the adequate production of amnionic fluid by the more normal twin prevented this phenotype and indicated that lung development depends purely on the volume of amnionic fluid present (Mauer et al. 1974). The anomalous twin also had normal respiratory function. It died of uremia at 12 days of age. Similar observations were later made of MoMo twins, where one had sirenomelia.

Monoamnionic placentation has also been observed in MZ triplets. Sinykin (1958) described the triple survival of MoMo triplets whose placenta is shown in Fig. 25.42. We have observed a monoamnionic triplet placenta of stillborns. The pregnancy was terminated with prostaglandins at 27 weeks when fetal death had become evident. One was a tiny acardiac fetus, one was an anencephalic, and the third was a normal macerated fetus (Fig. 25.43). The

Fig. 25.40 Large anastomoses are seen between cord vessels of the MoMo twin placenta in Fig. 25.39

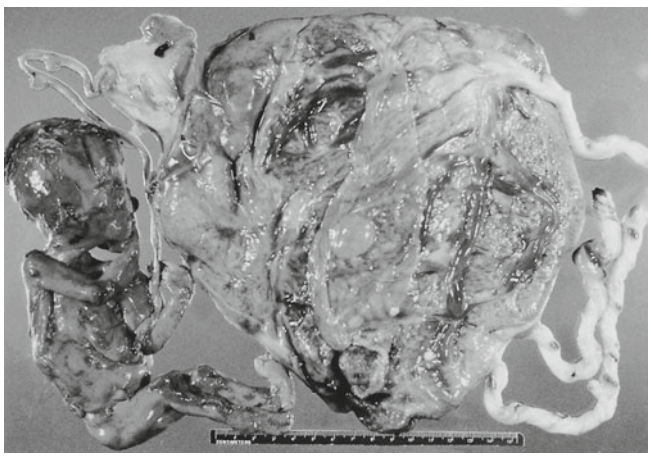


Fig. 25.41 A DiMo twin placenta with macerated fetus papyraceus at *left*, having velamentous insertion of its cord. The surviving fetus had porencephaly and was presumed to be the recipient in a transfusion syndrome

long-standing nature of thrombotic events in such twins is evident from the frequent mineralizations found in their placental vessels (Fig. 25.44). Exceptionally, triplets may be conjoined as well. This was described by Athanasiadis et al. (2005). These triplets, joined in the abdominothoracic area, had a single umbilical cord with six blood vessels.

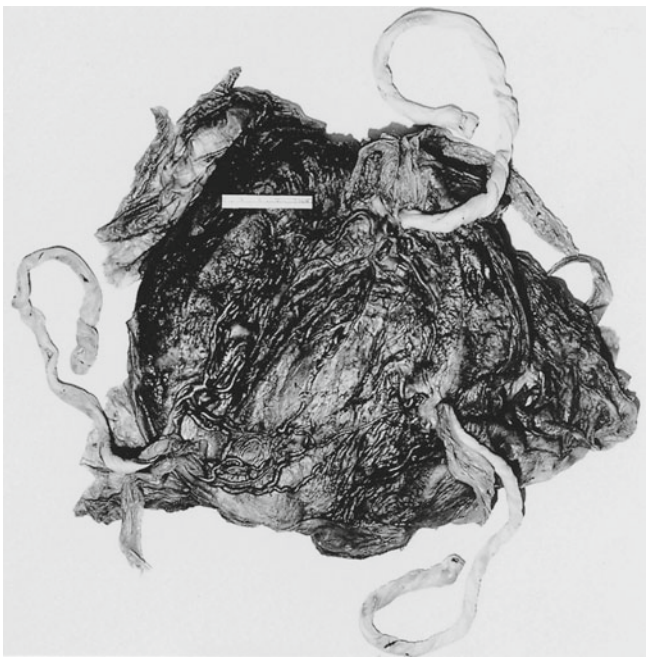


Fig. 25.42 A MoMo triplet placenta at term. There were anastomoses among all circulations and no entangling of cords. The triplets survived (Courtesy of Dr. M. B. Sinykin, San Antonio)

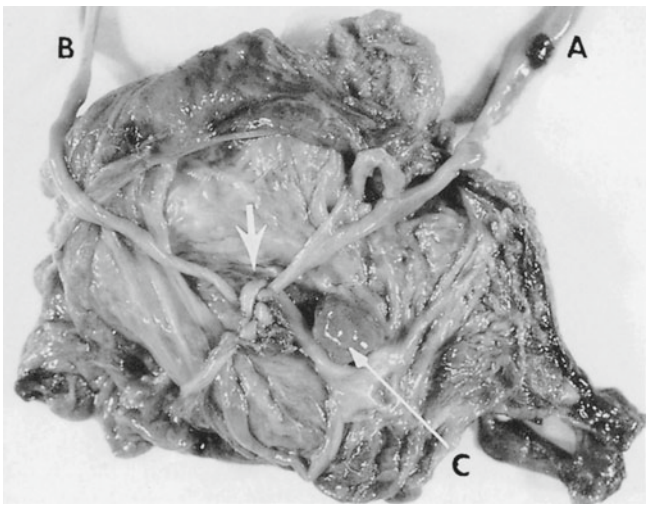


Fig. 25.43 Monoamnionic triplets, all of whom were macerated. Labor was induced at 27 weeks. Triplet *A* was structurally normal; *B* was anencephalic; *C* was a diminutive acardiac fetus (*large arrow*). Note the extensive knotting (*small arrow*)

It would be expected that MoMo twins, who are probably determined between days 8 and 10 of development (Fig. 25.10) may differ in the number of yolk sacs they possess. Figure 25.45 shows two early gestations of MoMo twins with an only partially divided yolk sac. It is considered to be the product of splitting on day 11 if the developmental table shown is precise enough for such inference. In another set of stillborn MoMo twins (with a dichorial triplet), we have seen two yolk sacs;

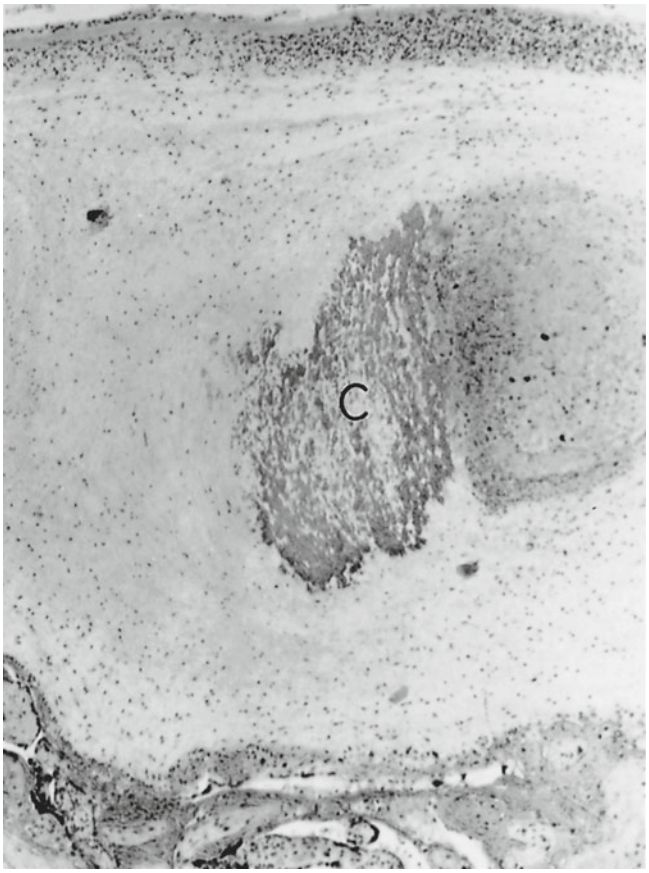


Fig. 25.44 Calcification of the vascular wall and an old thrombus in the placental surface vessel of one of MoMo twins that was macerated. (*C*) calcification

that placenta also had two velamentous cords and presumably had its embryological origin prior to the placenta with partially divided yolk sac.

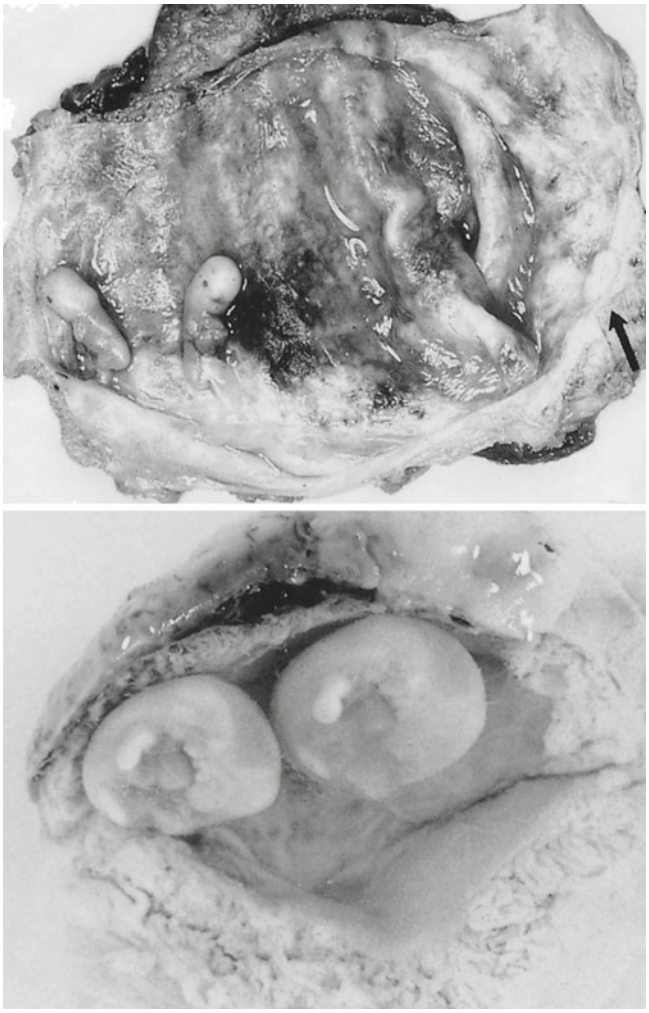


Fig. 25.45 Monoamnionic twin abortuses, structurally normal (*top*). Note the partially duplicated, bean-shaped yolk sac (*arrow*). Therapeutic abortion of DiMo twins was done at 33 days' gestation (*bottom*)

25.9 Diamnionic Monochorionic Twin Placenta

The DiMo twin placenta is the commonest form of placentation of identical or monozygotic twins. Each twin is enclosed in its own amnionic sac, and the "dividing membranes" are composed of two amnions only (Figs. 25.1, 25.2, 25.3, and 25.4). As will be seen in these photomicrographs, the amnion possesses epithelium **and** connective tissue. The presence of a layer of connective tissue has, regrettably, occasionally been mistaken as being diagnostic of chorion; that is the reason for being so didactic about the identification of these dividing membranes. These amnionic membranes can be moved freely over the chorionic surface. Because they are often moved before birth, it is not unusual to find the dividing membranes at a place that does not correspond with the "vascular equator" of the two twins' placental halves (Fig. 25.46). DiMo placentas usually have two yolk sacs, but

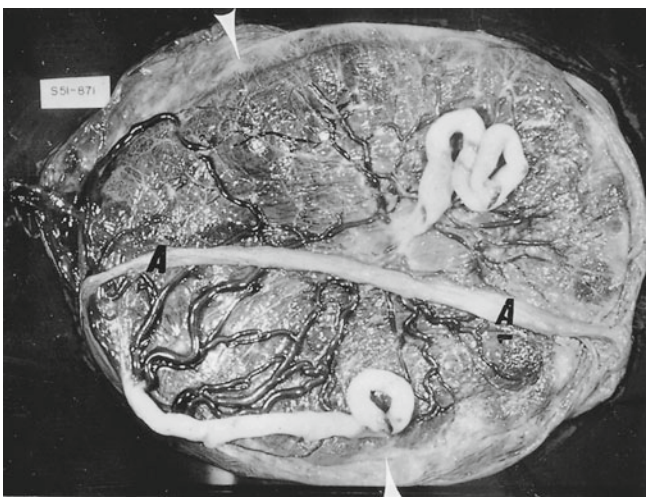


Fig. 25.46 A DiMo twin placenta with apposing amnions (*A*, *A*) meeting at angles to the vascular equator (*arrowheads*). Note the marginal insertion of the cord at *left*

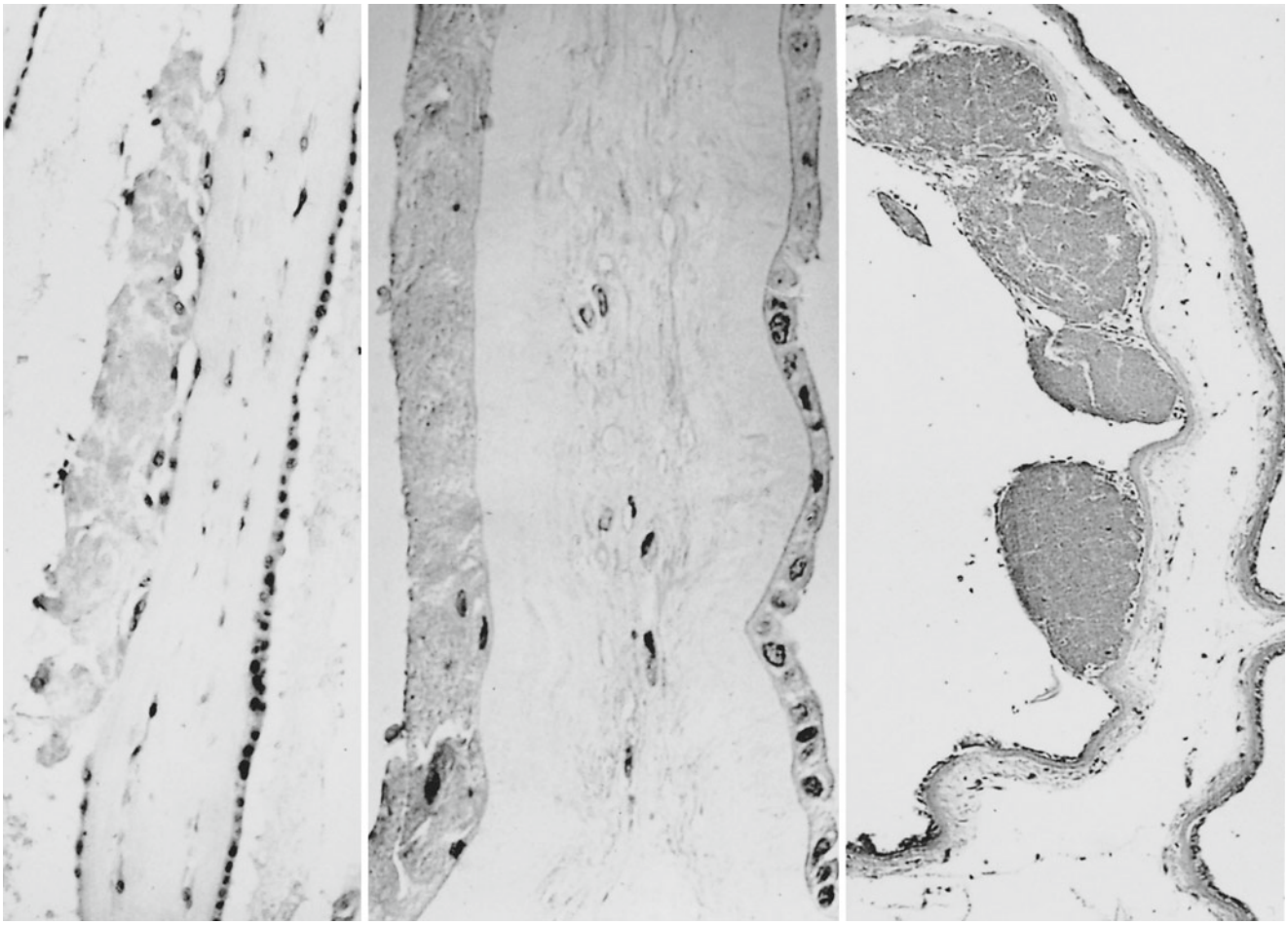


Fig. 25.47 Various degenerative features of the left amnion of dividing membranes in cases of DiMo placentas with one fetus dead (*center*, *right*) and amnion nodosum (*left*)

single yolk sacs are common in the twin transfusion syndrome. Virtually, all of them also have vascular anastomoses, as was delineated earlier in this chapter. An understanding of the importance of monochorionic placentation for twin growth has been reviewed in a comprehensive contribution by Trevett and Johnson (2005). The cord insertion is, as in all twin placentas, more often marginal or velamentous than that of singletons. Single umbilical artery (SUA) is also commoner in one or both of these twins (Thomas 1961). Yoshida (1998) found that SUA occurred in 3% of twin gestations, while it was found in 0.53% of singletons. Because the amnion does not have its own blood vessels, the dividing membranes must survive on the nutrients and oxygen contained within the amnionic fluid. This notion is supported by the finding of amnion necrosis in cases of fetal death, or amnion nodosum when one of the twins is oligohydramneic (Fig. 25.47). In such cases, only the amnionic epithelium degenerates. The underlying connective tissue is generally preserved. In cases of prenatal infection, the inflammation is also lacking in these dividing membranes, and meconium pigmentation is sparse when it is found elsewhere in the amnionic cavity. What has been surprising with the increasing practice of ART is the fact that MZ twinning is often superimposed upon multiple embryo transfers and that the placentation of these twins is then usually (?always) a DiMo placenta. This does not rhyme with the notion that it is perhaps due to improper handling of the blastocysts and disruption of the zona pellucida before implantation, as this would be expected to have led to DiDi MZ twins. Jain et al. (2004b) have examined some aspects of this and found that MZ twinning was higher when blastocysts were directly transferred than when 3-day embryos were implanted. At present, the mechanism that leads to MZ twinning in ART is not fully understood.

The lack of intersac transfer of solutes is illustrated by the results from injection of hypertonic saline when abortion was intended. Kovacs et al. (1972) injected 200 mL of a 20% NaCl solution into one sac after having removed 380 mL of amnionic fluid at 22 weeks. Cardiac activity stopped in 2 h in one twin, and labor commenced 20 h later. The DiMo twins weighed 300 g each; the injected fetus was macerated, but the other was alive at delivery. Only the amnion of the injected

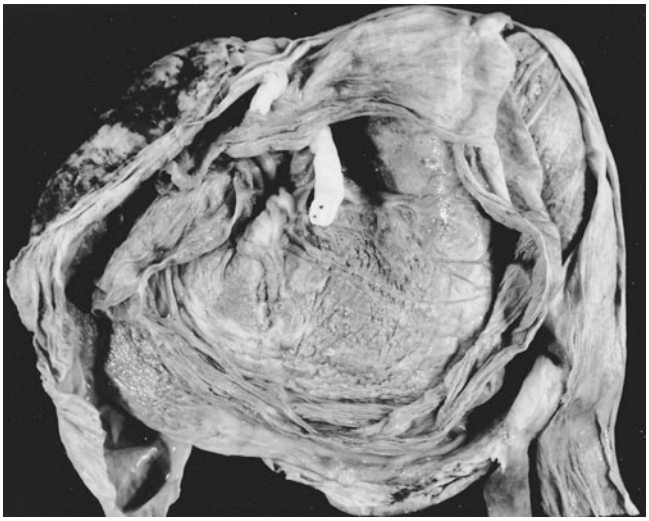


Fig. 25.48 A DiMo twin placenta (550 g) of MZ twins. One amnionic sac is enclosed by the other. The outer sac contained a smaller fetus with velamentous insertion of the cord (Courtesy Drs. V. Anderson and Z. Weinraub, Martin Luther King Hospital, Los Angeles, California)

side was necrotic. Hoch et al. (1972) made similar observations in a dichorionic twin pregnancy, but in this placentation, it is more expected that solute transfer does not occur between the two sacs. Finally, a most unusual DiMo twin placenta, sent to us in consultation, is illustrated in Fig. 25.48. This placenta shows one amnionic sac literally contained within the other; the twins differed appreciably in size.

25.10 Diamnionic, Dichorionic Twin Placenta

The DiDi twin placenta may be composed of separate disks, or the two placental portions may be intimately fused. It is the most common type of twin placentation and shares with the other types an increased frequency of marginal and velamentous insertion of umbilical cords. The fused placentas present the appearance seen in Fig. 25.49. When the fetal vessels are injected, there is generally no exchange of the injection fluid between the circulations of the two fetuses. Exceptions of this rule will be discussed below. This finding is also borne out by a sharp line that divides the placentas, easily seen when one twin has died before birth (Fig. 25.50). A frequent and unusual feature of DiDi twin placentas is the phenomenon of "irregular chorionic fusion," a feature well shown in Fig. 25.51. In such placentas, the membranes do not meet over the areas perfused by the individual fetuses; in fact, the placentas may be separated, and a portion of one may be covered by the membranes of the other. This phenomenon is best explained

Fig. 25.51 A DiDi twin placenta with irregular chorionic fusion. The chorion laeve of the left placenta overlaps one-third of the placenta at right. There is no vascular fusion

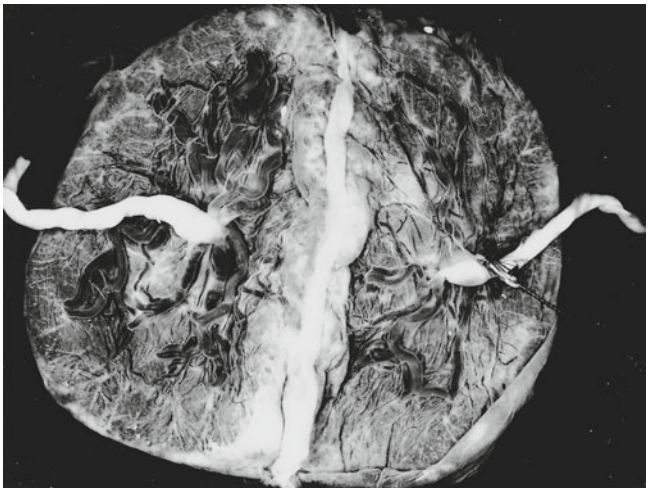


Fig. 25.49 A DiDi twin placenta intimately fused. Left cord has SUA; right cord is being injected without transfer of fluids

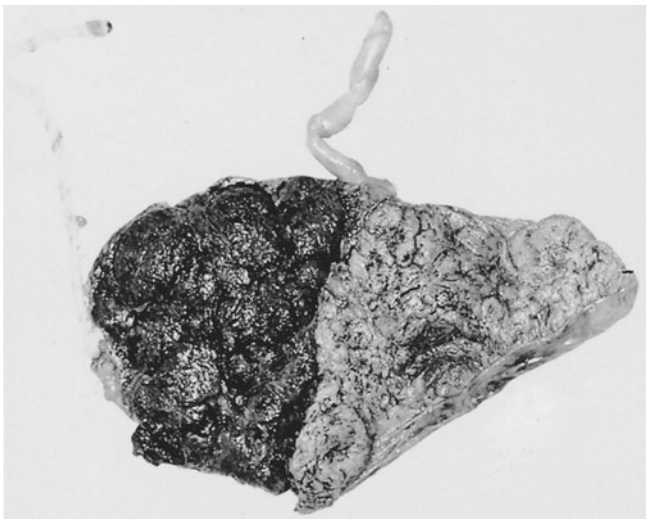
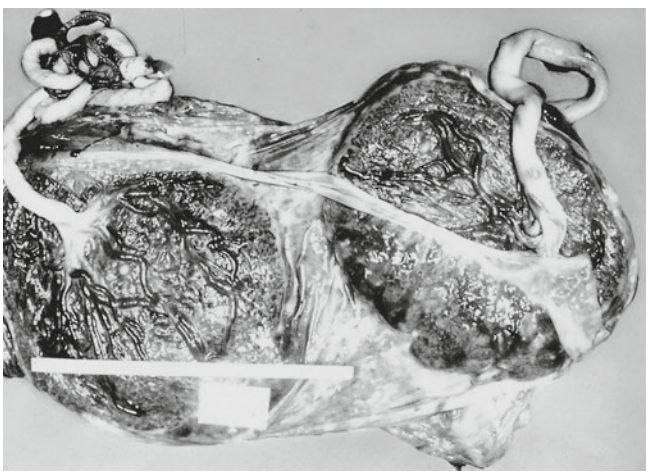


Fig. 25.50 A DiDi fused twin placenta, maternal surface. Twin at *left* is Rh-negative and living; twin at *right* is Rh-positive and macerated. There were two corpora lutea at delivery. Note the clear dividing line between the two placentas



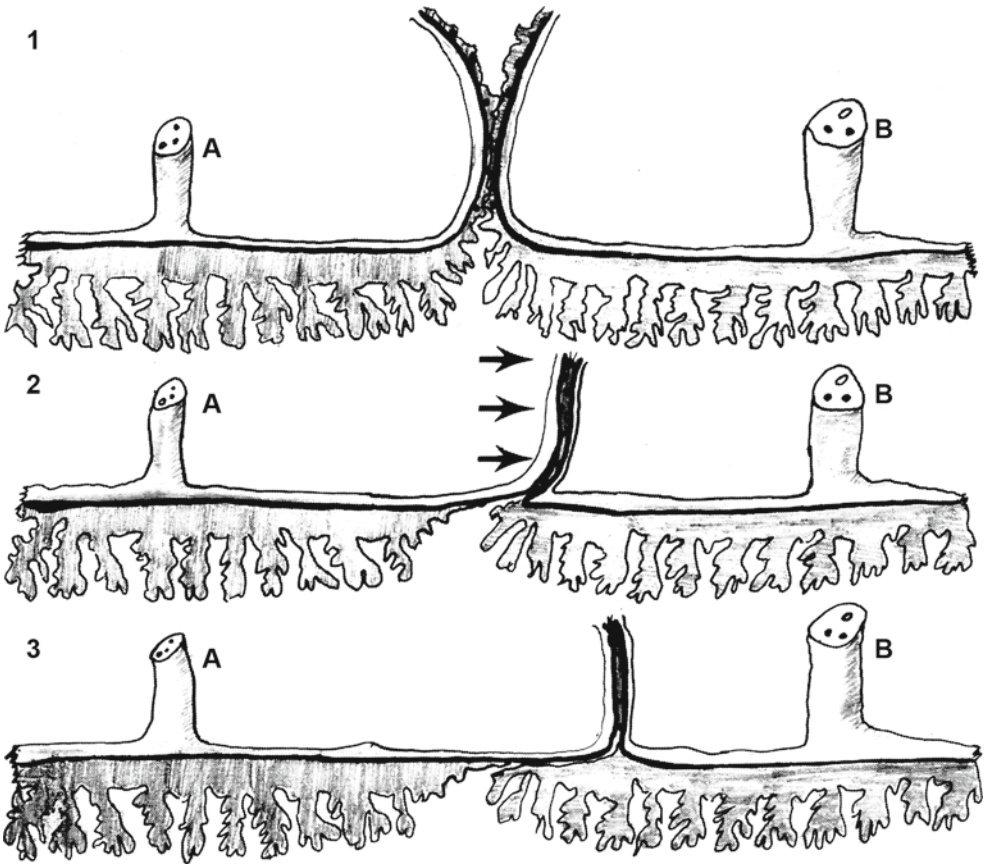


Fig. 25.52 Presumed mechanism that leads to irregular chorionic fusion as in Fig. 25.51. *1, 2, 3* designate step-wise changes over pregnancy; *A* and *B* specify the umbilical cord and arrows point to the movement of the "dividing membrane"

by assuming that the intra-amnionic fluid pressure of one cavity gradually expands its sac, pushing the other away (Fig. 25.52). It is not unlike the process of lifting the marginal chorion in cases of circumvallate placentation. It has no influence on the well-being of the fetuses, and no vascular fusion takes place in the areas of overlap.

When the fetal outcome of fused DiDi twin placentas is compared with that of separated DiDi placentas, Buzzard et al. (1983) found that there is a greater difference in birth weights with fused placentas. The inference is that placental proximity has a prenatal influence on fetal development, perhaps because of competition for space during placental expansion. On occasion, prenatal diagnosis mistakes the membrane relations and other features of consequence to fetal survival. Thus, Baergen et al. (1995) described a placenta after recurrent leakage and hemorrhage, also with SUA; the placentas were fused but one twin had died because of being born within an extramembranous gestational condition.

25.11 Vanishing Twin Phenomenon

It is not uncommon that one twin dies long before birth. If the pregnancy continues undisturbed, this fetus may disappear when it is very young. It may become flattened (fetus compressus, fetus papyraceus); or when it is large, it may macerate, lose much of its fluid and become misshapen. Although fetus papyraceus has long been known, the phenomenon of a "vanishing twin" is a recent addition to our nomenclature. The term should be reserved for multiple pregnancies that are identified sonographically during the first 15 weeks of pregnancy and that have, as their outcome, a single fetus. It must be appreciated, however, that the rate of occurrence will always be underestimated. For instance, we have seen many placentas from ART practices where we know that several blastocysts were placed and implanted but in whose placentas there was no morphologic evidence of a vanished twin (see Chap. 27).

The seminal report on the vanishing twin was that of Levi (1976), who repeatedly studied sonographically 6,690 early pregnancies. Of 118 patients identified to have twins, only 86 sets of twins were delivered. When the diagnosis of twins was made prior to 10 weeks, the "rate of disappearance" was 71%. When the diagnosis was made between 10 and 15 weeks, the disappearance rate was 62%. When twins were first diagnosed after 15 weeks, none disappeared. Similar figures of twin resorption (70%) were reported by Robinson and Caines (1977).

The "vanishing twin" is thus a feature of early pregnancy; its diagnosis is made by the ultrasonographic finding of

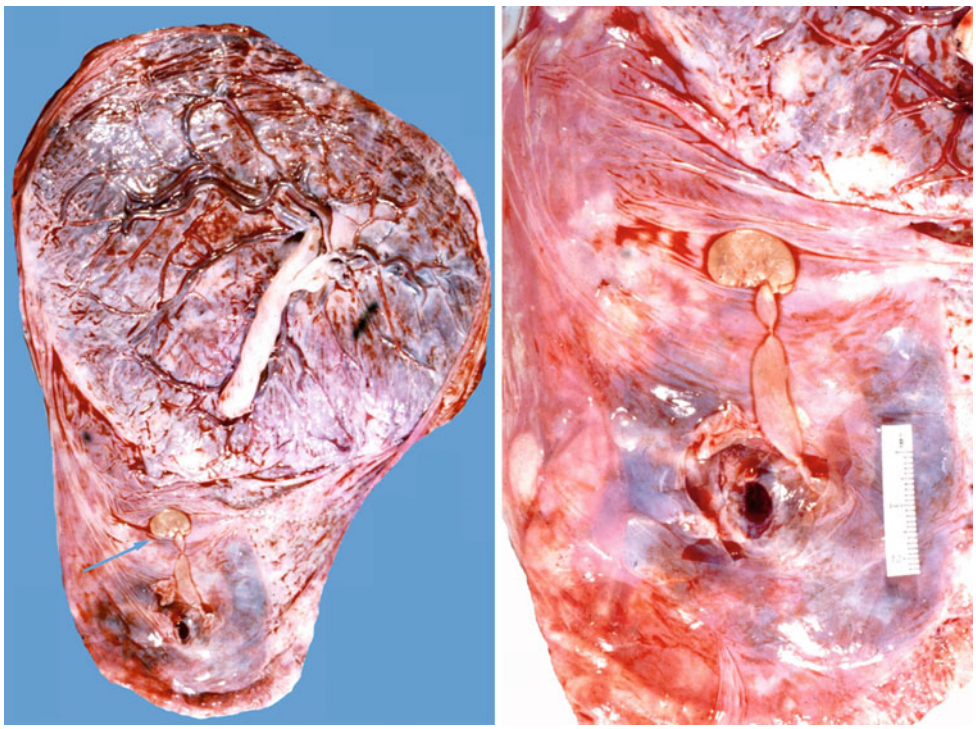


Fig. 25.53 A DiDi separated twin placenta at term. The patient presented with alleged "abruption." A normal term twin was delivered; a second placenta with a tiny (2 cm) embryo was found in the membranes. When its sac was opened (*right*), a yellow embryo of the opposite sex was attached to a swollen umbilical cord. The dead embryo points (tin blue *arrow*)

two echogenic "rings" denoting the presence of two sacs. Although the existence of vanishing twins is not doubted, the possibility of error in the diagnosis of twin gestations was mentioned by Levi (1976). It was expanded upon in greater detail by Landy et al. (1982), who reviewed the literature and wrote a letter of inquiry to colleagues. Later, Landy and Keith (1998) reviewed the topic in some depth, although only 9 of 68 pregnancies were monochorionic, thus precluding an in-depth analysis of the possibly greater effect in MZ twins. They also considered the possible contribution of aneuploidy of the vanished twin and the contribution by ART. It is possible that a yolk sac or amnionic sac, that is still separate from the chorion, or other features of early embryonic life are occasionally mistaken for twin cavities (e.g., Green and Hobbins 1988). Moreover, only rare reports of placental examination have accompanied these studies. Even more rarely have empty sacs or old hemorrhages been identified. An exception is the report by Jauniaux and his colleagues (1988). They reported the placental findings of ten such cases, five of which came from in vitro fertilization, five were spontaneous. First trimester bleeding was the only clinical evidence of this occurrence. In five cases, the vanished twins were identified as "well delineated plaques of perivillous fibrin deposition, associated in one case with embryonic remnants." There are other reports of frequent early vaginal bleeding episodes in these patients. Those events may represent the spontaneous abortions of twins. If the reported cases are applicable to the general population, the excessively high frequency of calculated twin gestations is surprising. Two searching papers by Anand et al. (2007) attempted to ascertain whether vanished twins had any significant effect upon the cerebral capacity of the survivor. No unequivocal results were obtained.

The term "vanishing twin" was perhaps first used by Jeanty et al. (1981). It is now an established entity in obstetrics, and more careful study of the placenta is needed to secure its place. When such a twin is found sonographically or only a remnant of a second sac is identified, every attempt should be made to obtain some karyotype information from the chorionic sac at birth. The results from such studies may eventually indicate whether these vanishing twins are chromosomally abnormal. Additionally, restriction fragments length polymorphism study (RFLP) should define zygosity readily.

Such fetuses would perhaps have been aborted were it not for the presence of a normal twin in the same uterus. Gruenwald (1970) described three such specimens two of which, however, are best considered to be fetus papyracei. One specimen consisted of a local thickening in the membranes that, when sectioned, disclosed ribs and other fetal tissues. We have seen numerous placentas with vanished twins enclosed in the membranes, but their presence had not been detected sonographically or was not anticipated. Figures 25.53, 25.54, 25.55, and 25.56 show what their appearance may be. In all of these specimens, clear evidence of a second sac existed. In two of these cases and in several others we have observed, tiny embryos could be identified. Those embryos had surely died before 8 weeks' gestation. The fact that they were still recognizable suggests that when a "vanished twin" cannot be detected in the

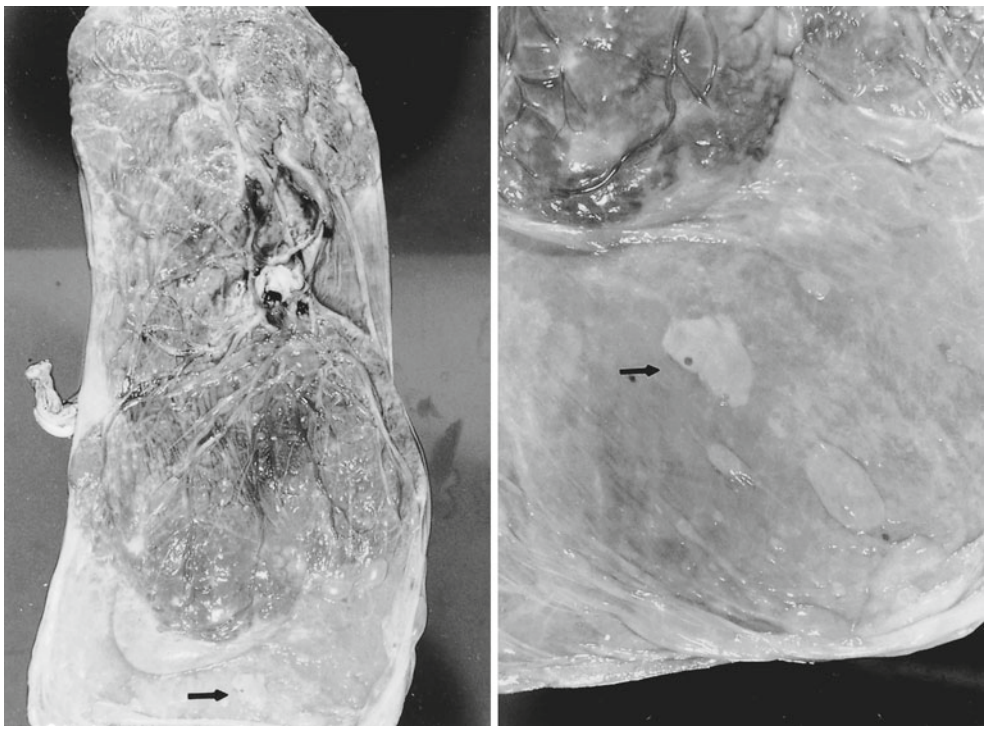


Fig. 25.54 A term placenta with a separate embryo in the membranes (*arrows*). This embryo is similar to that shown by Bergman et al. (1961). The ocular pigment is readily seen. No placental remains were seen

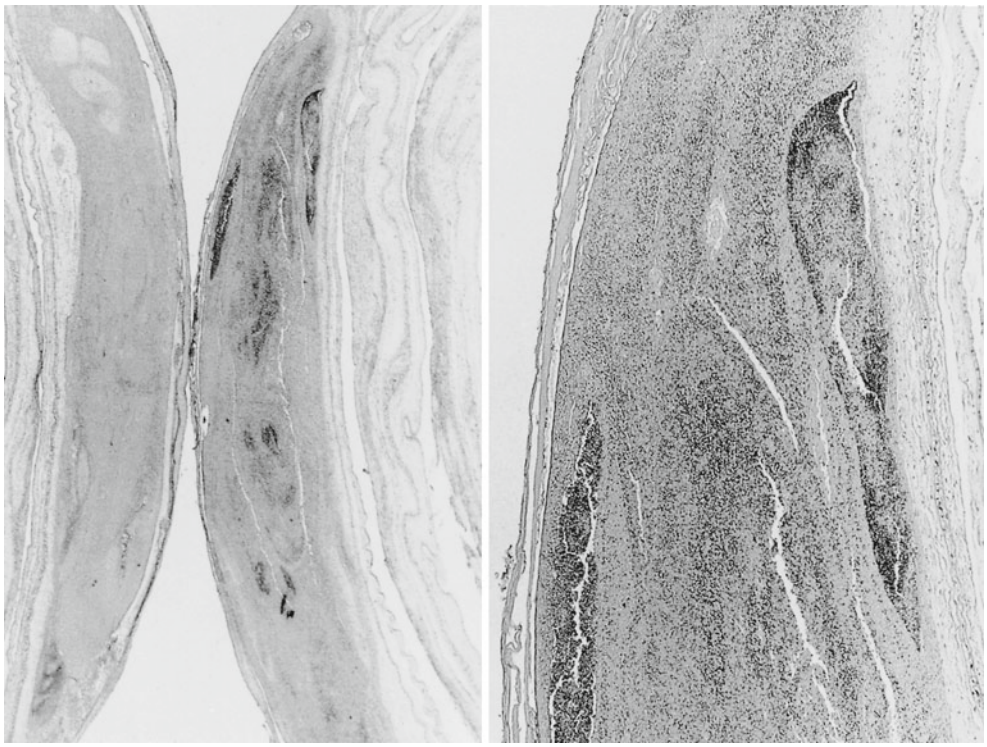


Fig. 25.55 Membrane roll with embryo of Fig. 25.54. Macerated embryonic structures are visible. H&E, ×16 (*left*), ×60 (*right*)

term placenta, the diagnosis must have been either erroneous or an empty sac of a "blighted ovum" had been present and aborted. It is surprising in the embryos shown here how long an embryonic structure can coexist with a normally developing twin. A similar early, vanished embryo was first shown by Bergman et al. (1961) in their description of a "blighted fetus." The tiny embryo, also present in the membranes, was essentially similar to the one shown in Fig. 25.54. The "empty sac" feature was further discussed in the prospective study of 1,000 pregnancies by Landy et al. (1986). They calculated a minimum twinning incidence from this material as 3.29%, if not 5.39%. This is

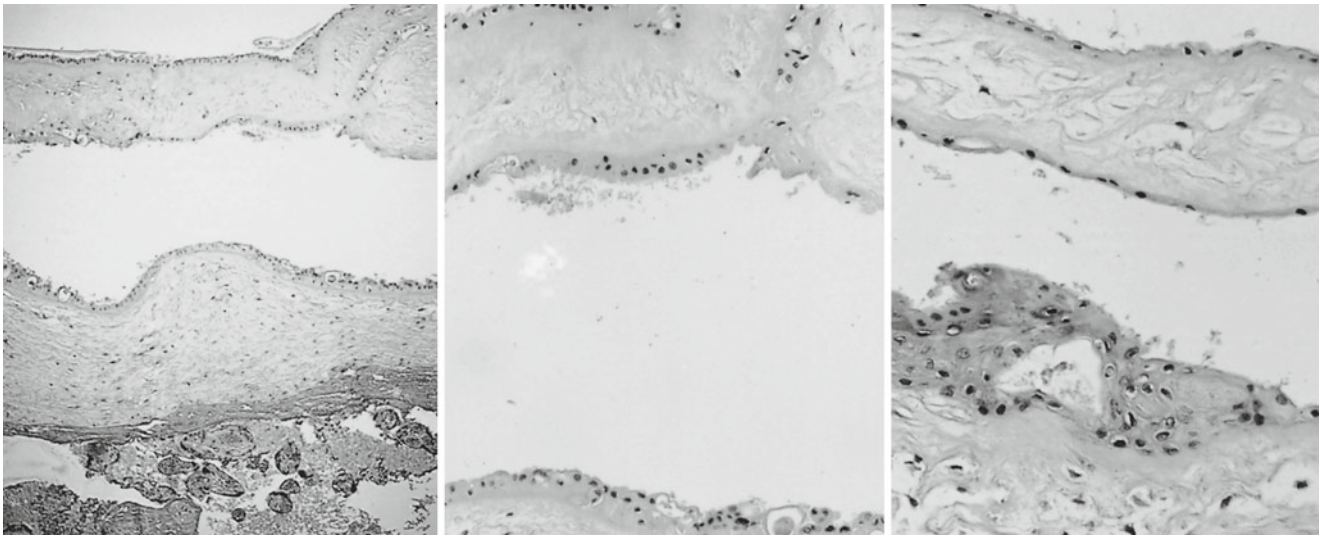


Fig. 25.56 Mature placenta with vanished twin. A subamnionic sac containing debris is the remnant of a DiMo placenta. Note the squamous metaplasia (*right*), vacuolation (*center*), and amnion nodosum-like degeneration (*left top*). H&E, ×16 (*left*), ×40 (*center*), ×60 (*right*)

very much higher than the currently estimated twinning frequency of the general population. These authors suggested that "vanishing twins" may possibly be the source of rhesus sensitization. In view of the small quantities of blood potentially present to stimulate the mother, this proposal seems to represent an unduly pessimistic concern. Sulak and Dodson (1986) have presented evidence for two vanished triplets by demonstrating an empty chorionic sac. When the placental sac of the surviving singleton was studied, it was found to be filled with debris. Kapur et al. (1991) found an empty cavity of a former twin associated with a sirenomelic co-twin whose pregnancy was terminated at 18 weeks. Triplets had been diagnosed sonographically 4 weeks after conception by in vitro fertilization. It is more difficult to be certain that such structures, as shown in Fig. 25.57, are the remains of vanished embryos, in this case a triplet, although we prefer to believe this view over ascribing these rests to be teratomas. In their study of 189 sonographically studied twin pregnancies, Yoshida and Soma (1986) found that 21 twins died. Nine qualified for the term vanishing twin. The association with prenatal bleeding was also emphasized by these observers. Sebire et al. (1997c) identified 102 monochorionic and 365 dichorionic twins between 10 and 14 weeks; they found a higher fetal loss rate in the former (12.2% vs. 1.8%) before 28 weeks. Perinatal mortality and prematurity were also significantly higher in monochorionic twins.

In the differential diagnosis, it must be cautioned that retromembranous hemorrhages (often falsely referred to as "subchorionic hemorrhages") may occur after amniocentesis, and they can also occur "spontaneously," i.e., without our knowing the cause. Such hemorrhages must not be mistaken for vanished twins. The typical sonographic appearance of a small vanishing twin with normal co-twin at 14 weeks is shown in Fig. 25.58.

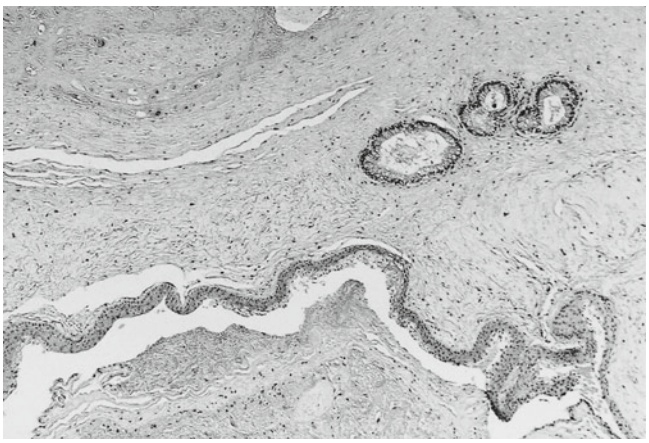


Fig. 25.57 Remnant of a triplet in the membranes of a term DiMo twin placenta. Note the inclusion of columnar, mucus-producing epithelium and a cyst with squamous lining in the chorion. H&E, ×60

The presence of vanished twins or of a fetus papyraceus has posed other difficult clinical problems. It has thus been reported that the maternal α-fetoprotein (AFP) may be significantly elevated in pregnancies complicated by a vanishing twin (Lange et al. 1979). The finding of high AFP and acetylcholinesterase levels has led to therapeutic abortion, the vanished twin not having been diagnosed (Winsor et al. 1987). There may also be an elevation of the amnionic fluid acetylcholinesterase levels. In the case described by Cruikshank and Granados (1988), this elevation was blamed on coexisting aplasia cutis. It goes without saying that such gestations also are not recorded as twin gestations in most hospital statistics.

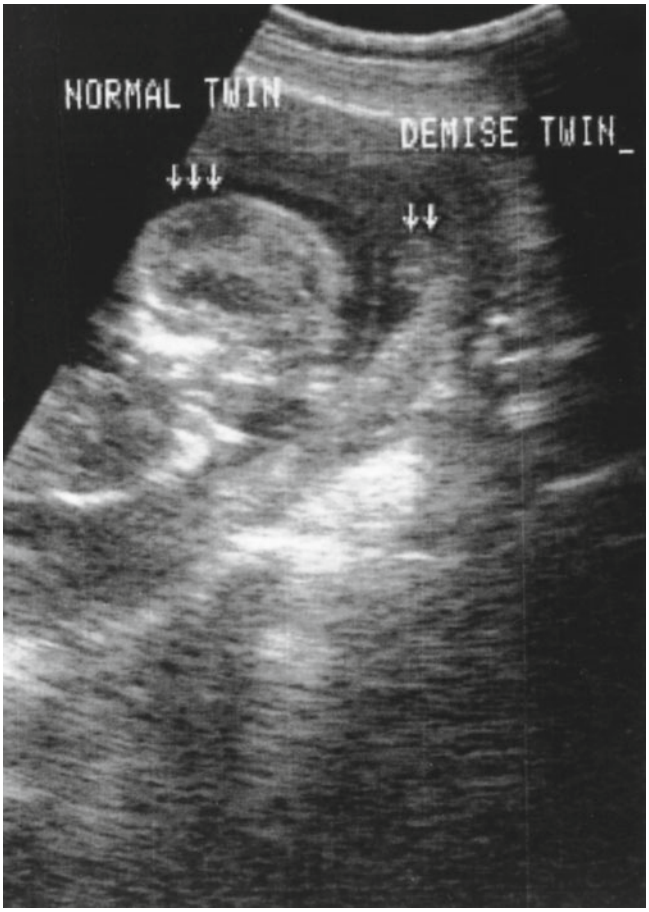


Fig. 25.58 Sonogram at 14 weeks with one normal and one dead ("vanishing") twin. The latter still has a separate cavity and measures 1.7 cm (Courtesy of Dr. J.D. Stephens, San Jose, California)

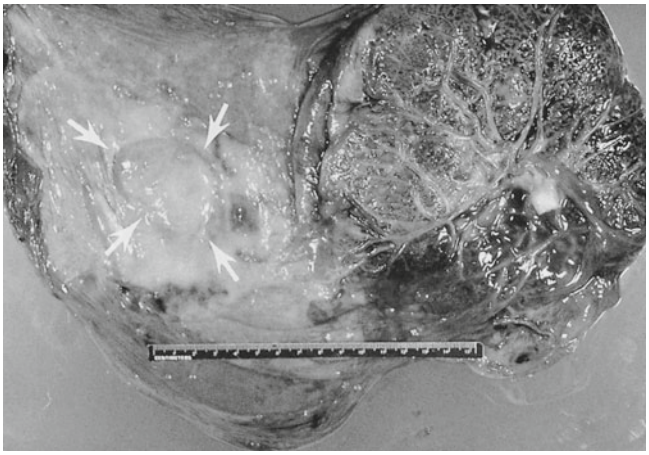


Fig. 25.59 Diminutive fetus papyraceus in the membranes of a normal twin's placenta (*arrows*). Its dichorionic placenta was a flattened mass of fibrin

25.12 Fetus Papyraceus

A fetus papyraceus forms when one of twins or higher multiple pregnancies dies during gestation and becomes compressed as pregnancy continues. There is no clear distinction between the vanishing twin and a fetus compressus or papyraceus. Although such fetuses exist fairly frequently, they are often overlooked. They may be so compressed that small ones are found only when a careful inspection of the placenta and its membranes is made (Fig. 25.59). We recommend that radiographs be obtained when such areas of thickened membranes are found and that the area be dissected carefully. The case shown in Figs. 25.60, 25.61, 25.62, and 25.63 is a typical circumstance (Jackson and Benirschke 1989). Sonographically, a typical fetus compressus was demonstrated (Fig. 25.60); at delivery, it was a separate mass of fibrin compressed in the membranes of the normal twin's placenta (Fig. 25.61). Careful peeling of the DiDi membranes showed the fetus compressus with umbilical cord (Fig. 25.62), whose skeleton was normal by radiography (Fig. 25.63). The fetus compressus of Fig. 25.64, on the other hand, was enclosed in a separate amnion. It was an acardiac twin with SUA and had six toes. The frequency of finding a fetus papyraceus has increased substantially in recent years. This is mostly the result of intentional "reduction" of fetuses in ART patients in whose pregnancies too many embryos existed, where premature birth was anticipated, and/or in whom a smaller number of infants was requested. This ablation is commonly undertaken by intracardiac injection of 1 mL KCl, an example is shown in Fig. 25.102. It is advantageous to take radiographs of such fetuses because these occasionally disclose unknown anomalies; in this case, an encephalocele was discovered. Yaron et al. (1999) incisively discussed this issue in their study of 143 triplets (12 controls) that were reduced to twins. It lowered the frequency of prematurity and IUGR.

Several of these compressed fetuses had living co-twins with skin defects (Fig. 25.65). Some have well defined, infarcted placentas (Figs. 25.50 and 25.65). In others, one can demonstrate that twisting of the umbilical cord at its fetal insertion was the presumed cause of demise. The cause of death, however, is not always discerned. Thus, when the donor in the transfusion syndrome dies, its placenta may be so atrophied or infarcted that the causative vascular anastomoses can no longer be verified. Chromosome preparations of the macerated twin are rarely feasible because of the advanced state of maceration. Cytogenetic examination may be possible, however, from samples of the chorionic membranes, as would be RFLP study which should be attempted. At least once such a study of the DNA of a fetus papyraceus showed it to have a dizygotic relation to the living twin (Lemke et al. 1993). Acardiac fetuses are readily distinguished radiologically and by dissection from the normal, usual fetus papyraceus. A careful study of these vanished twins is doubtlessly worth the effort. While it seems useless to dissect a fetus papyraceus, it proves to be quite feasible

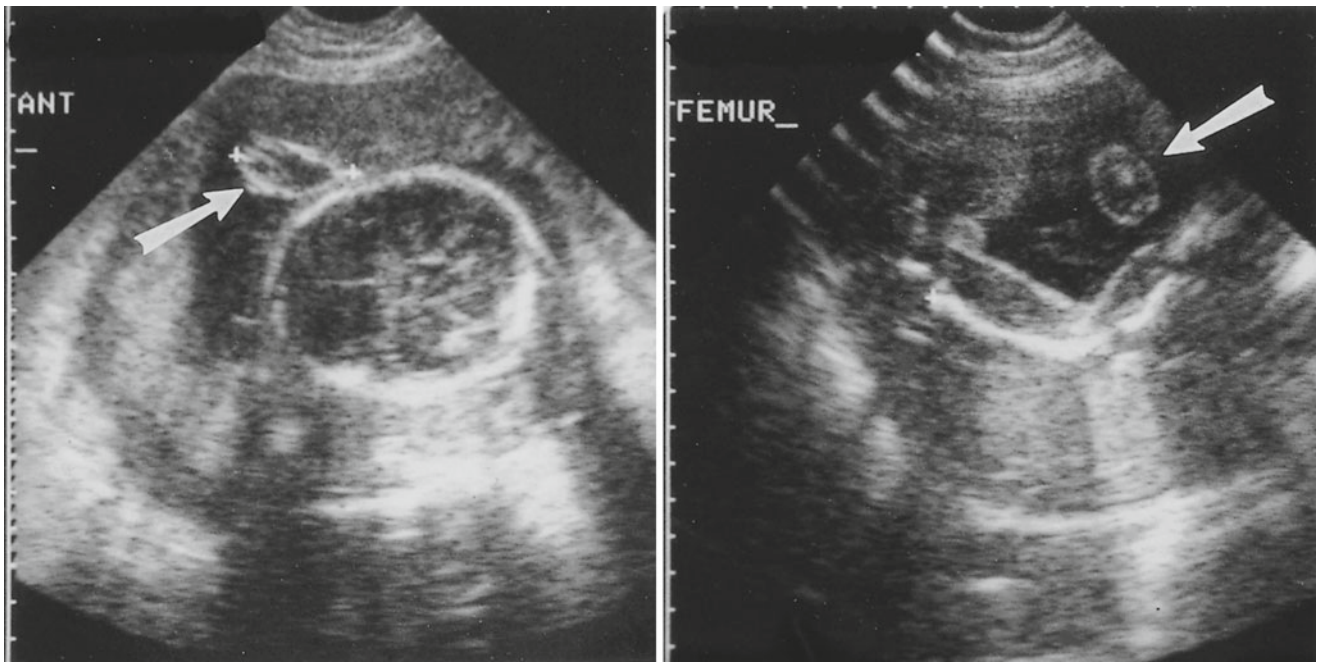


Fig. 25.60 Sonogram of twin pregnancy with fetus papyraceus. The skull is seen at the *arrows*; the normal twin's skull is next to it (*left*); femora are at right (Courtesy of Dr. G. R. Leopold, San Diego)

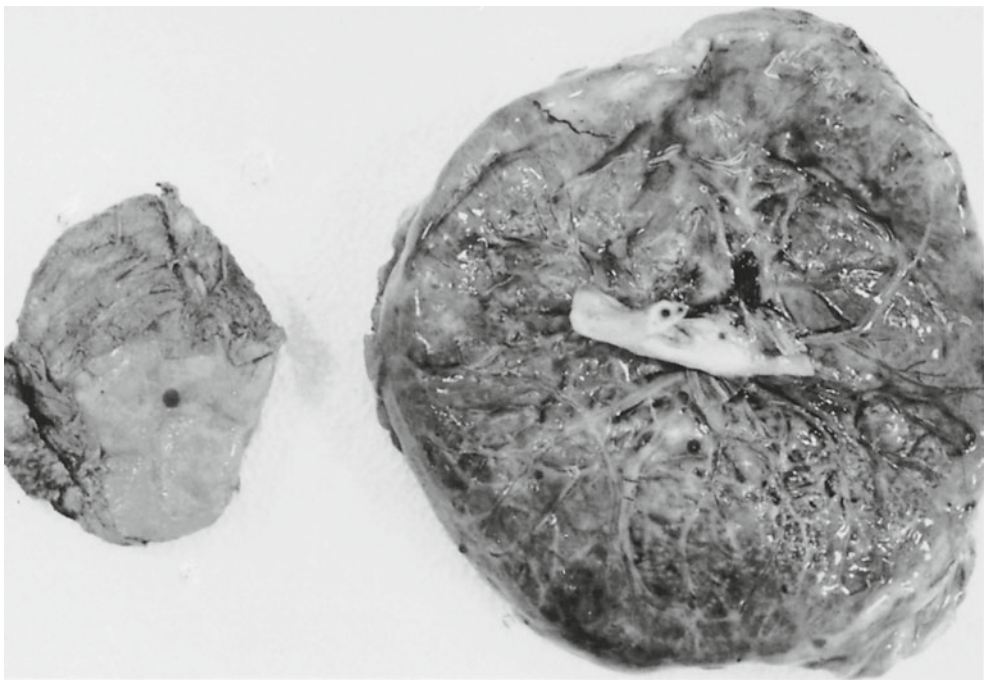


Fig. 25.61 The specimen at term shown in Fig. 25.60. The fetus papyraceus was in a separate mass at left

when it is done in a continuous stream of water. It has been suggested that vanishing twins may be associated with the CNS defects of cerebral palsy in the survivor (Pharoah and Cooke 1997), but their later systematic inquiry (Newton et al. 2003) showed this not to be the case. Moreover, the detailed study of Hargitai et al. (2003) of placentas in patients with cerebral palsy found no "vanished twins." When fetal demise occurs later in the gestation of monochorionic twins with vascular anastomoses (and then usually with larger fetuses), however, cerebral palsy in the survivor is a distinct possibility as Liu et al. (1992) determined (see also Glinianaia et al. 2002). A thoughtful comment on the (small) prevalence of CP in twins vs. the overall CP problem needs to be considered; this is important so that in larger prospective series

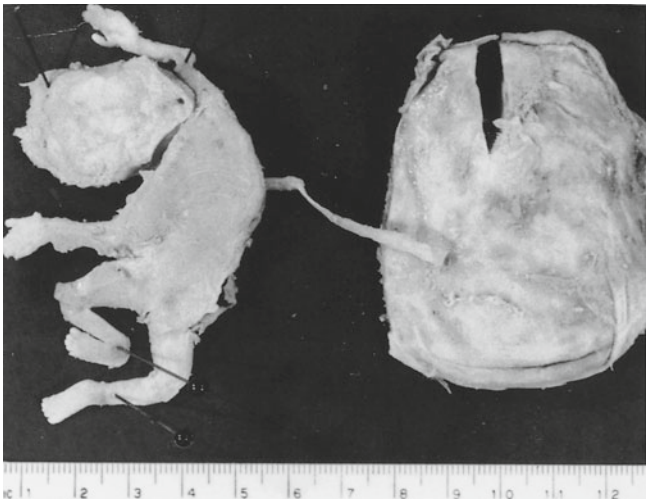


Fig. 25.62 Same case as in Figs. 25.60 and 25.61. The dissected fetus is attached to a short umbilical cord

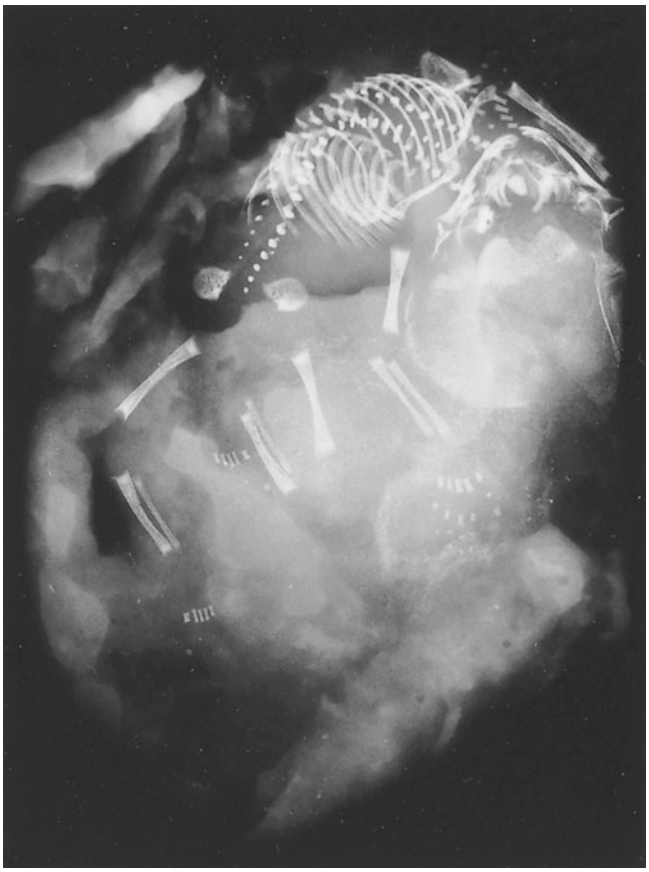


Fig. 25.63 Radiograph of the specimen in Fig. 25.62, showing a normal skeleton

zygosity, ART and chorionicity can be individually determined for their individual relevance to the origin of CP in multiples (Blickstein 2004).There is little doubt that MZ twins have a greater frequency of cerebral impairment when one fetus dies in utero. Numerous studies attest to this; Pharoah (2001) attributed much of this to immaturity; Cincotta et al. (2000) merely called for further study of this relationship; Matsuda and Kouno (2002) found a 22% incidence of cerebral palsy in TTTS; Resch et al. (2004) identified hypocarbia in premature babies as the principal risk factor; Lopriore et al. (2006b) found 14% of twins after laser ablations for severe TTTS to suffer impaired CNS status; Rossi and D'Addario (2009b) found no difference in CNS impairment of donors (9%) and recipients (10%) of the TTTS; Jelin et al. (2008) described that antenatal MRI examination identified CNS abnormalities in 7 of 21 cases with antenatal demise of one twin; Zach et al. (2007) found 25% of CNS injuries after fetal demise. Other investigators have weighed in on the possible neurodevelopmental sequelae of TTTS. Thus, Cincotta et al. (2000) followed 23 children and found that 22% had significant abnormalities. Banek et al. (2003) studied outcomes after laser ablation and identified minor abnormalities in 11%; major CNS deficits were found in another 11% of cases. The ensuing letters by de Lia and Worthington (2004) and the replies need to be read for a complete assessment, not only regarding the complex methods of surgery but also to appreciate the difficulty of correct evaluation. When no laser ablation is undertaken, the CNS morbidity is even higher (Lopriore et al. 2003). It might also be mentioned that, on very rare occasion, after demise of the recipient twin, the donor (!) may develop acutely hydrops fetalis (Ries et al. 1999). Wataganara et al. (2005) showed that laser ablation in TTTS leads to a persistent elevation of circulating cell-free fetal DNA levels in the maternal circulation.

It is thus apparent that CNS damage in monochorionic twins is not only excessively high but that it requires careful evaluation in order to seek, reliably, the causes for their occurrence so that possible preventative methods can be employed. This aspect is discussed without complete resolution by Lopriore et al. (2006b). They considered as possible causes of "cerebral blood flow disorders" IUFD of one twin with exsanguination but emphasized that low birth weight was an important aspect. In the past, much attention has been paid to the consideration that thrombotic material and the like could be recirculated into the surviving twin, thus causing CNS damage. This hypothesis has recently been reawakened by the publication of Mittelbronn et al. (2006). They described triplets with TTTS and a macerated fetus; the triplets had hydranencephaly and cortical polymicrogyria, and one had further visceral "thrombotic" events found at autopsy. They reviewed much of the relevant literature and essentially deny the idea that hypoperfusion (after fetal demise) could have led to this CNS result, as we believe it might. A similar report comes from Olowu et al. (2006), but then Pharoah (2007) found from a survey that children with cerebral palsy are significantly more prone to have other anomalies anyway. In a later review of this topic and with much greater

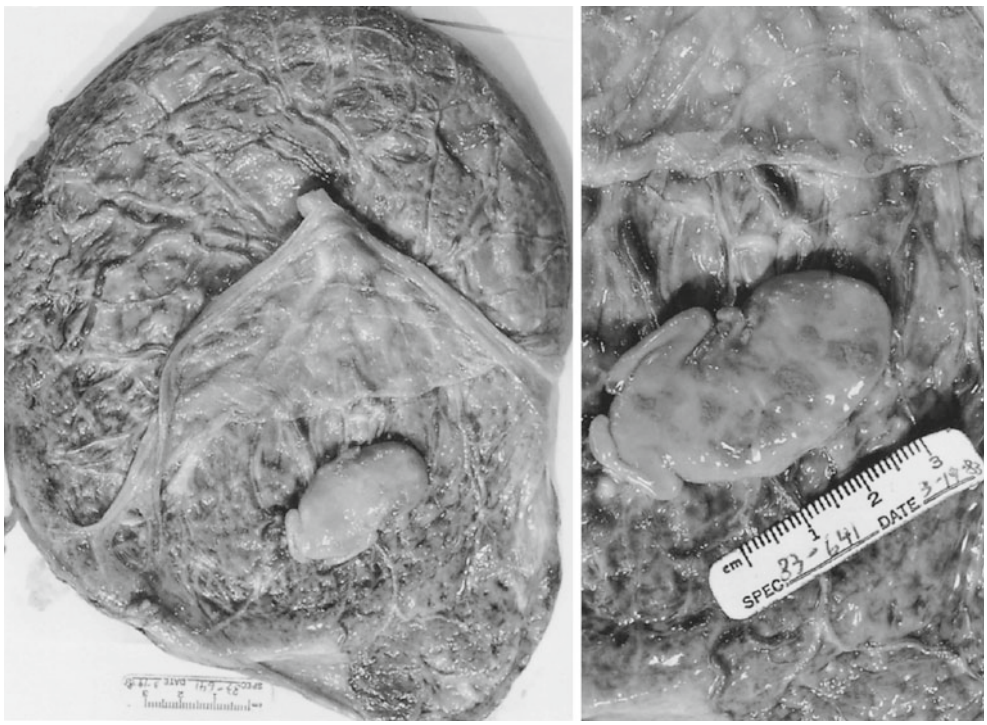


Fig. 25.64 Fetus papyraceus in a separate amnion (DiMo placenta). It had SUA and six toes and was an acardiac upon dissection

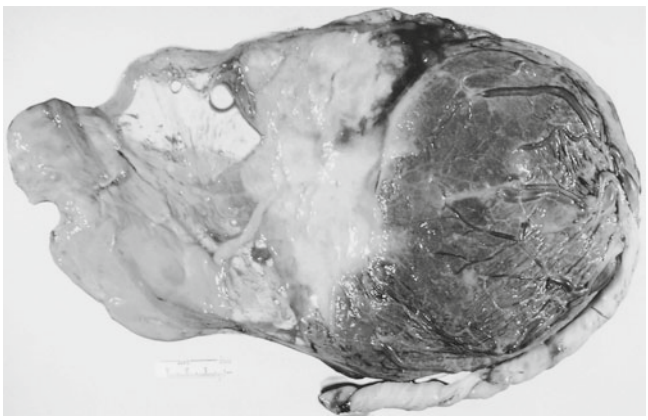


Fig. 25.65 Typical fetus papyraceus with cord visibly attached to the infarcted twin placenta (DiMo). The surviving twin had scalp defects

numbers surveyed, rather more abnormalities were present in surviving twins when one twin had died earlier (Pharoah et al. 2009).While not addressing the neurodevelopmental sequelae of fetal demise in monochorionic twins, Graef et al. (2006) followed the largest number of TTTS twins up to 3 years of age. They had normal outcomes in 86.8% and major defects in 6% of their TTS twins. In a recent publication, Lopriore et al. (2009a) related that neurodevelopmental defects are more common in patients with high "Quintero stage," low gestational age at birth, and late laser ablation therapy. Numerous additional studies have addressed this important question of CNS damage to the fetus of TTTS. They are easily accessed in Pub Med, but these issues are as yet only partially resolved, although they are of importance for the design of further investigations and for legal purposes, as doubtless there is an increased risk for CNS damage after one monochorionic twin has died.

This author (KB) has had a long-standing familiarity with the consequences of fetal demise and CNS damage in the survivor; he was the initial person involved in the tragic case recorded at length by Werth (1998) and has been involved in many legal battles to explain this unusual phenomenon of CNS damage after demise of one twin. While initially postulating the possibility of DIC from the dead twin's circulation (Benirschke 1961) in a complex case, he was relieved when sonographic Doppler flow evidence was produced to indicate that "back-bleeding" into the vasculature of the demised twin may account for significant CNS hypoperfusion and consequent destruction, as was the case in Eng and Chang (see Kormann 1869; Jou et al. 1993). Added to that, since many such twins are markedly premature, their probability of developing periventricular leukomalacia is enhanced anyway. Moreover, when the placentas are examined in recent twin deaths, the pallor of that fetus' region that was once the recipient (and plethora of the donor's) territory is impressive (see Benirschke and Masliah 2001). It is of course of concern that such events take place despite the generally superior success of laser ablation of TTTS. The feature to be addressed next, however, is completely speculative, but it is my opinion that it needs to be explored as it may be capable of being changed. As is well known to all the obstetricians who undertake laser ablations, often large quantities of amnionic fluid are being removed (I have seen up to 5,000 mL). This is done in anticipation of reducing the risk of further dilatation of the

endocervix that results from the hydramneic pressure. This intrauterine pressure can be measured, as was done in six cases of severe TTTS between 22 and 28 weeks' gestation by Hartung et al. (2000). They found similar pressures in donor and recipient, as expected. Before amniocentesis, the pressures reached 47 mmHg, and following drainage of 1–3,000 mL of fluid, the pressure sank to 14–26 mmHg. I speculate that this pressure is not only felt as pressure upon the fetal placental circulation but also as pressure upon the fetal head. In these early stages of gestation, the head is readily compressed and, similarly, decompressed. Thus, when suddenly large quantities of fluid under pressure are removed, perhaps the reduction of pressure upon the head could decompress its cerebral vasculature and induce focal hemorrhages. This has been somewhat supported by the very irregular expansion of the superficial placental fetal blood vessels after rupture of membranes. At least this possibility warrants further exploration in patients whose amnionic fluid is removed or in cases where such reduction of fluid is not being practiced at laser ablation. Careful recording of the amounts of fluid removed is rarely done, and there are no studies to record the CNS outcome of the cases that have unusually large quantities of fluid removed.

When maceration is advanced, the fetus may have the appearance of a **lithopedion** (Fig. 25.66). This feature is more commonly found when a fetus is retained for months beyond the expected gestation; indeed, it need not even be a twin (e.g., El-Sherbini 1963). The formation of a lithopedion is particularly commonly described in retained fetuses of nonhuman primates, e.g., Mueller-Heubach and Battelli (1981), and Swindle et al. (1981). Miller and Dillon (1989), who cited relevant literature on the frequency of lithopedion, estimated that perhaps 400 cases had been described. They presented the case of a 94-year-old woman with lithopedion that had been present for probably 61 years without doing harm. One of the most unusual placentas of a presumed former twin in our collection is depicted in Fig. 25.67. It is the placenta of a normal infant at term, with marginal insertion of the cord. In the center of the larger placental mass was what appeared to have been the site of insertion of another cord, with fetal vessels radiating to it. No twin was found, as was also the case with Moshiri et al. (1996), who found 16 cases of lithopedion reported in the literature. They added another case, occurring in an 86-year-old woman and presumably having originated 44 years earlier. Not to be outdone, Speiser and Brezina (1995) found a lithopedion in a 92-year-old woman that had been present presumably for 60 years. It had the size of a 31-week gestation fetus.

On occasion, a large fetus papyraceus presents with dystocia at delivery (Leppert et al. 1979). A fetus papyraceus may also be one of triplets (Roos et al. 1957; Benelli 1962) (Fig. 25.43). It has also been reported to us that a triplet placenta was associated with two fetus papyracei (Shih personal communication; see also Esposito 1963). They may be of monochorionic or dichorionic gestations; congenital anomalies other than acardia have been occasionally identified on dissection. The co-twin of a fetus papyraceus may also have anomalies, such as microcephaly, absent ear (Roos et al. 1957), gastroschisis (Weiss et al. 1976), ileal atresia (Saier et al. 1975), or pulmonic stenosis (Baker and Doering 1982;

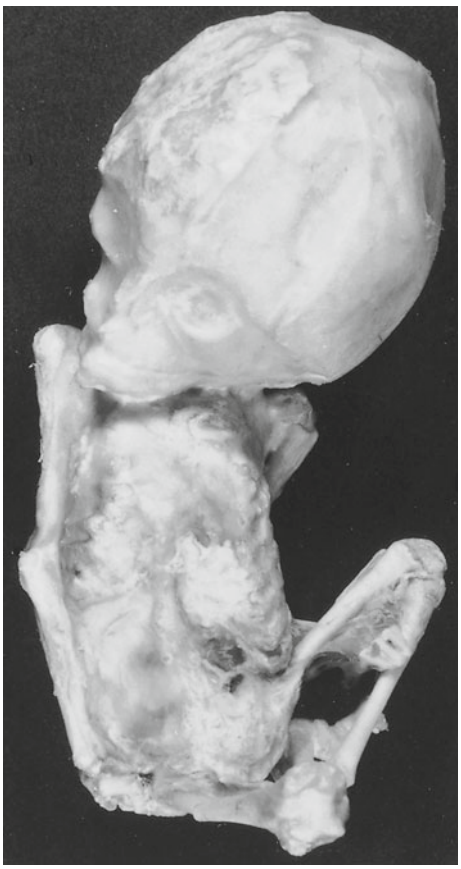


Fig. 25.66 Fetus papyraceus with the appearance of a lithopedion

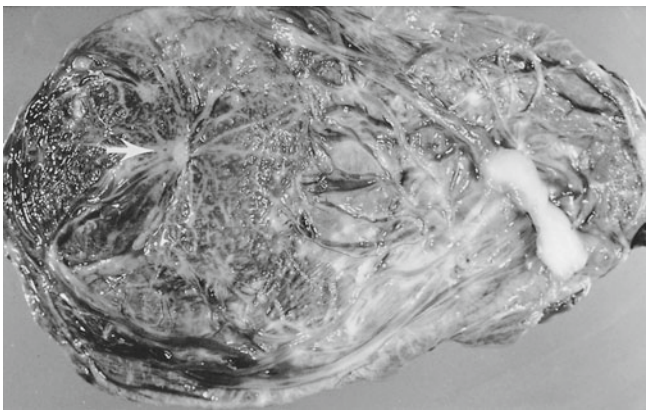


Fig. 25.67 Term placenta with near-marginal insertion of the cord. At the *arrow* is a structure that has the appearance of a second cord, with fetal vessels radiating toward it. No twin was found

review by Szymonowicz et al. 1986). In a discussion of a case of ileal atresia, Sander (1983) drew attention to the possible cause of these anomalies. He suggested that they may have a prenatal thrombotic etiology, in analogy with the phenomenon of DIC discussed above. Whether the occasional scalp lesions in co-twins of fetus papyracei are analogous to the aplasia cutis described by Mannino et al. (1977) is not clear. Demmel (1975), who reviewed all types of neonatal skin defect, does not mention the occurrence of macerated co-twins with these cases, but then, the placenta was probably not examined in his somewhat older case population. A case similar to that of Mannino et al. (1977) was presented by McCrossin and Roberton (1989). Although their case was complicated by toxoplasmosis, the extensive skin defects of this neonate were essentially similar to the aplasia cutis described by Mannino et al. They were also in the process of healing at birth, and as early as 18 weeks' gestation a macerated, much smaller twin was demonstrated sonographically. Lemke and colleagues (1993) described extensive aplasia cutis in a twin associated with a dizygotic fetus papyraceus; regrettably, the placenta was not studied. Interestingly, O'Donoghue et al. (2008) reported two instances of aplasia cutis following laser fetal ablation surgery among 30 complex monochorionic gestations. Better follow-ups of these now frequently undertaken laser ablations may yield more such cases in the future.

Innumerable reports of fetus papyracei have been published in the literature. The bulk of these cases from the older literature may be found in the comprehensive review by Kindred (1944) and publications of the material from the clinics of Litschgi and Stucki (1980), Yoshida and Soma (1986), and Johnson et al. (1986). Kindred reviewed 150 cases that had been published up to 1944. Of the 141 cases with adequate information given, 66% were dichorionic twins, and three cases were MoMo twins. Mills (1949) was critical of many of Kindred's concepts. He reported three sets of monochorial twins, one of which was macerated. He wanted to separate mummified from compressed fetuses when many authors make no such distinction. In our opinion, that question is moot. Litschgi and Stucki (1980) observed five dichorial and eight monochorial (one MoMo) twins. They suggested that when a macerated twin is recognized, delivery should occur by the 39th week. That this advice is not uniformly accepted was mentioned earlier in the chapter.

For unknown reasons, death of the other twin may follow when a fetus papyraceus is present (Camiel 1967; Yoshida and Soma 1986). Forman (1956), who described a case with dichorionic placenta, stated that fetus papyraceus was first mentioned by Pliny (70 AD). Johnson et al. (1986) attempted to ascertain the incidence of fetus papyracei in 34,677 deliveries from their hospital. A total of 515 twins were observed; of which, 27 (5%) had a single intrauterine fetal death; 16 of 25 live-born co-twins survived (64%). The placenta was monochorial in 70%. One survivor had multiple infarcts, another had a gangrenous leg at birth, and several had thrombi. Puckett (1988) discussed the management of pregnancies when a second trimester twin dies, and Chescheir and Seeds (1988b) observed the spontaneous disappearance of hypofibrinogenemia following in utero death of a twin. They suggested that prophylactic heparin therapy is not warranted when one of twins dies. Enbom (1985), who reported two cases of antenatal death of one of DiMo twins, was also fearful of this thrombotic complication and reviewed the literature. The survivors did not show sequelae of DIC. Foot necrosis and thrombosis of placental vessels were recorded in the survivor after fetal death of one twin by Margono et al. (1992). That this can occur in the living recipient twin of TTTS was shown by Hecher et al. (1994a).They observed necrosis of digits while the donor twin was still living and attributed it to both the recipient's high hematocrit and "steal" because of the presence of a single umbilical artery. Bass et al. (1986) observed persistently elevated amnionic fluid AFP and acetylcholinesterase levels after death of one twin, findings supported by Streit et al. (1989).

Carlson and Towers (1989) also found that in 17 multiple gestations with fetal death of one twin they studied, there was significant risk to the survivor. Their review suggested that fetal death of one twin occurs as often as in 2.6% of multiple gestations and three times more often in monochorionic than dichorionic twins. This occurrence is the reason why Cox et al. (1987) have used fetal blood sampling in the surveillance of such surviving twins.

Szymonowicz et al. (1986) reported six cases of a monozygotic twin surviving with CNS defects after death of a co-twin 1–11 weeks before delivery. They also reviewed the 16 reports in the literature (with a total of 53 such cases) and concluded that delivery should be seriously considered when one twin dies in utero. In their survey of these cases, 72% had CNS defects, 19% had gastrointestinal (including liver and spleen) defects, 15% had renal lesions, and 8% had pulmonary lesions. Anderson et al. (1990) found not only CNS necrosis but saw also bowel injury in two of four cases with prenatal demise of a monochorionic twin. Szymonowicz et al. described placental thrombi in some of their cases and continuing hematuria that lasted 2 weeks in such a survivor, suggesting a continuing process that was initiated before birth. Their "vascular disruption" hypothesis suggested infusion of thromboplastins, but they gave no account of the placental vascular anastomoses of their cases. The report by Liu et al. (1992) of 41 cases with one prenatal death gave similar findings and suggested that exsanguination is the primary cause of injury to the survivor. Other aspects of intrauterine death of one twin are discussed in some detail by D'Alton and Simpson (1995).

25.13 Twin-to-Twin Transfusion Syndrome

The twin-to-twin transfusion syndrome (TTTS) is considered to be a specific entity in twins, caused by the unidirectional, prenatal transfusion of blood through A-V anastomoses in the usually monochorionic twin placenta. It occurs in approximately 10% of monochorionic twins with frequently dismal prognosis (Gul et al. 2003). A particularly good review of the various complications, the diagnosis of the syndrome, the hypothetical renin-angiotensin contribution, surgery etc. was presented by Habli et al. (2009) in a volume on Fetal Surgery. In TTTS, one twin is the "donor," and the other is the "recipient." Its severity totally depends on the nature and direction of the anastomotic circulation, but it is interesting that on rare occasion the villous tissue may not even be fused; Lopriore et al. (2006a) depicted three cases in which the placental masses seemed to be separated by membranes, and yet anastomoses were demonstrated. The syndrome was first clearly delineated by Schatz (1882, 1885), when he observed a set of monochorial twins with gross discordance in size and development. One was edematous and urinated many times before dying at 12 h of age; the other was a hypotrophic twin who never urinated and who had an empty bladder at death (53 h). The atrophic twin had decubiti of the knees and ankles, much like the aplasia cutis described by Mannino et al. (1977). Schatz (1882) had already suggested that the fetal vessels were anastomotic through a "third circulation" which he was subsequently able to demonstrate clearly by injection of the DiMo placenta. He hypothesized also that the anastomoses were the cause of the fetus papyracei. In fact, he had described the "stuck twin" from clinical observations alone. This "third" circulation was then clearly perceived as proceeding from one of the donor's superficial (terminal) arteries into a shared cotyledon, whence it drained into the venous circulation of the recipient (Fig. 25.68). This anastomosis is thus basically a capillary one. It is not always easy to demonstrate unless careful injections are made with thin liquids of selected areas in the placenta. Even then, especially when in the severest cases, only tiny vessel connections are sought; injection may be difficult. It is highly speculative just how it is that such complex anastomoses of twin placental vascular beds develop and why they are so variable. Two particularly comprehensive reviews for clinicians that considered also the sonographic findings were written (in German and then in English) by Plath and Hansmann (1998), and Fisk et al. (2009). The first article also includes acardiac and fused twins and has extensive pictorial support. More detailed investigations of the pattern of vascular development in DiMo twins were undertaken by de Paepe et al. (2005). They sought to relate the patterns to magistral and disperse vascular patterns and found that in TTTS, magistral and mixed patterns were more

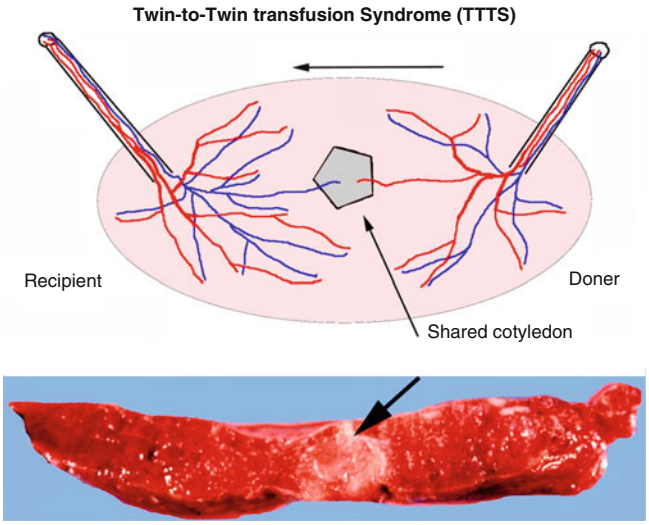


Fig. 25.68 (*Top*) Principal vasculature connection that causes the transfusion syndrome of MZ twins. (*Bottom*) The shared cotyledon here was injected with water; it appears blanched. Note that the right half of this placenta is slightly paler than the recipient's left half

common. Gaziano et al. (2000) produced a diagram of the hypothetical implantation of such twin blastocysts and suggested that the monochorionic monozygotic "twin blastocyst has an intrinsic polarity defect at implantation." This is difficult to comprehend, and it lacks anatomic support at this time. Perhaps the embryo splits with different cell numbers, and hence the onset of cardiac perfusion of placental villi differs temporally. All this is speculation at this time, and the only new insight that we can foresee how new data can become available is by descriptions of really early stages of DiMo twin specimens. With the advent of successful therapy by laser ablation of the connecting vessels by De Lia et al. (1985a), there has been a veritable flood of publications, some of which will here be considered in some detail. Insight has come from four or five different centers in Europe and the USA, centers that have dominated in the practice of laser therapy. Often, they have also differed in their approaches, in assessing the results, in the interpretation of the fluid mechanics of this syndrome and other aspects that pertain to interpreting the TTTS. Moreover, De Lia et al. (2000) have recently invoked that the syndrome is influenced by aberrations of the maternal metabolism and that these need to be corrected in order to optimize fetal survival. Despite experience with many laser ablations, Lopriore et al. (2009b) found that small (usually marginal) persisting anastomoses remain in 32%; most, however, were inconsequential.

Because A-V anastomoses may be multiple and of varying size, and they may also proceed in opposite directions, the syndrome is variable in its consequences. This point has been elegantly shown with Doppler ultrasonographic studies of pregnancies complicated with this syndrome (Pretorius

et al. 1988a). Pretorius et al. found it easy to demonstrate greater placental vascular resistance in one fetus, findings that were also shown in the therapeutic intervention in this syndrome by De Lia and Cruikshank (1989). Pretorius et al. (1988a) were unable to predict from their studies which was the donor, and they were also unable to anticipate the outcome. They confirmed that "the transfusion syndrome is an extremely complex dynamic physiologic state." Hecher et al. (1994b) delineated the Doppler signals of artery-to artery (A-A) anastomoses and later described the various anastomoses as they were identified during surgery (Diehl et al. 2001). In 126 cases of severe TTTS, they saw AV anastomoses in all, 31% had also A-A, and 12% had V-V connections. Denbow et al. (2000) as well as Umur et al. (2002) found that A-A anastomoses largely protected against the severe forms of the TTTS, while V-V connections reduced perinatal survival. Denbow et al. (2004) were able to determine modest flow rates in A-A anastomoses by Doppler waveform analysis. Similarly, Tan et al. (2004b) demonstrated the flow and concluded that "…detection of A-A anastomosis predicts higher perinatal and double survival in TTTS, independently of disease stage." In an interesting case report, Tan et al. (2004a) showed the acute first onset of TTTS in a twin gestation in which a previously patent A-A anastomosis became obliterated. A somewhat oversimplified classification (A to D) was proposed for monochorionic placental anastomoses by Bermúdez et al. (2002). Nevertheless, it demonstrated that, for all intents and purposes, the "deep" A-V anastomoses only are the critical ones; importantly, Huber et al. (2006) showed conclusively that laser ablation of communicating anastomoses is the best option for prevention of further damage. But other problems with this system as well as the method of demonstrating anastomoses for this classification were pointed out by Taylor et al. (2003). This reply to the paper addresses primarily the method of demonstration of anastomoses and the protective effect of large direct surface A-A connections. Needless to say, these points are critical for understanding TTTS and, especially, for appropriate therapy. An interesting and relevant case of triplets with TTTS was described by Eytan et al. (2005). They saw a set of triamnionic monochorionic triplets where one donor supplied two recipient fetuses and in whose placenta they demonstrated the many A-V anastomoses but were also able to identify a large A-A anastomosis between the two recipients and a small A-A communication between one donor and one of the recipients. Probably, it is the size of A-A anastomoses that is important in deciding whether a twin will or will not have TTTS. There have been a number of recent studies to suggest that A-A connections are common in TTTS; but when reviewing the photographs, the connections are vastly smaller than that shown in Fig. 25.18 and which is the commonest vascular connection in monochorionic twin placentas (see Murakoshi et al. 2003; van Meir et al. 2010; Suzuki 2010). Thus, the identification of A-V connections remains the most important aspect of placental examinations as it is their direction and number that assigns prognosis to the TTTS outcome.

In order to anticipate more adequately the timing and method of therapy, Quintero et al. (1999, 2003b) introduced a method of "staging" the TTTS (stages I–IV). It has also allowed better follow-up of the results and is now being widely employed, albeit often with modifications (Fisk et al. 2004). De Lia and Cruikshank (1989) found markedly greater vascular resistance in the donor. Bromley et al. (1992) suggested from their experience with 12 sets that, when clinical manifestations were clear-cut at 20 weeks, the prognosis with conservative therapy was poorer than when the syndrome was diagnosed later in gestation, and this has been confirmed by several larger studies recently (Stamilio et al. 2010; Bebbington 2010; Salomon et al. 2010; Baschat et al. 2010; Skupski et al. 2010). In general, TTTS has a poor prognosis if it remains untreated. A more recent review of the sonographic techniques, especially the findings at Doppler study and others employed in this differential diagnosis is to be found in the German publication by Plath and Hansmann (1998). Taylor et al. (2000a) attempted to predict the outcome of TTTS by prenatal sonographic features; absent A-A anastomosis, abnormal venous pulsatility, and reversed end-diastolic flow in the donor's artery had poor prognosis. Later (2000b) they were able to detect A-A anastomoses (better in later gestation) and "mapped" sonographically also the A-V connections (2000c). Ishii et al. (2004) have since shown that excessive flow in the umbilical vein of the recipient changes after laser surgery. But there is still much controversy over the presence of A-A anastomoses in stage III TTTS, as can be seen in the contribution by Taylor et al. (2004) and the detailed criticism by van Gemert et al. (2004). Indeed, what is observed endoscopically as specific color or pulsatility may not reflect in what is seen by injection studies later. Actually, very few publications of injected placentas from the postlaser studies exist, and these show that some of the A-V districts were actually "missed" at surgery (De Paepe et al. 2004). As indicated above, Bermúdez et al. (2002) have proposed a categorization of TTTS placental types; they proposed the following: (a) no anastomoses (0%), (b) only deep anastomoses (100%), (c) only superficial anastomoses (5.6%), (d) deep and superficial anastomoses (79.12%). They recommended this classification for the purposes of adjudicating results from laser surgery and thereby suggested also that, despite direct superficial connections, TTTS may still occur. Most recently, de Paepe et al. (2010) have examined deep A-V anastomoses in 284 DiMo placentas and identified their presence in 95% of TTTS placentas. They suggested that an "imbalance" was not imperative for the development of TTTS.

It is important to realize that the precise angioarchitecture of cotyledonary perfusion has not been sufficiently delineated and that this is extremely difficult to do. The focal injections with milk, water, air, etc. do not provide a permanent record that can be scrutinized minutely. Therefore, plastic injections have been performed such as shown in Fig. 25.21. Even when these are handled with a delicate digestion procedure, they are hard to interpret. The situation is worse when a placenta has had laser surgery and is examined perhaps weeks after the procedure. Wee et al. (2005) have attempted to correct this in a plastic injection procedure that is detailed in their report, and then they followed this by acid corrosion of monochorionic placentas (one with TTTS). Their findings contradict what has been generally assumed to be the case for "shared cotyledons." They suggest from their study that intercotyledonary fine anastomoses exist **below** the chorionic plate that cannot be seen externally by inspection. Wijngaard et al. (2007) have demonstrated this impressively. When examining the color pictures of Wee et al. (2005) in some detail, we conclude that the possibility of overlooked deep connections cannot be completely ruled out but also that these putative anastomoses are hard to characterize because the acid digestion has also removed the chorionic plate. If these subchorionic anastomoses truly exist (and the mechanism of their formation is hard to envisage), then this would make selection of shared cotyledons for laser ablation even more difficult than it already is. But also, the success with most ablations becomes more difficult to understand, and more work of this is needed (the laser-treated twin placenta with TTTS is shown in Fig. 25.84). Finally, when we examined placentas after successful laser ablation of shared cotyledons that are the cause of TTTS, we frequently found only very superficial villous infarction, while one would have expected that an entire fetal cotyledon would become infarcted when surface vessels are occluded. The best possible explanation for this unusual finding is that, as the placenta expands in thickness, adjacent cotyledonary expansion "undermines" the former infarct, and this is shown in the diagrammatic Fig. 25.83.

Clinically, the transfusion syndrome is typically first recognized by acute hydramnios that develops around midgestation. Many authors have made crucial observations since Schatz' description (e.g., Wurzbach and Bunkin 1949), and a summarizing review comes from Lopriore et al. (1995). When sonograms or radiographs are obtained after the hydramnios appears, the presence of a twin pregnancy is often recognized for the first time, although the sizes of the twins may already be significantly different (Schneider et al. 1985; Brown et al. 1989). In these cases, the placenta is later almost always found to be monochorial. The occurrence of acute hydramnios is considered to foreshadow a somber prognosis (Weir et al. 1979); one twin may show edema, best recognized sonographically in the scalp (Wittmann et al. 1981). The amounts of amnionic fluid vary enormously. Thus, we have learned of a remarkable case of DiMo twins with severe hydramnios; at 20 weeks' gestation, the amount of amnionic fluid was 5,000 mL (withdrawn); another estimated 2,000 mL was left unaspirated (K.L. Staisch, 1976, personal communication).

Not all authors agree with the concept that anastomoses may be the ultimate cause of the hydramnios in monochorionic twin pregnancies (Krauer 1964). Perhaps the first to voice his opposition to Schatz' notion of excessive urination of the recipient twin was Forssell (1912). He incorrectly interpreted that the placentas had "endarteritis" in their main stem vessels and that the cause of the hydramnios was a degenerative amnionic epithelial change. These changes are clearly secondary. There is so much variation in the clinical expression of the transfusion syndrome that care must be exercised before making the diagnosis on clinical grounds alone (Wenstrom et al. 1992). Magnetic resonance imaging (MRI) has been usefully employed for the differential diagnosis (Brown and Weinreb 1988). Not all hydramnios with twins, particularly chronic hydramnios, is due to the transfusion syndrome (Dorros 1976). Accurate sonographic differentiation of the dividing membranes should therefore be attempted (Mahony et al. 1985; Townsend et al. 1988; D'Alton and Dudley 1989). When acute hydramnios is found in a twin pregnancy, the second twin often has little or no amnionic fluid (oligohydramnios). This twin may move much less than the recipient, so the term "stuck twin" has been applied to this feature (Hashimoto et al. 1986; Brown et al. 1989; Patten et al. 1989a; Mahony et al. 1990). When Berry et al. (1995) evaluated hematologic and chemical parameters in such twins by cordocentesis, they found that all stuck twins had a minimally 2.4 g/dL less hemoglobin concentration. On rare occasion a stuck twin may result from triploidy (Wax et al. 1998).

To better explain the mechanism of hydramnios in this syndrome, Nageotte et al. (1989) proposed involvement of the atrial natriuretic peptide (atriopeptin) in the pathogenesis of TTTS. They found markedly elevated atriopeptide levels in the recipient and lower levels in the donor of this syndrome (2,251 vs. 43 pg/mL and 134 vs.79 pg/mL). They suggested that the hormone is released because of the recipient's hypervolemia, and that its elevated levels may be responsible for the renal effects. Talbert et al. (1996), as well as Bajoria et al. (2002, 2003), found elevated atrial natriuretic peptide and endothelin-1 levels in the recipient twin and inferred it to be a sequel of failing heart in the recipient, perhaps also being important for amnionic fluid regulation (see also Habli et al. 2010). Moreover, Crombleholme et al. (2010) have suggested that the recipient's survival improved when maternal nifedipine therapy was instituted 1–2 days prior to laser ablations.

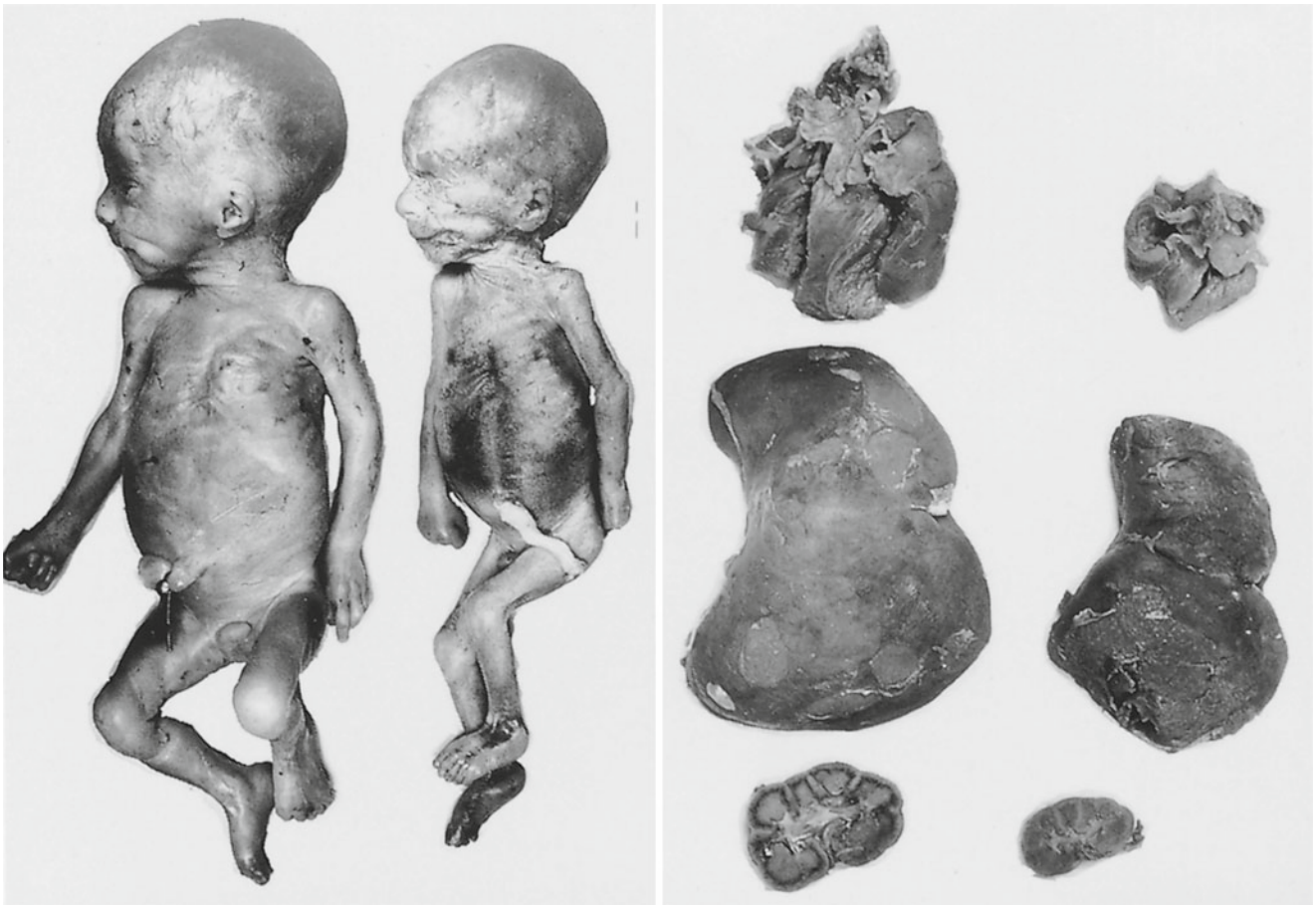


Fig. 25.69 Twins with the typical transfusion syndrome. MZ twins at 27 weeks, delivered after two amniocenteses (4,000 and 3,000 mL) had partially relieved the hydramnios. Recipient (*left*): 540 g, edema, heart 12.5 g, liver and one kidney less severely hypertrophied. Donor (*right*): 410 g, heart 2.7 g

This prenatal unidirectional exchange of blood results in deprivation of nutrients from one twin and excessive development of the other. The twins may be remarkably discordant, as seen in the classical example shown in Figs. 25.69, 25.70, and 25.71. One twin was dehydrated and anemic and possessed organs that were significantly smaller than expected for the stage of development. The recipient was plethoric and had much enlarged organs and higher mean arterial blood pressure after birth that quickly became normal (Cordero and Johnson 2002; Cordero et al. 2003). The discrepancy was particularly striking in the heart, but other organs were similarly affected, and Chmait et al. (2005) have recently described the catch-up growth of growth-restricted donors after laser ablation therapy. Lazda (1998) believed that the discordance of fibroelastosis occurring in two recipient twins was the ultimate result. In the absence of A-A anastomoses, the hydramnios leads to very premature labor or to rupture of the membranes, with delivery before the 30th week of gestation. Alternatively, one twin may die and become a fetus papyraceus (Fig. 25.72). In that case, the

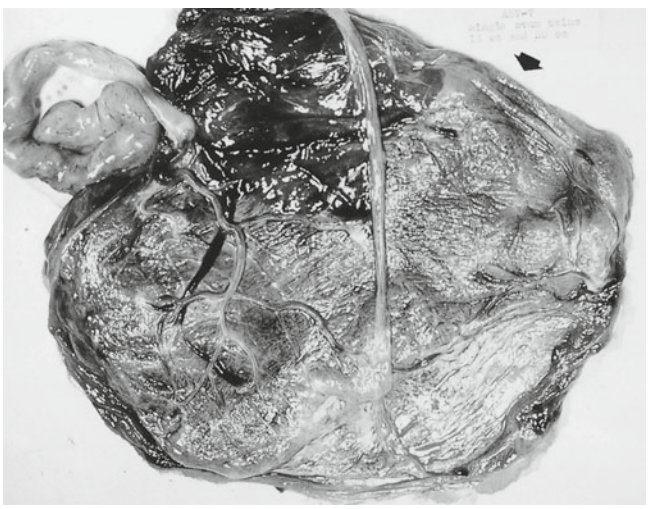


Fig. 25.70 Placenta of the DiMo twins in Fig. 25.69. Recipient had an edematous cord (*left*). The cord of the donor (*right*) is torn and was marginal. Note the area of "common villous district" (*arrow*; see also Fig. 25.71)

hydramnios ceases nearly immediately, and the pregnancy may reach term. The same is true when the anastomoses are obliterated by laser therapy (De Lia et al. 1990, 1993). Another alternative of the development of TTTS was described in some detail by Nikkels et al. (2002). They found acute onset of TTTS at 25 weeks following spontaneous thrombosis of a venous connecting branch.

The development of intracranial hemorrhage in the recipient has been witnessed to occur already in utero, and periventricular encephalomalacia in the donor of this syndrome may also take place (Hurst and Abbitt 1989). Other pathophysiological consequences of the syndrome have occasionally been recorded when prompt neonatal studies were undertaken. The set of DiMo twins with the transfusion syndrome whose data are shown next were delivered at 27 weeks' gestation, and they were studied unusually well. The mother had preeclampsia, hydramnios and placenta previa, and she had required a Cesarean section. Both twins developed hyaline membrane disease and intraventricular hemorrhage. Their data were made available to me by colleagues from Minnesota. Because the results are so impressive, they are shown here.

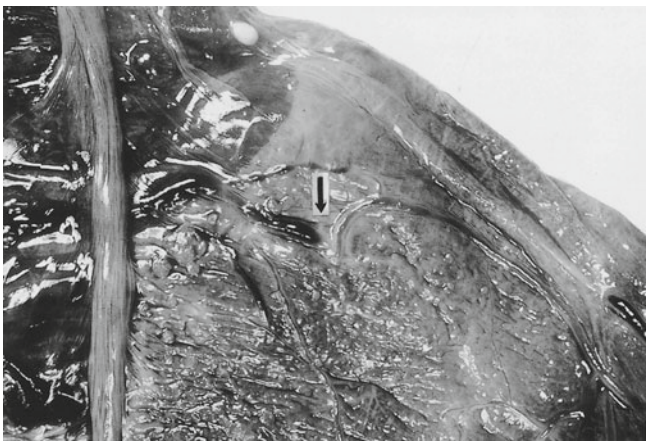


Fig. 25.71 Common villous district of the case in Figs. 25.69 and 25.70 is shown at the *arrow*. An artery from the donor (at *right*) dips into the placental tissue and emerges as a congested vein, coursing to the recipient (at *left*). The oval body at top is the remains of the yolk sac (single); there is also slight amnion nodosum in this cavity of the donor, who had oligohydramnios

Parameter	Donor twin	Recipient twin
Age at death (h)	25	28
Birth weight (g)	732	1,100
Head circumference (cm)	23.5	26
Initial hemoglobin (g/dL)	3.2	22.4
Initial hematocrit (%)	12	70.5
Blood pressure (mm Hg)	20	50
Liver at autopsy (g)	42.4	32.2
Pancreas (g)	1.5	2.1
Kidneys, two (g)	7.7	13.8
Adrenal glands, two (g)	3.9	3.1

Some other cases in which clinical values are given are listed as follows (weight in grams, hemoglobin in grams per deciliter, hematocrit in percent):

Source	Donor	Recipient
Klingberg et al. (1955)		
Weight	1,770	2,690
Hemoglobin	3.7	25.2
Hematocrit	87	
Sacks (1959)		
Weight	1,431	2,084
Hemoglobin	5.5	24

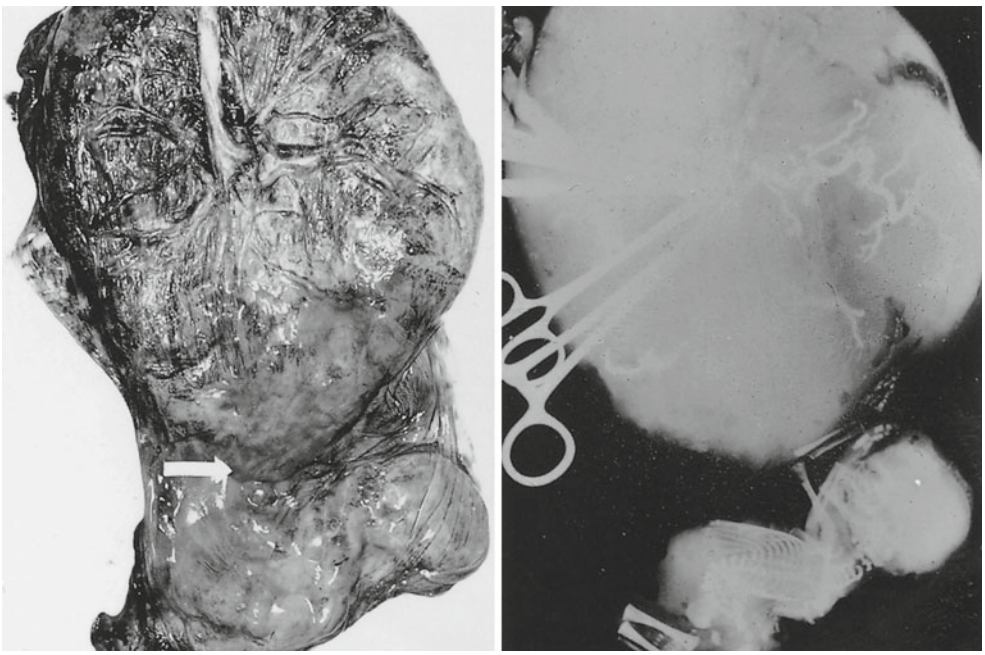


Fig. 25.72 A DiMo twin placenta with fetus papyraceus. Severe hydramnios at 20 weeks abated spontaneously. One twin died at that time: The pregnancy normalized, and a normal twin was delivered at term with this fetus compressus. Its placental portion was completely infarcted

Source	Donor	Recipient
Weight	1,424	1,843
Hemoglobin	18	30
Hematocrit	58	75
Weight	2,041	2,523
Hemoglobin	12.8	33
Hematocrit	93	
Weight	1,021	1,162
Hemoglobin	15	27
Hematocrit	41	80
Kresky (1964)		
Weight	1,900	2,600
Hemoglobin	11.3	22.1
Hematocrit	42	77
Bolens et al. (1968)		
Weight	2,410	2,510
Hemoglobin	25.9	13
Hematocrit	90	47

Many other reports of blood values at birth have been published, with wide variations. At times, the hematocrits reached astounding values. In a case referred to us, the plethoric newborn had necrosis of one leg due to arterial thrombosis. The other extremities infarcted shortly thereafter (Dr. J. Pritchard, personal communication). Partial necrosis of the left foot of a recipient twin was seen at fetoscopic laser surgery of a case of TTTS by Hecher et al. (1994a). The fetus had an absent right umbilical artery, and vascular "steal" was assumed to be the etiology. Polycythemia was believed to have been the cause of necrosis of the lower extremity in a recipient twin reported by Scott and Evans (1995). Similarly, Dawkins et al. (1995) found a foot necrosis due to hyperviscosity of a recipient twin whose TTTS had been managed aggressively with amniocenteses. Skin necrosis on the thigh, resembling aplasia cutis, was observed in the survivor of a transfusion syndrome case with laser surgery at 16 weeks (Stone et al. 1998). It is not certain how this defect occurred; it healed quickly after birth at 31 weeks. Some of the reports contain expressive color photographs of the twins (Becker and Glass 1963). There is no correlation between the infants' size, the length of gestation, and the degree of plethora observed at birth. Moreover, the plethoric twin may be the smaller of the two, as seen in Fig. 25.73. This discrepancy can be explained only when the anastomoses are carefully delineated, and the circumstances of birth are known. This topic was especially well discussed in the case reports by Donnenfeld et al. (1989), and Bendon and Siddiqi (1989). An equally striking case is shown in Figs. 25.74 and 25.75. The DiMo twins were both stillborn, but histological preservation was better in the anemic twin, and it is assumed that it died last. The weights of such twins (Figs. 25.74, 25.75, and 25.76) are important and are given next.

Organs	Anemic twin	Plethoric twin
Body (g)	550	410
CR length (cm)	20	17.5
Heart (g)	11.3	3
Lung (g)	11.9	5
Spleen (g)	1	0.5
Liver (g)	37.2	8.3
Adrenals (g)	2.3	1.4
Kidneys (g)	4.9	2
Thymus (g)	0.9	0.2
Brain (g)	70	40

The smaller twin was growth-restricted because of its velamentous insertion of the cord. This case does **not** represent a twin transfusion syndrome. The plethora was caused by reverse flow from the now-anemic twin, occurring through the large A-A anastomosis (demonstrated with milk injection) because of his longer survival. In several other cases of discordant twins that we autopsied, the donor was plethoric. Clinical information and sonography indicated in each case that the plethoric twin had died first; the anemic recipient died later (in one case from listeriosis). Autopsy confirmed the transfusion syndrome from the marked discordance of the cardiac sizes (Benirschke 1992, 1993; Benirschke and Masliah 2001). Indeed, it is our opinion that discordance of the relative cardiac size is **the** most important means for the diagnosis of the transfusion syndrome; it can even be recognized sonographically in dead twins. The fact that after birth of one twin (and after demise as well) rapid blood shifts may occur between the twins often negates the usefulness of hematologic values; furthermore, the placenta is frequently damaged for accurate analysis of anastomoses. This is forcefully supported by the studies on fetal organ growth of Naeye (1964a, b), Pridjian et al. (1991), and Barr (1996). Moreover, Lachapelle et al. (1997) found in all recipient twins they studied echocardiographically thickened ventricular walls, and Simpson et al. (1997) reported common cardiac dysfunction in the recipient twins, as did Bajoria et al. (2002). A thoughtful review of the diagnostic pitfalls comes from Weiner and Ludomirski (1994) who diagnosed the disease by finding divergent hematologic values from prenatal cordocentesis. They also showed that amniocentesis did not alter the degree of blood shunting between the twins. The ventricular hypertrophy of recipient fetuses, of course, is well known. But because of a variety of other cardiac complications such as pulmonic "atresia," tricuspid insufficiency, Doppler flow abnormalities, etc., another system of "scoring" (staging) TTTS than that advocated by Quintero et al. (1999) was suggested by Rychik et al. (2007). This is of special relevance as currently there is discussion of whether the TTTS of Quintero stage I cases should have laser ablation therapy. The question arises because some such twins will pursue a reasonably normal course (O'Donoghue et al. 2007). Thus, perhaps another

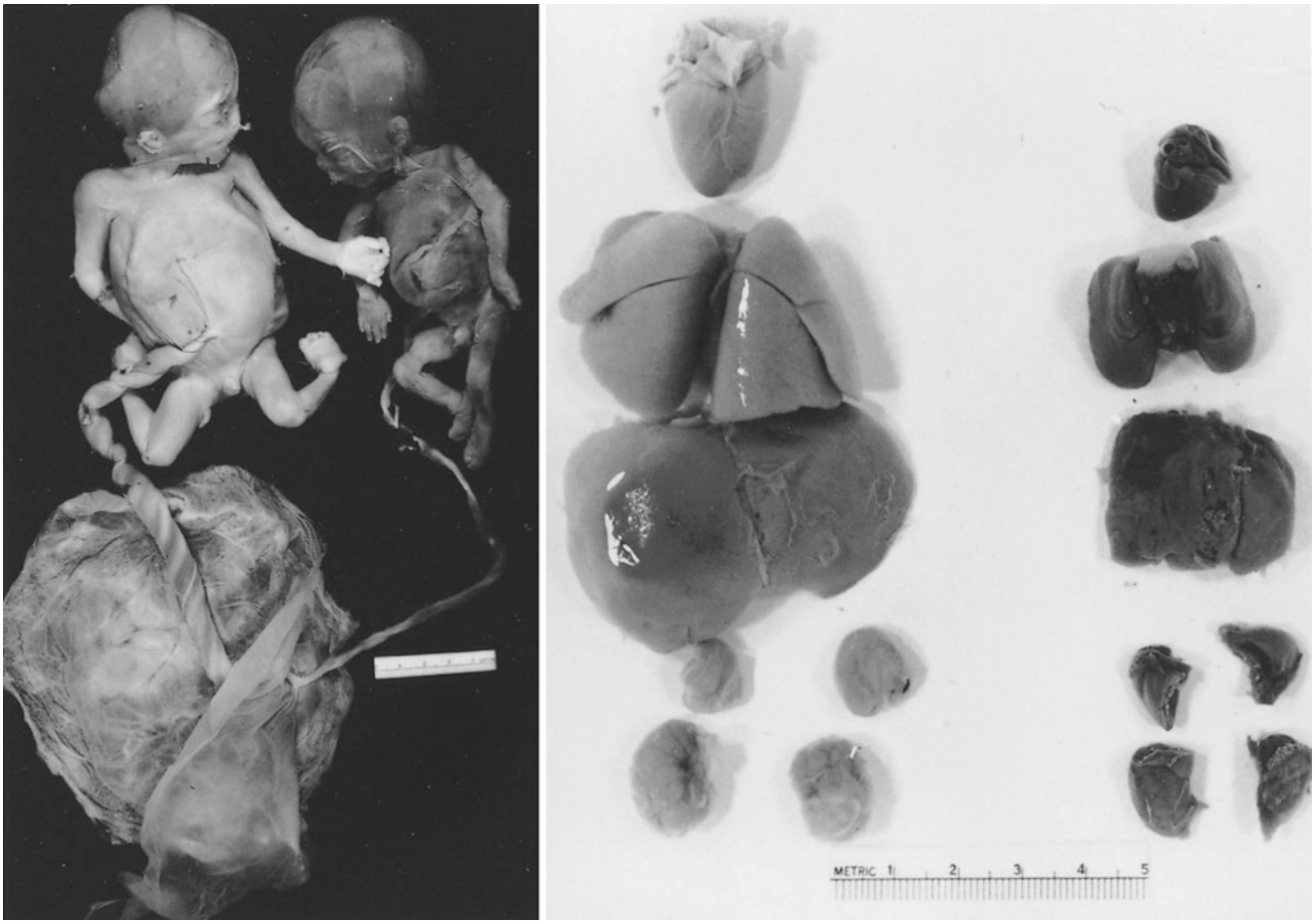


Fig. 25.73 Macerated DiMo twins with the transfusion syndrome at 28 weeks' gestation. The donor (B) is plethoric; the recipient (A) is edematous and pale. (A) 285 g, 15 cm CR length, heart 3 g, lungs 10 g, liver 17.5 g, kidneys 1.5 g. (B) 189 g, 13 cm CR length; heart 0.7 g, lungs 3 g, liver 4 g, kidneys 1 g. The plethora of twin B is thought to be due to this twin's earlier death, with exsanguination of A into B

system of scoring cases has more discriminating characteristics; the disparity of the two staging systems is shown in this chapter. Improvements in the scores are evaluated by Barrea et al. (2006), and Hyodo et al. (2003) evaluated the frequency of cerebral palsy in relation to cardiac function. These issues are currently under active investigation, and the resolution cannot be foreseen.

Several authors have addressed similar unusual findings. Lehndorff (1961), who also reviewed the relevant literature, assumed that in most cases, the transfusion takes place during the terminal periods of delivery, when pressure changes occur because of uterine contractions. Klebe and Ingomar (1972) also believed that much of the transfer occurs during labor. With variable cord clamping practices, it may occur immediately after birth. We have seen a pertinent case. New term twins with significant birth weights had hematocrits of 32% and 63%, respectively. The smaller twin was plethoric and had no problems; the larger twin was anemic and required transfusion. The smaller twin had velamentous insertion of his umbilical cord, with much old retromembranous hemorrhage behind the cord insertion. Injection of the DiMo placenta showed that two large A-A anastomoses existed, in addition to A-V shunts. The villous blood content appeared to be similar, but the smaller twin's placental portion was much smaller. Our interpretation was that the growth-restricted twin (because of the velamentous cord insertion) was eventually unable to withstand the blood pressure column that exerted from the larger twin and that took place through the A-A anastomoses; he thus became plethoric, perhaps during the terminal stages of labor. No cardiac hypertrophy was found in the larger twin; there was no hydramnios, and the fact that this pregnancy went to term suggested that it was not the classical twin transfusion syndrome. Features of long-term circulatory aberrations include cardiac hypertrophy, thromboses, and the presence of nucleated red blood cells. These findings bespeak the prolonged prenatal problem of adjustment to different circulatory phenomena.

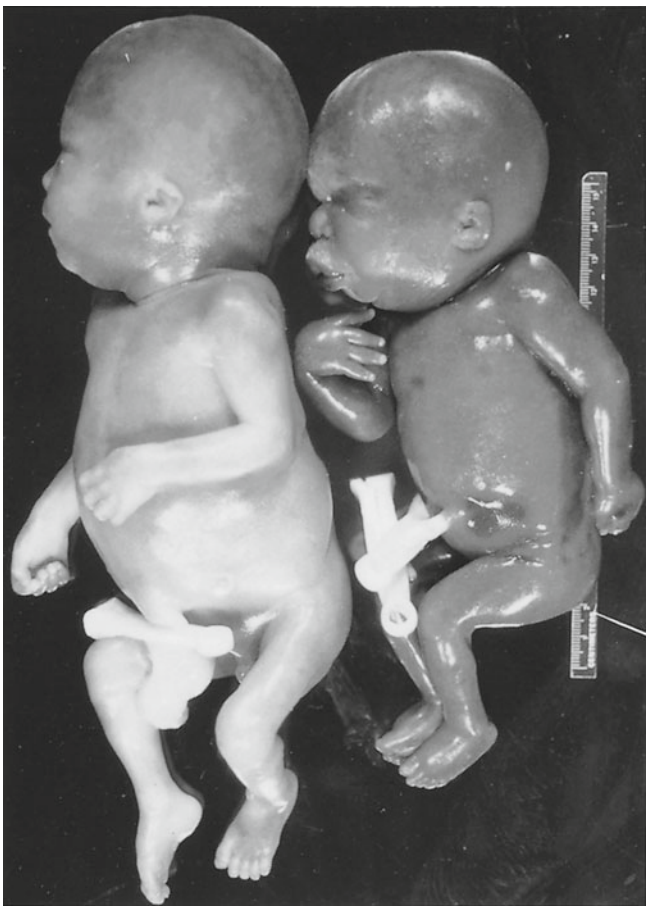


Fig. 25.74 DiMo twins, the smaller being severely plethoric. The smaller size of the twin at right is due to the velamentous insertion of the umbilical cord

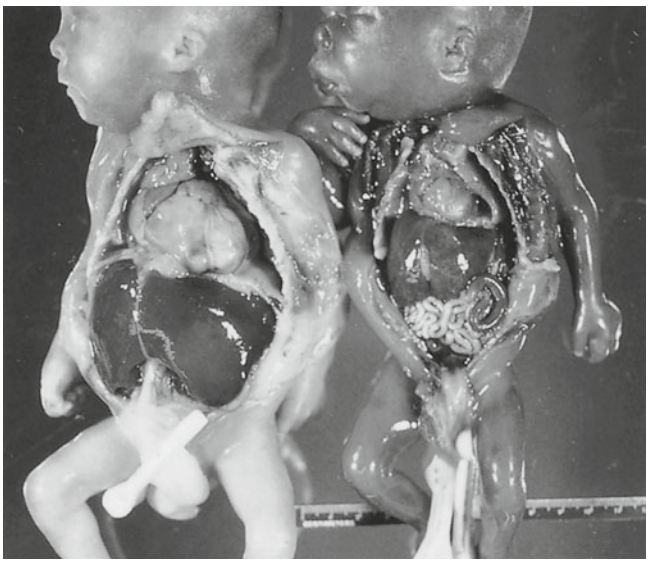


Fig. 25.75 Same twins as in Fig. 25.74. Note the smaller heart in the smaller and plethoric twin (*right*). See text

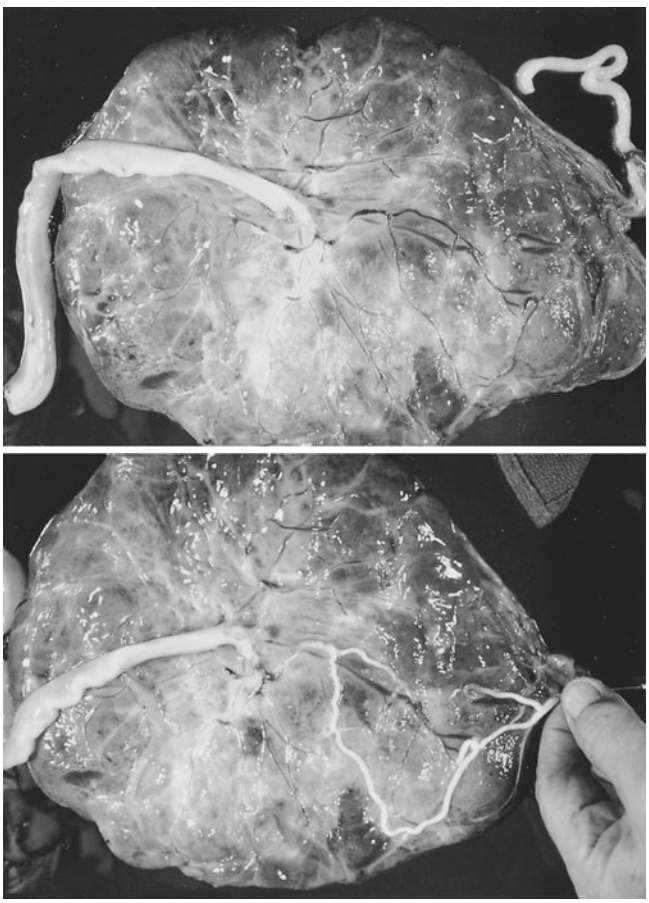


Fig. 25.76 Placenta of twins in Figs. 25.74 and 25.75. One large A-A anastomosis exists. Through this anastomosis, the larger twin, who died last, must have exsanguinated into the plethoric twin. This situation is **not** the transfusion syndrome

The youngest specimens that we have observed to have signs of a well-established circulatory imbalance were a set of DiMo twin abortuses of about 10–12 weeks' gestation (Fig. 25.77). Although those twins were still similar in size, their hearts were already grossly discordant. In another specimen of stillborn twins at 15 weeks, the plethora of the recipient was evident, and the cardiac hypertrophy already well expressed (2.28 vs. 0.67 g). Despite this marked discrepancy, the bodies were virtually identical in their sizes and weights. The differences of fetal size commence later in gestation, usually after 25 weeks (see also Benirschke and Masliah 2001). Another case of TTTS at 11 weeks was reported by Sueters et al. (2005) and was accompanied by an impressive color photograph. Aherne et al. (1968), and Arts and Lohman (1971) reported that the anastomoses in "typical transfusion syndrome" twins are usually transvillous and do not involve the larger surface vessels. It must be reemphasized that the mere plethora of one twin and anemia of the other do not necessarily signify the existence of the transfusion syndrome. To make the diagnosis of the transfusion syndrome, it is important that the twins be of different size, and as minimal

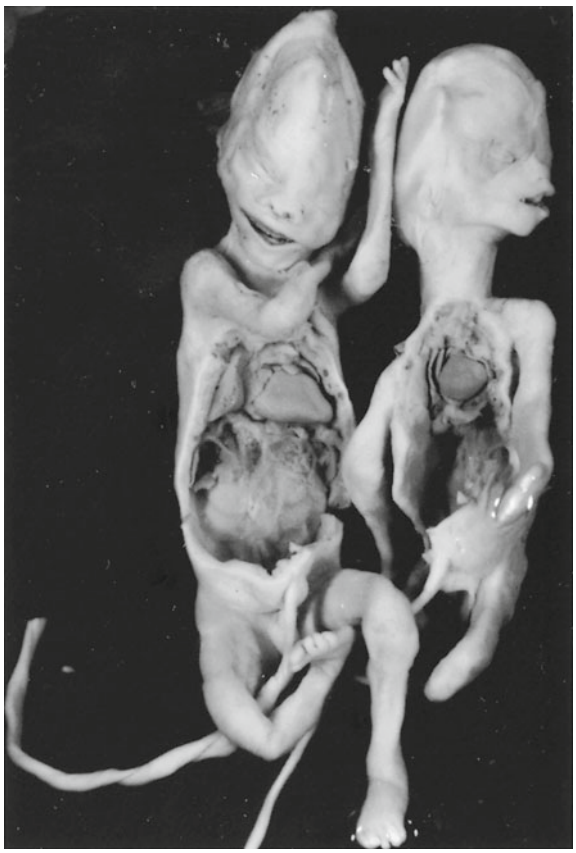


Fig. 25.77 DiMo twin abortuses with the transfusion syndrome, at about 11 weeks' gestation 31/20 g; 8/7 cm CR length; and hearts weighed 440 and 193 mg. This picture is the earliest evidence of the transfusion syndrome, with marked cardiac enlargement but relatively few bodily differences as yet

criteria, they should have different heart sizes as well. It is clearly possible that large A-A or V-V anastomoses allow rapid transfer of blood when pressure relations change during parturition, and that the anastomoses can result in anemia or polycythemia, but differences in blood values alone do not justify the term "transfusion syndrome." Indeed, there is much argument as to what clinical parameters to use when designating a set of twins as having the transfusion syndrome. In some opinions, it is a hemoglobin difference of more than 5 g/dL; others also wish to include a coincident weight difference of more than 20%. These aspects were discussed by Danskin and Neilson (1989), who studied 178 consecutive twin pregnancies with a variety of parameters. They concluded that generally acceptable guidelines are not yet available, as dichorionic twins with such differences were found in their series who clearly did not have the syndrome.

Quantitative placental studies have rarely been undertaken on the placentas of the transfusion syndrome, although Fick et al. (2006) showed that "unequal sharing" is an important aspect of monochorionic placentation and that it relates to fetal growth. Perhaps, they speculate, this is related to the type of cord insertion, but we wonder whether it could ultimately be the result of an unequal partition of the embryonic mass. Sala and Matheus (1989) have addressed this issue also with a relevant case. They found that the plethoric recipient had thinned trophoblastic villous covering and that the villous vessels were markedly distended. In contrast, the anemic "donor" had thick trophoblast and frequently "empty" villous capillaries. They also undertook a stereological study of the villous architecture and provided quantitative data of differences in villous development. Their case is unusual in several ways. For instance, the hydramnios that one might have expected was apparently not present; it was presumably absent because the pregnancy came to near term. That is distinctly unusual for the untreated transfusion syndrome. While there was the expected marked difference in neonatal sizes (2,470 vs. 1,920 g), hemoglobin levels (29.3 vs. 10.0 g/dL), and hematocrit values (75% vs. 24%), the placenta had an A-A anastomosis. The smaller twin had velamentous insertion of the cord. The fact that there was an A-A anastomosis and that the pregnancy was carried to 36 weeks' gestation makes this observation less typical, and the data may not fit the usual cases of the immature gestation with the classical syndrome; it would now be classified as "selective intrauterine growth restriction" (SIUGR). Bendon (1995) made a thorough study of 21 monochorionic placentas with injection of different colors. His findings indicated that the placental features are complex in the TTTS and that placental weight correlated with fetal weight, while hematologic values were often erroneous. Because of this remarkable complexity van Gemert and Sterenborg (1998), and van Gemert et al. (1997, 1998a, b) and Talbert et al. (1996) have constructed dynamic computerized models in order to understand the contribution of different types of anastomoses to the TTTS. They help in understanding the intricacies of the "third circulation" and must be read in the original papers because of their complexity. It is likely that through greater accuracy of Doppler flow observations in the placental surface vessels of monochorionic twins (see Gaziano et al. 1998) and similar physical models, we will learn more precisely what pathological alterations of blood flow are most responsible for the syndrome. This will also help the laser surgeon in the elimination of the offending vessels. van Gemert et al. (1998c) have suggested how therapy based on knowledge influences outcome. Because the umbilical cord coiling index (Chap. 12) in the recipient twin of three cases studied was twice that of the donor, Strong (1997) suggested that this "pump" may have implications in the etiology of TTTS. How best to demonstrate the "third circulation" (i.e., shared cotyledons) is shown in Fig. 25.78. The always available milk was used to inject specific "suspicious" shared cotyledons. They are thus clearly distinguished.

The frequency of the transfusion syndrome is difficult to estimate, but observations suggest that it is more common

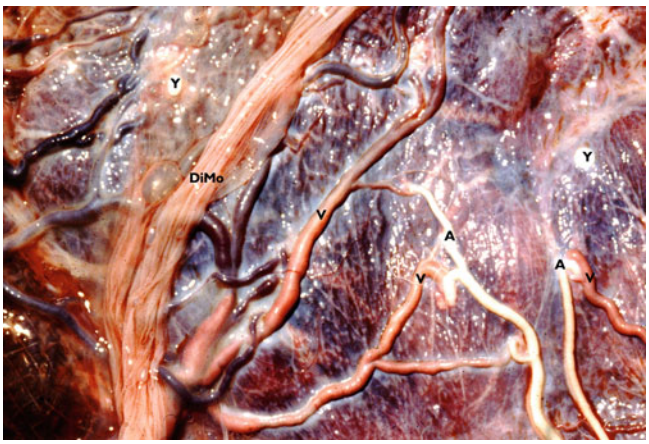


Fig. 25.78 DiMo twin placenta whose arteries were injected with milk. The "shared cotyledons" can be identified by the color change as the milk returns from the villous capillaries and is pink (*A* artery; *V* vein)

than is usually cited (Shah and Chaffin 1989; see also Lopriore et al. 1995). In general, figures of 15–20% of monochorionic twin pairs are cited. Urig et al. (1990) reviewed their cases of all twins and found the transfusion syndrome to have occurred in 1 of 30 twin pregnancies. They also emphasized that there is wide spectrum of severely affected twin pregnancies and less severe cases; thus, assigning a precise frequency and, accurately assessing therapeutic efficacy, is difficult. For unknown reasons, the syndrome has been reported to be very much more common in female twins (Nores et al. 1997). It is a fact, however, that MoMo twins, and especially the conjoined twins, are much more commonly of female gender. Possibly this influences the nature of anastomoses, and it just **may** be related to the process of X-inactivation.

Bebbington and Wittmann (1989) found 25 cases in their series of 595 multiple pregnancies, i.e., approximately 4% of twin gestations, which perhaps involve 5–10% of twins with monochorial placentas. Reviews of the syndrome are to be found in papers by Kloosterman (1963), de Marco (1964), Rausen et al. (1965), and Corney and Aherne (1965) and in more recent textbooks, but agreement of precise criteria is not easily obtained among the many points of view (Bruner and Rosemond 1993). Single cases from different countries make other literature available: Littlewood (1963), van der Kolk (1964), Verger et al. (1963), Tojo et al. (1971), Koranyi and Kovacs (1975), Tuncer (1970), Sekiya and Hafez (1977), and others too numerous to cite. When the condition is diagnosed before 28 weeks of gestation, the overall survival rate was found to be only 21% (Gonsoulin et al. 1990b). Hydrops correlated with poor survival in this study, but decompression by amniocentesis was not beneficial in the ultimate outcome. The condition has also been described in one of triplets and higher multiple births, as, for instance, in the triplets described by Sekiya et al. (1973), another by Chasen et al. (2002), and yet an additional case reported by Baschat et al. (2003). Berg et al. (2002) reported onset of TTTS at 11 weeks in an ART-conceived quadruplet gestation with quadramnionic, trichorionic placenta. The most remarkable and exceptional case of TTTS was reported by Quintero et al. (2003a); it described a male/female set of twins with monochorionic placentation and anastomoses.

Aside from the differences in weights and blood values, the transfusion syndrome has many other consequences. For instance, hyperbilirubinemia is often seen in the recipient (Conway 1964), and Reisner et al. (1965) found symptomatic hypoglycemia in the donor to be a frequent neonatal complication. They speculated that it may be an etiological factor for "mental subnormality" in the twin's future. Falkner (1965) challenged this idea on the basis that the investigators had inadequate data. Reduced placental perfusion in the territory of the donor was held to be responsible for the marked differences seen during placental examination of these twins (Aherne et al. 1968). They suggested that the small placental volume may also have consequences related to reduced nutrient retrieval from the placenta which, they deduced, would lead to fetal malnutrition. Conversely, one may speculate that the presumably lower blood pressure of the donor circulation prevents a normal placental expansion and that it may relate to the high incidence of velamentous cord insertion. The constant loss of blood proteins into the recipient twin through the A-V shunt may be another important factor for poor fetal growth. Oberg et al. (1999), for instance, showed remarkably different development of the renal tubular apparatus. They interpreted this to general hypoperfusion of the donor twin. Abraham (1967) has shown dramatic differences in the villous structure of the two twins' placental villi. He suggested that the term "parabiotic circulation," as used for experimental animal studies (Linke and Kuni 1969) and sometimes applied to this syndrome, is not an appropriate designation. The term was popular at a time when immunological phenomena were first studied in depth, but it should no longer be used for twins. Abraham (1967) showed the lack of uniform concordance of hemoglobins with birth weights of 53 pairs in an interesting way:

Twin	No. with low hemoglobin	No. with high hemoglobin
Big	6	24
Small	19	4

The remarkable anemia of one twin's placental portion and polycythemia of the other's placenta was studied by Michaels (1967) and Aherne et al. (1968). Not only are the macroscopic features striking in their color difference, but the histological structure of villi can differ substantially as well (vs. 25.79 and 25.80).The discordant organ development in twins with the transfusion syndrome has been vari-

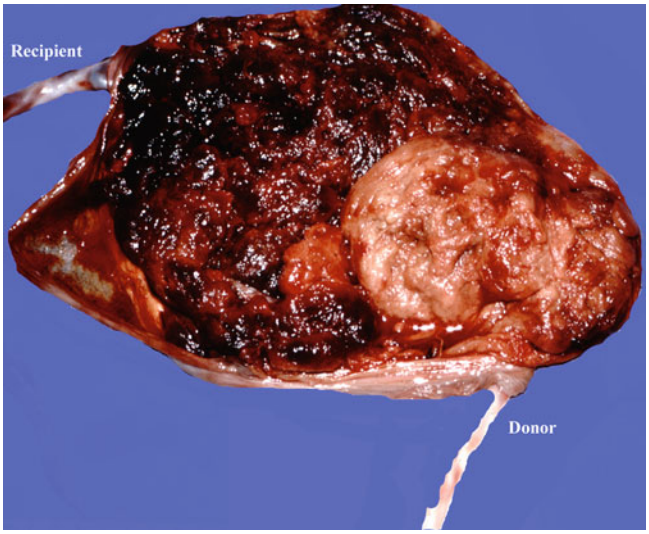


Fig. 25.79 A DiMo twin placenta at 34 weeks. Recipient had congestive heart failure (2,160 g, hyperbilirubinemia, blood pressure 70 mmHg). Its placental portion (*left*) is plethoric and thicker. The donor (anemic, thin portion of placenta at *right*) weighed 940 g and died neonatally (Courtesy of Dr. S. Kassel, Fresno, California)

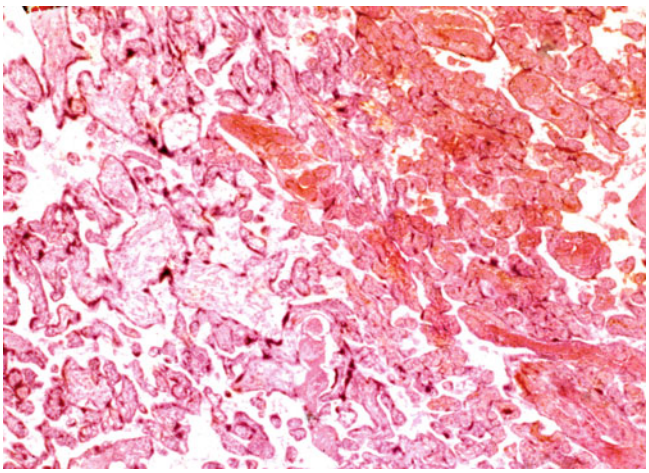


Fig. 25.80 Histological appearance of the two twins' placental portions. The donor's placenta (*left*) is much more immature in appearance than the villi of the recipient (*left*), which are smaller and congested. H&E, ×160

ously studied by several authors. Thomas (1962) found not only hypertrophy of cardiac muscle fibers in the plethoric twin but also that hyperplastic changes existed. Fesslova et al. (1998) observed echocardiographically features of cardiac hypertrophy in this condition, judged to be reversible. Barrea et al. (2005) studied the cardiovascular response of TTTS in more detail and with sophisticated methods. Their conclusion was that the recipient suffers more commonly damage has cardiac hypertrophy, predominantly ventricular dysfunction, and also that despite amnioreduction, the cardiovascular dysfunction persists. Naeye (1964a, b, 1965; Naeye and Letts 1964) undertook the most comprehensive organ analyses. Within this framework, Naeye was much concerned with hypoglycemia. By quantitative studies of tissue components, he found that the donor had significantly reduced, and the recipient had significantly increased cytoplasmic material. Differences of nuclear size and composition were less striking. He likened the findings to malnutrition in the donor and was particularly concerned with the reduction of brain weight. Recent studies of fetal growth parameters in various categories of twins (grouped according to placental type) confirm the important findings of Naeye (Pridjian et al. 1991). DiMo twins were found to "have a high degree of brain-sparing growth restriction in the smaller twin and cardiac hyperplasia in the larger twin, most likely caused by hemodynamic inequalities." When Chauhan et al. (2004) studied the chorionicity of 126 sets of twins sonographically in an effort to determine if IUGR related to the type of placentation, they found that monochorionic twins had twice as much discordance in growth when compared with dichorionic placentation. Winner (1963) asserted that the different development was perhaps due to unequal genetic contribution from unequal splitting of the twins. That opinion does not bear in mind the complex nature of the syndrome. It is perhaps an ill-founded criticism. Naeye correctly retorted (1963), for example, that the presumed erythropoietin production by the donor would be equally distributed between the twins and that the already plethoric twin would be stimulated to even greater hematopoiesis by infusion of blood from the anemic co-twin. Schwartz et al. (1984) described subcutaneous erythropoiesis in the donor twin, akin to the familiar "blueberry muffin spots" of newborns with cytomegalovirus and rubella virus infections.

Marx (1956) described the glomerular hyperplasia of the recipient twin's kidney in a report of an hydropic triplet with the transfusion syndrome. He conjectured that the increased perfusion of the kidney, under higher pressure, was responsible for this enhancement of glomerular development. He deduced, as did Schatz, that this situation led to the increased urination and hydramnios. The urine output (Kirshon 1989) and pathophysiology of the syndrome was further elaborated on by Achiron et al. (1987), but the direct cause of this glomerular hyperplasia remains unresolved. Studies in patients with polycythemia (Corrin 1961) have shown that it is not the cause in that disease. Glomerular hyperplasia has been observed in patients with tetralogy of Fallot (Bauer and Rosenberg 1960) and with cor pulmonale (Ellis 1961). In these situations, hypoxia was thought to be the most important etiological factor. In addition to changes in glomerular structure, Naeye and Blanc (1972) found dilatation of renal tubules. They deduced that excessive urination was the cause of the hydramnios. That the recipient urinates excessively had been decisively demonstrated by Schatz (1882). In the interesting discussion that followed that paper, Schatz expressed the opinion that the donor may have some amnionic fluid

remaining because of sweating. Shah and Chaffin (1989) found a 55% overall mortality due to this syndrome. An interesting observation was reported by Popek et al. (1993). They found three monochorionic twins with prenatal calcification of the pulmonary artery in the absence of valvular anomalies. Two twins were "pump" twins of an acardiac fetus, the other the "recipient" of the transfusion syndrome. The authors speculated that this complication was due to increased prenatal cardiac output (see also Samon et al. 1995; Wee and Muslim 2007). Mahieu-Caputo et al. (2000) and Kilby et al. (2001) studied the renin-angiotensin system in the kidneys of donor and recipient twins and found overexpression of renin in the donor's glomeruli. Galea et al. (2008) also felt that the so-called RAS components (renin-angiotensin system) may influence the clinical manifestations of TTTS in the twins. These authors not only measured renin and angiotensin levels, isolated RNA etc., but they did also immunohistochemistry in placental villi and kidneys. That such disparity of angiotensin and renin expression occurs very early in TTTS was shown by Guilherme et al. (2009) in stillborns at 13.5 weeks. Various renal sequelae were found and discussed extensively such as tubular apoptosis by De Paepe et al. (2003). They are secondary phenomena, however, not primary features of the TTTS. It might here also be mentioned that Bajoria et al. (2000), finding significantly different amino acid concentrations in the two twins, believed that this is an indication that the severe growth restriction of the donor may not be due primarily to the anastomotic loss of blood but that it is the possible result of impaired transplacental transport of amino acids. We differ with this interpretation.

We have twice attempted to recreate the transfusion syndrome in sheep, pregnant with fraternal twins. Having inserted intravascular catheters, we transferred daily 10 mL blood from the female to the male twin over 17 days. Our findings included male/female: 3,600/3,375 g; hearts, 24.5/23.5 g; livers, 96.5/86.0 g; spleens, 10.5/5.2 g; kidneys, 27/22 g; and cotyledonary weights, 440/370 g. The second experiment, done closer to term, gave similar results. Thus, one can simulate the transfusion syndrome experimentally and perhaps better understand the adaptations that occur subsequent to the twin transfusion. Wilson (1979) studied the postnatal growth of dissimilar twins and concluded that "monozygotic twins become progressively more concordant with age…while dizygotic twins became less concordant."

It was earlier stated that the recognition of twin-related hydramnios during early pregnancy has a bad outcome unless one twin dies. The transfusion then stops, and often the survivor is delivered near term and is normal (Fig. 25.72). At the other end of the spectrum, various management schemes have been proposed for the twins after their birth, e.g., that by Shorland (1971), which sought to correct the anemia, hypoglycemia, polycythemia, and hyperbilirubinemia. Before birth, incisive treatment is more difficult and controversial. The thoughtful review by Blickstein (1990) puts the various diagnostic modalities and treatment regimes into an unbiased perspective. Temporizing for a month by repeated amniocentesis and withdrawal of fluid is sometimes feasible for a while (Figs. 25.69, 25.70, and 25.71) but not for long (Feingold et al. 1986; Vetter and Schneider 1988; Lange et al. 1989; Elliott et al. 1991; Elliott 1992; Reisner et al. 1993). There is a large literature on this topic, and the results are not uniform. Nevertheless, when in an international trial of amniocentesis vs. laser ablation was conducted, it was stopped prematurely because the results were infinitely better with laser therapy (Senat et al. 2004). That publication (and the additional papers by Ropacka et al. 2002; Odibo and Macones 2002; Moise et al. 2005; Rossi and D'Addario 2008) reviewed many of the prior publications of various techniques (corticoids, amnioreduction, septostomy), and it is followed by a succinct editorial of Fisk and Galea (2004). At present then, careful sonographic evaluation, followed by laser ablation of the offending anastomoses, would seem to be the best means of treating TTTS. Presumably also, the results of therapy depend on the nature of the anastomoses and also on the timing of onset of hydramnios. Indeed, currently there is discussion whether so-called early-onset growth disparities of DiMo twins have different placental characteristics and different outcomes. Lewi et al. (2008) found that unequal sharing of the placenta was more characteristic of early-onset SGA and that late-onset discordance was more often associated with a better prognosis.

Garry et al. (1998) have shown significant pressure differences in TTTS. Some authors strongly advocate amniocentesis as therapy (Mahony et al. 1990; Urig et al. 1990; Elliott et al. 1991; Saunders et al. 1992; Dickinson 1995; Dennis and Winkler 1997), while Gonsoulin et al. (1990a) showed in a careful study that the 21% overall survival rate was not improved by amniocentesis when the syndrome is diagnosed before 28 weeks. Pinette et al. (1993) also believed to have shown that early aggressive amniocentesis is an effective therapy, but prolongation of gestation was minimal. Bromley and colleagues (1992) found only a 25% survival rate when the diagnosis was made before 20 weeks, more when the diagnosis was made later and when conservative therapy was instituted. Grischke and colleagues (1990) were similarly skeptic, and one wonders why the therapy is still being used at all when laser ablation has been so successful. Bebbington and Wittmann (1989) found that gestational outcome depends mostly on age at delivery and that amniocentesis may be beneficial. In a pregnancy in which hydrops and hydramnios had developed, Trespidi et al. (1997) were also more reserved although their results are fairly encouraging. Smith et al. (1997) provided some Doppler study evidence of "improved hemodynamics" after many amnioreductions. Despite this, there were many dysmorphic findings in the still small donor at delivery. Garry et al. (1998) measured intra-amnionic pressures in TTTS, before and after amniocentesis. It was

significantly higher than in normal gestations and was reduced to normal levels by amniocentesis, findings similar to those obtained by Meagher et al. (1995). In the editorial comments preceding this chapter, however, cautionary words are introduced that do not correspond with our views. It was suggested that hemoglobin differences in TTTS were not necessarily correlated with hydramnios, but the fact that exchange of blood through anastomoses at the time of delivery can obscure such data that were not considered. The accumulation of fluid is primarily the result of fetal urination, and this has been examined and modeled in great detail by several investigators (Umur et al. 2001a, b, 2002). It is too complex for consideration here. The developing hydramnios, of course, is the primary cause of premature delivery in untreated TTTS; rarely, it can also lead to uterine rupture. Tutschek et al. (2004) reported such a case where rupture occurred at 19 weeks, presumably because of previous uterine scarring. De Lia et al. (1985a) treated the mother of TTTS in utero with digoxin at 27 weeks. They observed reversal of fetal cardiac failure in the recipient twin. The fetuses survived after Cesarean section, which was done at 34 weeks. Parenthetically, it is worth mentioning that these authors estimated that 2,200 fetuses succumb annually in the Unites States from this syndrome alone. Moise (1991) and Jones et al. (1993) failed to arrest the syndrome in three pregnancies by administering indomethacin, while Al-Takroni et al. (1995) seem to have more success in their case. Another means of therapy is to divide the intervening amnionic membranes. Saade et al. (1995) did this in two cases with instant filling of the stuck twin's sac; they reported no outcome, however. In the nine cases done by Berry et al. (1997), no cord entanglement occurred, there was a change in arterial flow, but no real impact on survival seems to have occurred. Despite all precautions taken at selective fetal laser ablation therapy, the dividing membranes that are composed of two thin amnions only may be injured, and occasionally monoamnionic twins are created (Wijnberger et al. 2008 – abstract). In addition, amnionic bands can be created and fetal entanglement may result. Winer et al. (2008) have labeled this the pseudoamniotic band syndrome (PABS); of 420 treated twin pregnancies they identified 8 cases, all initiated in the recipient twin and usually (7 of 8) after demise of the donor twin. They discussed the possible manner of this syndrome without coming to clear answers, however.

Wittmann et al. (1986) chose to sacrifice the donor of a severe transfusion syndrome case at 25 weeks' gestation. They inserted a needle into the heart under sonographic guidance. After the fetus died, the hydramnios disappeared and the pregnancy stabilized. No obvious maternal coagulopathy developed, and the healthy 2,890 g survivor was born at 37 weeks. The fetus papyraceus weighed 180 g. The placenta was DiMo. Subsequently, Baldwin and Wittmann (1990) summarized their favorable experience with this procedure in three cases of the transfusion syndrome. Weiner (1987) had earlier reported a similar experience. In the days that long preceded sonography, we had unsuccessfully attempted a similar procedure (Benirschke and Driscoll 1967). Another failure was reported by Chescheir and Seeds (1988a). They filled the pleural space of the donor with fluid until there was cessation of cardiac activity. This maneuver normalized the urine output of the survivor, but the hydramnios did not abate. Infection terminated the pregnancy prematurely. One certain way of preventing CNS damage of one of the twins is cord ligation, as was practiced by Crombleholme et al. (1996) in the abnormal MZ twin affected by congenital heart disease. Others have recommended selective feticide by cord occlusion (Rossi and D'Addario 2009a; Lewi et al. 2006), but the pendulum has now swung to the more commonly practiced laser ablation of the A-V districts unless an acardiac fetus is present or other anomalies dictate cord ablation of one twin.

Under ideal circumstances, it may become possible in the future to selectively "obliterate" the interfetal vascular connections, which should then lead to complete normalization of the pregnancy. Schatz (1885) already suggested that occasionally, some vessels may thrombose and thus reduce further blood exchange. De Lia et al. (1985b, 1989) began experimentation with the obliteration of selected fetal surface vessels in experimental animals by treatment with neodymium:yttrium-aluminum-garnet (Nd:YAG) laser. They were successful with this procedure in sheep and rhesus monkeys and then successfully treated three patients with the transfusion syndrome (De Lia and Cruikshank 1989). Delivery occurred several months after the vascular obliteration; and marked improvement of urination in the donor, with expansion of its amnionic sac, occurred immediately. The placentas showed the scarred cotyledons supplied by the coagulated vessels. Such therapy is now the routine for most cases of the transfusion syndrome. De Lia et al. (1990, 1995) have published much greater details of their experience, including a set of triplets in other articles. These publications also provide additional insight into the instrumentation, methodology, and vascular findings in the twin placentas. In the meantime, DeLia, J.E has done more than 100 cases (1998, personal communication). The results have improved over time, and now at least 80% of patients can take one healthy child home after this therapy. The procedure is now referred to as "FLOC" (fetoscopic laser occlusion of chorioangiopagous vessels). In one case, the authors pursued the vessels across a tear made in the dividing membranes. But this disruption of dividing membranes may not be without hazard. As indicated earlier, amnionic bands may form, or the MoMo twins resulting may entangle their umbilical cords. In addition, the amnion, when disrupted, may adhere to the chorion at laser sites. The prenatal therapy by laser obliteration of vessels has since been practiced successfully by many other teams (Natori et al. 1992; Ville et al. 1992, 1995, 1998). It is now even possible to undertake the ablation

when anterior placentas are present, and with the exception of the complexity and the need for instrumentation, it is clearly the most decisive therapy for the transfusion syndrome. Currently, the evidence is that laser surgery executed by competent surgeons yields better results than repetitive amniocentesis (Ville et al. 1998). An unexplained finding in the transfusion syndrome is the recognition that the recipient has much higher levels of proteins, but that immunoglobulin G (IgG) levels were much out of line in a study by Bryan and Slavin (1974).When on occasion the laser ablation fails, this may be the result of failure to recognize all A-V shunts or due to the presence of unusual connections. Thus, Poch et al. (2005) have described such a failure and attributed it to the existence of a "direct A-V fistula" in the donor twin's vascular bed. Only once or twice before have such *direct* A-V connections been reported to exist in singletons. They are clearly exceptional. As mentioned earlier, TTTS can occur in triplet or higher number gestations as well. That they are also accessible to fetoscopic ablation was detailed by Sepulveda et al. (2005). Chmait and Quintero (2008) have added to this extensive literature by delineating factors of importance in doing such operative fetoscopy and the surgical management of TTTS. We have seen extensive thromboses of surface veins when numerous ablations were performed, but the outcome was deemed to be good and it was without embolic phenomena in the twins.

When ablations are accomplished successfully and when then the placenta is examined many months later after the TTTS has abated, we find that only small, subchorionic infarcts are found. They are shown in Figs. 25.81 and 25.82. From this finding, we infer that the "problematic" communications develop very early and affect only a small connecting cotyledon. One possible explanation for this is the subsequent formation of additional cotyledons and their undermining the early and now infarcted cotyledon as is shown in Figs. 25.83 and 25.84.

This chapter is not the place to review in detail all of the ultimate outcomes of twin pregnancies. One aspect, nevertheless, is noteworthy. Because monozygosity largely eliminates genetic effects, the transfusion syndrome has served as a model to analyze aspects of the etiology of mental retardation. Several investigators have found that the smaller of MZ twins has a slightly lower IQ than the larger twin (Kaelber and Pugh 1969; Hohenauer 1971; Babson and Phillips 1973). The larger the twins' size difference was at birth, the greater were the effects. Record et al. (1970) did not confirm these results using the data from the Birmingham Twin Study; they pointed out that the differences are postnatal in origin rather than due to monozygosity and placentation. Likewise, Fujikura and Froehlich (1974), and Buckler and Robinson (1974) studied the postnatal equilibration of MZ twins who had been born with marked natal differences. They found

Fig. 25.81 Small infarcted superficial cotyledon that has resulted from laser ablation many months earlier

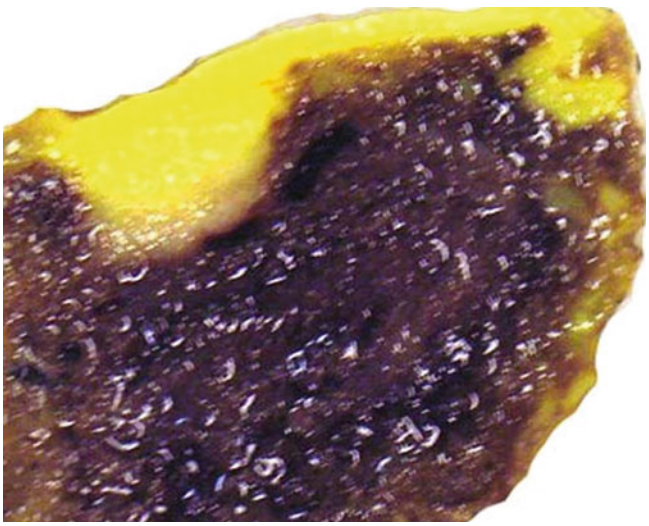


Fig. 25.82 Gross appearance of such an infarcted cotyledon, as shown in Fig. 25.81

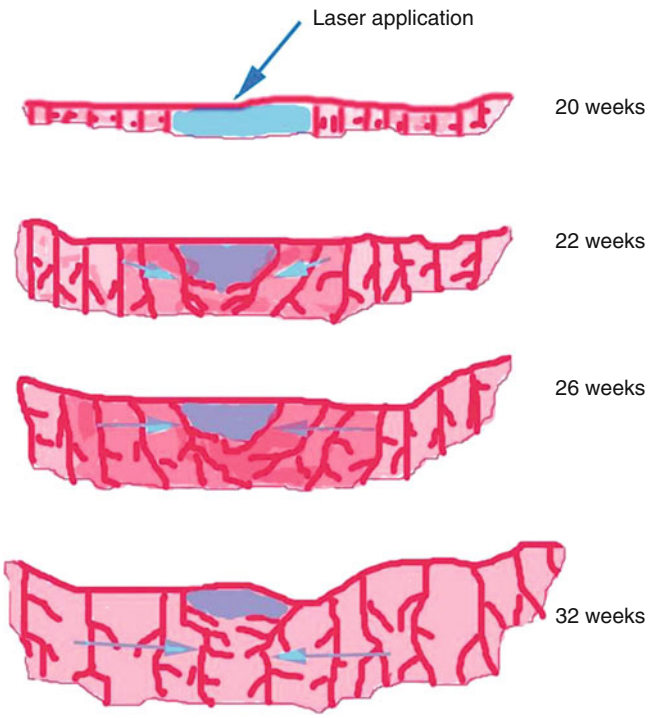


Fig. 25.83 Diagram to suggest the possible mechanisms that underlie the previous two pictures

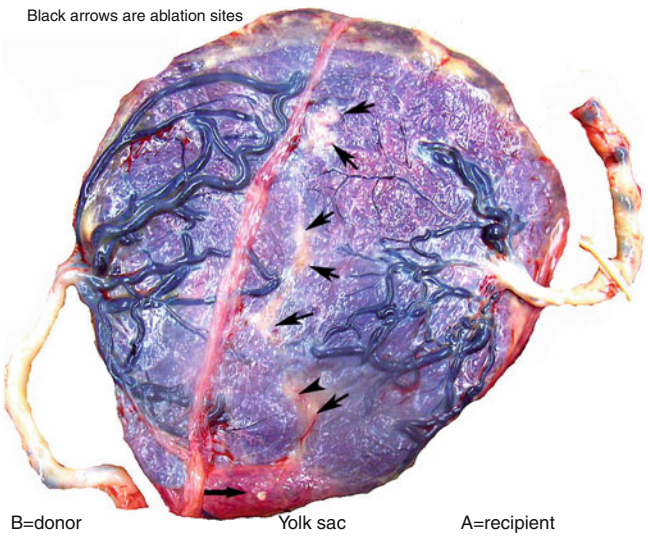


Fig. 25.84 Gross appearance of TTTS placenta after laser ablations had been done 3 months earlier. There are at least seven laser ablation sites at *arrows*. A single yolk sac remnant is present, as is often the case. The insertion of the donor's umbilical cord is marginally inserted

only "negligible differences in… intelligence and educational attainment." The complexity of the problem is exemplified by reanalyses of the various data published by Munsinger (1977) and his critic Kamin (1978). The former believed that prenatal influences can be shown to have this deleterious effect; the latter did not. Both affirmed that future studies of this vexing question must include placental data. Denbow and colleagues (1998) found CNS damage in both the donor and recipient of the TTTS and called for more detailed follow-up studies as well. The criticism of former studies is echoed by O'Brien and Hay (1987) in an incisive analysis. These authors found differences when male co-twin development was compared with that of female co-twins. They also studied the effect of placentation on handedness. Left-handedness is known to be more frequent in "birth-stressed" individuals, and it may be for that reason that left-handedness is more frequent among twins (Coren 1994). A good example of left/right-handedness of MZ twins is shown by Frothingham (1997/1998) in twins, one of whom suffered adrenal insufficiency but who was also opposite-handed and cut their hair on opposite sides. This topic, however, is most complex as was decisively reviewed by McManus (2002) in an excellent book.

25.14 Amniopatch

It has been the experience of obstetricians who perform intra-amnionic surgery that, occasionally, the site of entry into the fetal cavity does not "heal" and that leakage of amnionic fluid continues after the procedure. In order to avert continuous drainage and possible infection, a variety of protocols have been developed in order to "seal" the defect. Two large reviews consider this topic. Quintero (2003b) has employed platelets and cryoprecipitate, amnion grafts, and laser welding to eliminate the rent. In some cases, the region of presumptive healing was later examined fetoscopically. The experience is mixed; in some cases, good success was achieved, but it failed in others. Importantly, because of the presumptive rapid release of large quantities of vasoactive substances from the platelets, their quantity was reduced in later attempts. Devlieger et al. (2006) also used these agents and had similar sudden deaths of fetuses. They also described experimental sealing of membrane defects at the internal cervical os. It goes without saying that PPROM from ascending infection precludes such therapy. These contributions reviewed many earlier papers that were either experimental studies or used in attempts at sealing ruptured membranes. We have experience with one such case. The mother had IVF; rupture of membranes was spontaneous, and an attempt at amniopatch was made. The fetus died very shortly after the introduction of the platelets and cryoprecipitate, we believe from the sudden release of vasoactive contents of the platelets. The placenta was not inflamed, had markedly edematous and cloudy membranes, and a separate white sheet of coagulum had covered the fetal head. Histologically, it was eosinophilic and acellular. Other sealants are now being tested in vitro

by Cortes et al. (2005) who have much experience with prenatal surgery. They employed amnion and bioglue and followed this with tensiometry. Good results were obtained experimentally.

25.15 Acardiac Twins

Acardiac twins are the most severely malformed fetuses that one can imagine. They range from small, teratoma-like masses to large fetuses with a great variety of anomalies. The absence of a heart is not obligatory to the diagnosis of this entity, as a severely malformed heart is occasionally present. Schatz (1898) has called these twins then "hemicardia" or "hemiacardius," but Frutiger (1969) pointed out that this term is incorrect. He proposed the term "pseudoacardius" for those cases in which remnants of cardiac structures are found. A wide variety of names have been applied to this spectrum of acardiac fetuses; a veritable taxonomy was created, as in Schwalbe's and Schatz's writings. The most comprehensive treatise that encompasses all these attributes is the seminal book of Schatz (1898), who made the major contributions to our understanding of acardiacs. A total of 88 cases from Japan were summarized by Sato et al. (1984), and we have reviewed 49 acardiac pregnancies (Moore et al. 1990).

A human acardiac fetus is one of MZ twins or higher multiple births whose development is severely disturbed, and who usually has no cardiac remnants. There is good evidence that acardiacs are more common in higher multiple births than in twins (James 1977b). That an acardiac can develop at all is due to the presence of two anastomoses in the monochorial placenta. An A-A anastomosis brings blood from an usually normal co-twin to the "monster"; and a V-V anastomosis returns the blood. The normal twin provides the cardiac flow to the acardiac but in a reversed fashion. The reversal of blood flow has been proved to exist with the use of Doppler sonography (Pretorius et al. 1988b; Quintero et al. 1994; Coulam 1996; Zucchini et al. 1993) and is now referred to as "twin reversed arterial perfusion" (TRAP) (van Allen et al. 1983). One interesting exception to the nature of the twin placenta has been published by French et al. (1998). These authors found a typical acardiac amorphous with anastomoses to a normal twin in a verified DiDi placenta and determined by genetic studies that the twins were monozygotic as well. This challenges our understanding of how the chorionic vascularization in early placentation is accomplished. Schatz observed that the frequent presence of omphaloceles in acardiacs is an important obstruction to venous return and believed in an etiologic role. Later studies have not borne out this finding, as many acardiacs lack an omphalocele. Schatz believed that this kind of obstruction could be the cause of many such anomalous infants. We believe that the presence of the two types of placental anastomoses is the fundamental cause of the acardiac dysmorphism, and it is just possible that an absent Hyrtl anastomosis contributes. Dichorionic (and DZ) human twins cannot develop into acardiacs as they usually lack the placental communications, but very rare exceptions have been recorded in which the two placentas have vascular fusions. No blood would be circulated through fetal vessels if a spontaneous acardia were to exist in a DiDi twin, and such an embryo would vanish early. The fact, however, that such placental communications do exist among many fraternal (DZ) twins of some other species was already recognized by Schatz, who discussed the acardiacs found in ruminants and carnivores. The most interesting aspect of the acardiac anomaly, of course, is its ultimate cause, and two theories have been examined: (1) primary cardiac abnormality and (2) the presence of AA + VV placental anastomoses. This has been fully examined by Gibson et al. (1986). Our feeling, however, is that a misdivision of blastomeres may be the ultimate cause of this unusual anomaly.

Fig. 25.85 Acardiac twin, having the appearance of a teratoma. The normal twin was 2,910 g, the acardiac ("holoacardius amorphous") weighed 40 g, had a diminutive cord, and was in a MoMo placenta with large anastomoses (Courtesy of the late Dr. N.J. Eastman, Baltimore, Maryland)

The wide spectrum of the appearance of acardiacs that one can observe is illustrated in Figs. 25.81, 25.82, 25.83, 25.84, 25.85, 25.86, 25.87, 25.88, and 25.89. One of these fetuses had the appearance of a teratoma, turned inside-out (see also Jamal 1999), another had remnants of a face and arms, and the third is unusual in that it had an exceptionally long umbilical cord. Despite the absence of any cerebral structures (although there was a spinal cord), the last-mentioned acardiac was sonographically witnessed to move actively. Also well shown in this fetus was the plethora, frequently observed in acardiacs. We believe it represents stagnation of blood, transfused by the pale, normal co-twin. The increased resistance to perfusion has been demonstrated by

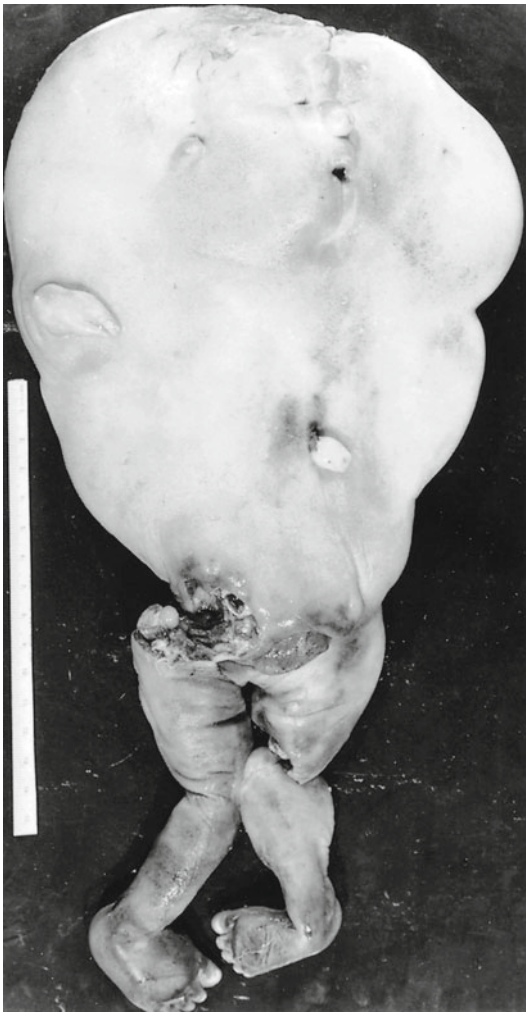


Fig. 25.86 Well-formed 1,210 g male acardiac delivered at 28 weeks. Co-twin died neonatally and had aortic hypoplasia. The acardiac had a skull, remnants of brain, a small spinal cord, and many organ remnants (Courtesy of Dr. J.D. Wilkes, New York, New York)

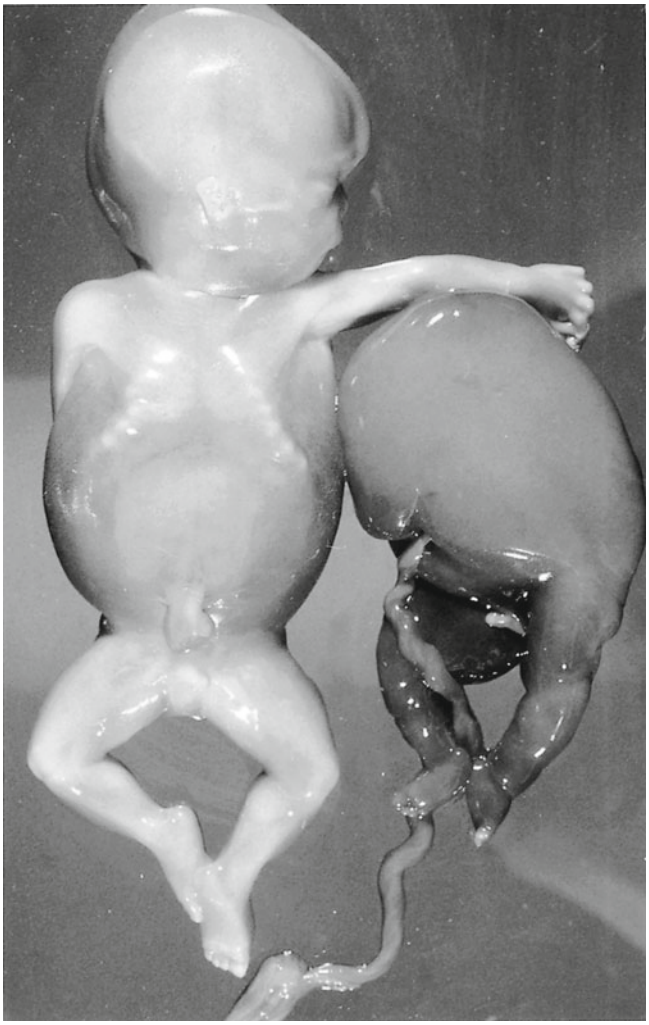


Fig. 25.87 Exsanguinated premature MoMo twin with plethoric acardiac fetus. This specimen is unusual because of the long umbilical cord. The fetus had been seen to move at sonography; it had no brain but a normal spinal cord

prenatal Doppler velocimetry (Sherer et al. 1989). The fetal mobility of an acardiac may be so great on occasion that they die because of cord entanglement (Fig. 25.89). In all of the twins shown, the placenta was MoMo but many others have been described with a DiMo placenta. In such cases, there is usually amnion nodosum of the acardiac's cavity because of its deficient or absent urine production. Sonographic examination of such cases then discovers a "stuck twin." Among the 30 acardiac twin pregnancies we studied and that had enough information, DiMo placentation was found in 22 cases and MoMo in 8 cases (Moore et al. 1990).

Dissection of the fetuses shows many gradations, ranging from a total absence of most organs to well differentiated structures of others, including gonads. Only liver tissue has never been observed by us; nevertheless, bile-stained meconium was present in the intestines and shown to be bile by mass spectrometry. Thus liver MUST have been present in the past. Schatz has written of the absence of the liver as well. More recently, however, Giménez-Scherer and Davies (2003) demonstrated some liver tissue (with degenerative changes) in three of 18 acardiac fetuses they dissected. Upper limb anomalies were other most prominent findings in Willes' case. Driggers et al. (2002) found a small liver in an interesting acardiac anomaly. It was extremely hydropic and possessed a "severely malformed, almost nonexistent heart." They suggested that at one time in early gestation, there had been a TTTS, but because of the cardiac anomaly, TRAP developed and caused the edema and other abnormalities. This is a novel way of interpreting the genesis of these complex anomalous twins. A female sex preponderance of acardiacs has been noted by James (1977b). For the study of acardiacs, it is usually best to obtain a radiograph of the specimen before dissection, as it gives some idea of the complexity of the abnormality, enables better classification, and

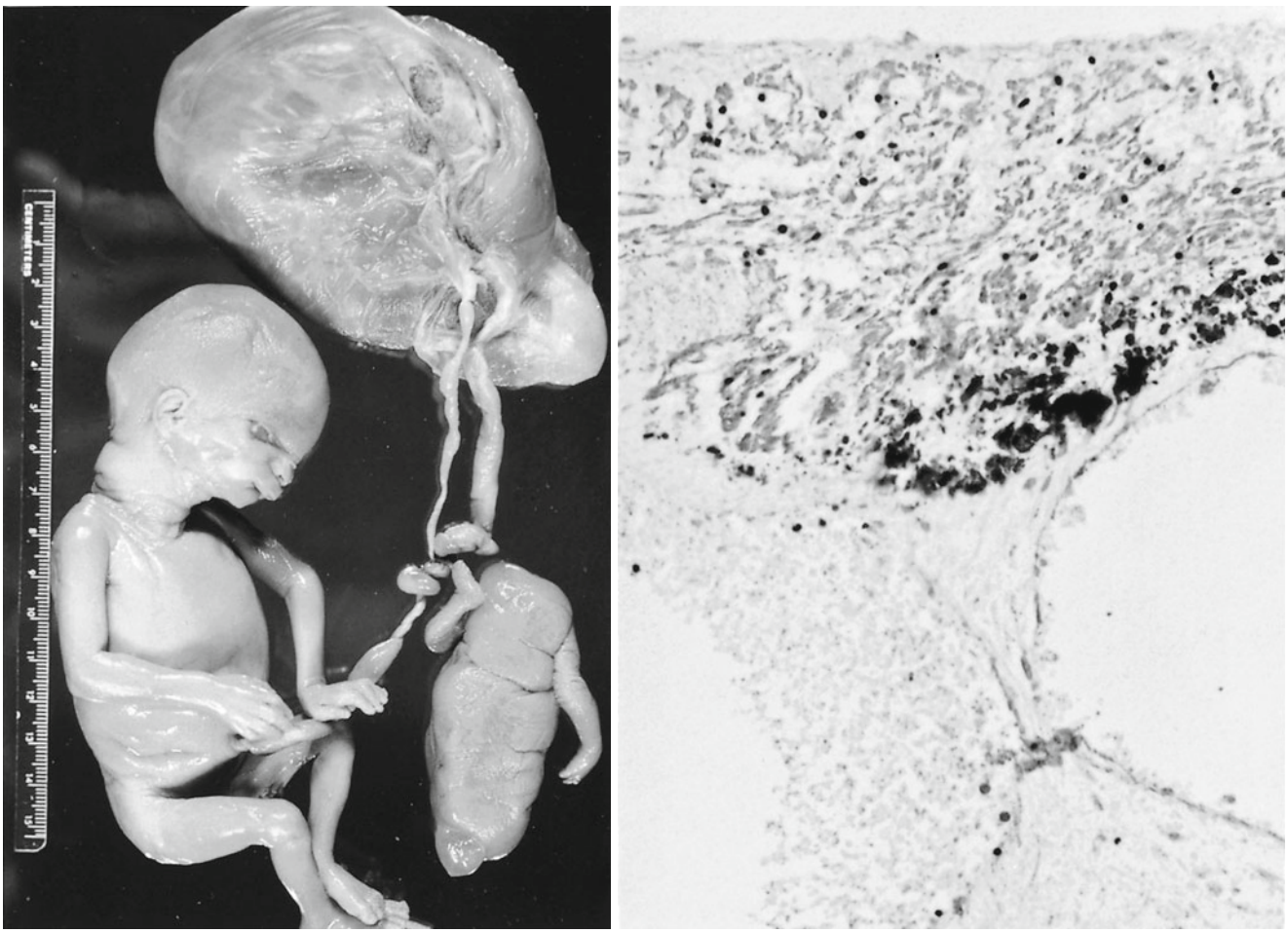


Fig. 25.88 Macerated MoMo twins, one an acardiac (150 and 20 g). The twins died because of entangling of cords. Note the single umbilical artery of the cord and large A-A and V-V anastomoses. The acardiac had a remnant of heart with calcification in the remaining muscle fibers. H&E, ×160 (Courtesy of Dr. S. Kassel, Fresno, California)

delineates if a skull is present (Dicker et al. 1983; Bhatnagar et al. 1986).

Most acardiac fetuses have only a single umbilical artery. The absence of one umbilical artery, though, cannot be held responsible for the development of the anomaly since it is not invariable. In contrast to Schatz' ideas, an omphalocele has been absent in at least one-half of the cases we have seen. One of the few hemiacardiacs we dissected possessed a two-chambered heart (Benirschke 1970a). This heart and that of another hemiacardiac exhibited endocardial fibrosis. The first twin shown here also had a fairly well-formed head with a brain and a bilateral cleft palate. One of monochorionic quintuplets with five amnions was an acardiac fetus (Hamblen et al. 1937) (Fig. 25.90), and we described triplets with one acardiac in the previous edition of this book; and many other triplets, one being an acardiac, are recorded in the literature (e.g., Sanjaghsaz et al. 1998). They may be MZ triplets (Ross 1951; Landy et al. 1988) or multizygotic (Stoeckel 1945; Wylin 1971; Kirkland 1982). The acardiacs described by Amatuzio and Gorlin (1981) were conjoined and associated with a MoMo triplet in heart failure. Parenthetically it may be mentioned that some pregnancies complicated by an acardiac (as in fetus papyraceus discussed earlier) have unexplained high levels of α-fetoprotein and acetylcholinesterase in their amnionic fluid (Entezami et al. 1997; Winsor et al. 1987). Kaplan (1994, her Figs. 6, 7, 8 ,9 ,10, 11, and 12) depicted monochorionic triplets, two of whom had the TTTS, a third was acardiac.

One of the most remarkable specimens is that described by Fujikura and Wellings (1964) and shown in Fig. 25.91. This malformed specimen was attached to the chorionic surface 1.5 cm from the insertion of the umbilical cord of a larger fetus. This more normal twin had amelia of the right arm, phocomelia of the right leg, hydrocephaly, and myelomeningocele; his right umbilical artery was absent. The acardiac was described as a teratoma-like mass. Another description of what we consider to be more likely to have been an acardiac fetus rather than a teratoma is the case discussed by Sironi et al. (1994). We have previously expressed our reservation about chorionic teratomas and prefer to think

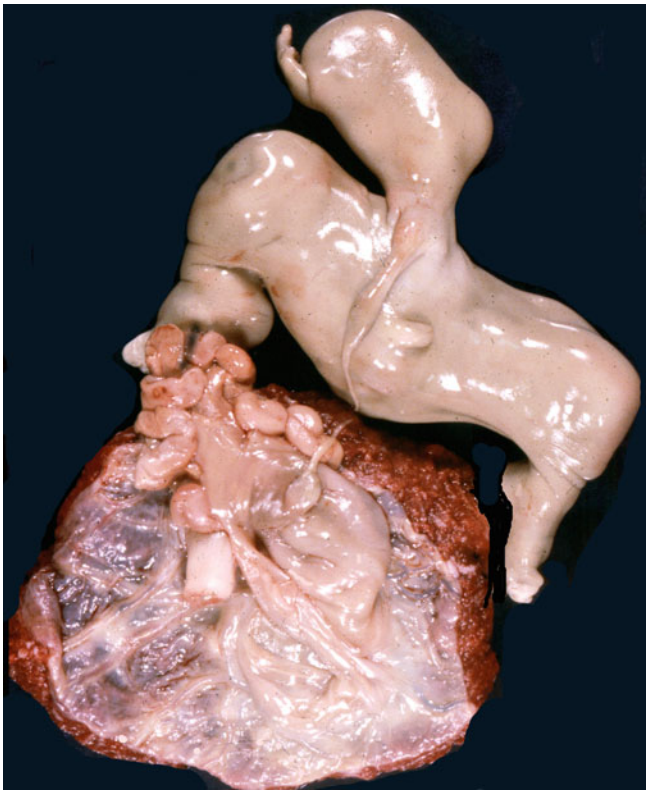


Fig. 25.89 Unusual acardiac twin whose abdominal contents were embedded on the placental surface (Emery et al. 2004)

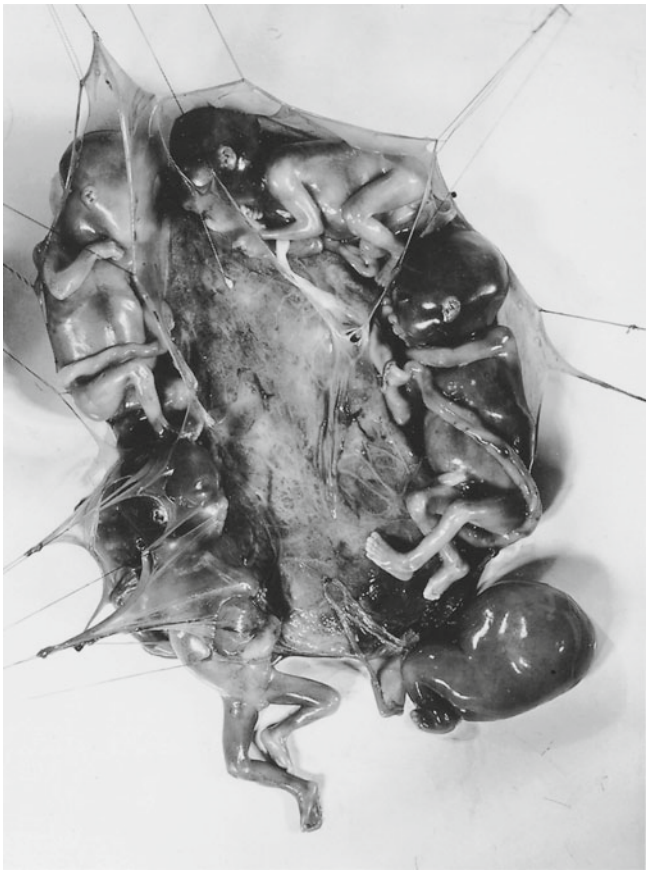


Fig. 25.90 Acardiac quintuplet in monochorial placenta with five amnionic sacs (*bottom right*). Note its plethora. Three yolk sacs were identified (From Hamblen et al. (1937), with permission)

of this specimen as acardiacs who lacked the development of a defined umbilical cord. The presence of a cord is usually a prerequisite for the diagnosis of "acardiac fetus" (e.g., Joseph and Vogt 1973), although the length of umbilical cords of acardiacs varies from 0 cm as in Fig. 25.85 (see also Frutiger 1969) to 53 cm as in Fig. 25.87. The "lack of organization," as emphasized by Fox and Butler-Manuel (1964) in a similar case, is not a strong argument that these masses are teratomas. Such disorganization occurs often in small "holoacardii amorphi" with good umbilical cords. Holoacardii amorphi are not true neoplasms ("teratomas"); they are part of the wide spectrum of acardiac twinning. Kreyberg (1958) reported a similar case and had the same opinion. The differential diagnosis (acardiac or teratoma) was further considered by Stephens et al. (1989), who reviewed 96 cases and presented an additional bovine acardiac fetus. It was their opinion that the presence or absence of an umbilical cord was insufficient evidence for diagnosis, and they relied more heavily on the finding of an axial skeleton. Emery et al. (2004) reported another most unusual case of acardiac twin in a MoMo gestation. Completely separated from the macerated acardiac was its intestinal content enclosed in a sac on the surface of the placenta (Fig. 25.89). It was conjectured that the phenomenon arose from a "detached" omphalocele. As stated earlier, Schatz had even suggested that the omphalocele was the cause of acardiac twin formation; thus, this may not be so surprising after all. An excellent example of such large omphalocele was provided by Chmait and Hull (2001). Schatz (1898) had already suggested that a spectrum may exist from normal gestation via TTTS to acardiacs, and the possibility needs to be considered that this spectrum arises because of unequal cell number contribution to the future twins at the "splitting" event.

The **incidence** of acardiac pregnancies is difficult to ascertain, as most are not reported. Gillim and Hendricks (1953) estimated it to be 1 per 34,600 births, or approximately 1 in 100 MZ twin pregnancies. This finding agrees with that derived by Napolitani and Schreiber (1960). Bhatnagar et al. (1986) based their estimate of 1 per 48,000 births on data from a variety of studies. They admitted the probability of a gross underestimate, and we agree with this, especially because the advent of ablation by various means of cord obliteration has led to a flood of publications. Most acardiacs are probably not reported in the literature. Well over 600 cases have been reported, and there are probably hundreds that go unpublished. Our own series now exceeds 50 cases, and many of these cases will remain undescribed.

Fig. 25.91 Diminutive acardiac that was likened to a teratoma. It is 1.5 cm from the cord insertion of a malformed twin with SUA. Large vessels led to the mass (Courtesy of Dr. T. Fujikura, Portland)

Acardiacs often develop hydrops, and the pregnancy is thus frequently complicated by hydramnios. Hydropic acardiacs may then become much larger than the normal co-twin. The hydropic acardiac described by Pavlica (1967) was such a case. It weighed 2,150 g, whereas the co-twin was only 850 g. It was further remarkable that its umbilical cord forked from that of the normal co-twin. Markavy and Scanlon (1978) have described additional hydropic acardiacs with hydramnios and considered that this problem may result from hypoproteinemia. They also observed thrombosis of one umbilical artery in one of these acardiac fetuses.

Because the hydramnios may be severe and the large acardiac may present problems with dystocia (Loughead and Halbert 1969), Platt et al. (1983) proposed that a ligature be placed around its umbilical cord through an amnioscope. Simpson et al. (1983) were successful in treating a pregnancy with a hydropic acardiac by digitalization. The mechanism of hydramnios and congestive heart failure is complex. It is likely related to the size of the acardiac fetus, but suggestions in the literature allude to a correlation with the presence of renal tissue in the acardiac (Moore et al. 1990). Prospective studies, with ascertainment of urination by the acardiac, are needed. Sullivan et al. (2003) recommended conservative approach to the treatment. Nevertheless, they lost one "pump" twin of the ten cases studied.

Another way of treating an acardiac pregnancy is by selective removal of the anomalous twin. Intervention in acardiac pregnancies has been advocated by Healey (1994) who reviewed the outcome of 184 such gestations. He found that 35% of the "pump" twins died (45% in triplets), mainly from prematurity, and Lewi et al. (2010) have added many other cases. Healey also ascertained other risk factors associated with acardiac gestations, such as SUA and MoMo placentation. Selective removal of the acardiac has been successfully accomplished by Robie et al. (1989). These authors removed a sonographically identified acardiac fetus at 22.5 weeks' gestation that weighed 710 g. A normal twin was subsequently delivered at 33 weeks' gestation. Ash and colleagues (1990) successfully managed such a pregnancy with indomethacin. It led to marked reduction of amnionic fluid volume so that a normal fetus (and 785 g acardiac) was delivered at 34 weeks. Porreco et al. (1991) occluded the umbilical artery of an acardiac fetus in utero with a metal coil. It stopped the reversed flow and led to normal delivery at 39 weeks. Rodeck et al. (1998) successfully thermocoagulated identified connecting vessels in four acardiac gestations. The short cord of most acardiacs was one reason for choosing this new methodology of therapy. McCurdy et al. (1993) endoscopically attempted to ligate the umbilical cord of an acardiac fetus at 18 weeks. Both twins died. Quintero et al. (1994) succeeded with ligating the umbilical cord near midgestation through a fetoscopic approach and salvaged the normal twin. The acardiac weighed 31 g at birth. Johnson et al. (2001a) provided evidence that the cord can be effectively obliterated by "bipolar cauterization" in acardiacs as well as the TTTS (Taylor et al. 2002), and Porreco (2004) used percutaneous sonographically-guided injection of alcohol successfully. In a DiMo twin with one twin having Turner's syndrome, Tsao et al. (2002) and Shevell et al. (2004) used radiofrequency obliteration of cord vessels successfully. Tan and Sepulveda (2003) reviewed the outcome of 74 acardiac twin pregnancies that were treated by different, minimally invasive methods. These included alcohol injection, monopolar diathermy, interstitial laser, and radiofrequency ablations. Their conclusion was that "…intrafetal ablation is the treatment of choice…because it is simpler, safer and more effective when compared with the cord occlusion techniques." Others have also advocated radiofrequency ablation of the umbilical cord as a less invasive method; thus, Lee et al. (2007) had 25 "pump twins" of 29 successful ablations survive to ~34 weeks' gestation and had no hemorrhages or abnormal coagulations in the survivor. This was commented upon by Morel et al. (2007) who had under-

taken a similar methodology in a sheep model and had suggested specific requirements for success (Morel et al. 2008). Moise et al. (2008) have used this methodology for other twin anomalies and even for severe cases of TTTS. Selective removal of an acardiac fetus was undertaken at 23 weeks after her death in utero by Ginsberg et al. (1992) with the normal twin proceeding normally to 39 weeks. Interestingly, the two cords branched one from another at their marginal insertion on the placenta and both fetuses as well as normal members of the family had a chromosomal inversion [46,XX,inv (10)(p12q25)]. Wenstrom (1993) felt that elective removal of this acardiac was unnecessary. Chitkara et al. (1989) reported on selective termination of 17 anomalous twins, 14 of which were aneuploid, but not acardiac fetuses. They emphasized the need for "operator skill" in this procedure and had much better success later on in their series. Intracardiac injection of potassium chloride was the most effective means to accomplish the feticide. Neither the mothers nor the surviving twins suffered DIC. Other cases were reviewed by Donnenfeld and his colleagues (1989). They attempted to ascertain the presence of intertwin anastomoses by prenatal angiography because of hydrocephaly in one twin. Complications led to fetal death and exsanguination of the normal twin into the abnormal fetus. Large A-A anastomoses were found in the monochorionic placenta. Holzgreve and his colleagues (1994) injected through a spinal needle multiple pieces of ethanol-soaked suture material into the umbilical cord of an acardiac, with immediate cessation of blood flow. Hydramnios disappeared and a healthy twin was born. Sepulveda et al. (1995) succeeded by injecting alcohol into the abdominal portion of the umbilical artery at 23 weeks' gestation. Again, hydramnios and heart failure abated promptly. Foley et al. (1995) ligated the umbilical cord of an acardiac fetus with a special device, followed by rapid resolution of hydramnios. These results all support the notion that hydramnios in such pregnancies results from cardiac failure of the "pump" twin. It was therefore of interest to Martinez-Poyer et al. (1997) to follow the redistribution of blood in the survivor after cord ligation in five sets of twins (four pump twins survived), done by Doppler flow studies. They concluded that ligation was not associated with an increased impedance to the blood flow of the survivor, although a significant influence on venous flow was seen. Coincidentally, in several of these reports, normal karyotypes were observed. Arias et al. (1998) successfully used endoscopic laser coagulation to stop the reversed perfusion.

Another acardiac fetus with forked cord ("funiculopagus") has been described by Averback and Wigglesworth (1978). These authors also reviewed the literature of this uncommon event. Their acardius was in a separate amnionic sac and was rather well developed. The umbilical arteries, derived from the umbilical cords that had joined close to the placental surface, fused and provided a completely common circulation. It is interesting that this could occur at all because of the presence of umbilical cord furcation, and in a DiMo placenta. When we ascertained the frequency of SUA in acardiacs, we found that SUA occurred 16 times in 29 cases; 13 had normal cords. Of 27 normal co-twins, 4 had SUA, and 23 were normal (Moore et al. 1990).

Not only are the acardiac twins malformed, but many of the co-twins have also congenital anomalies. Schinzel et al. (1979) suggested that about 10% of the co-twins are malformed. It is important to note that, with one possible exception, the sex of human acardiacs has been the same as that of the co-twin, providing it was accurately ascertained by, at least, a sex chromatin study (Benirschke 1959), morphological identification of gonads (Kappelman 1944), or cytogenetic analysis. Only Buxbaum and Wachsman (1938) described an aberrant case that of a female twin with an apparently male acardiac co-twin. The sex of the latter was assessed by finding "a structure that closely resembled a penis." That this finding is insufficient evidence for its male gender has been demonstrated to us. We saw an acardiac with a sonographically identified penile structure that was subsequently delivered with a normal female co-twin. On dissection, this penile structure was an enlarged clitoris and normal ovaries were present. The reason for the clitoral enlargement remained obscure. C. Kaplan (in letters) found an anomalous pump twin with encephalocele, including imperforate anus, an absent kidney, and many other anomalies in 46,XY twins. The acardiac had a single-chambered heart and SUA. Baldwin (1994) has made similar observations.

The most controversial aspect of acardiacs is their pathogenesis and etiology. Frutiger (1969), who described five acardiac cases, believed that the absence of the heart was secondary to the acardiac suffering a deficient oxygen and nutrient supply, a suggestion that had previously been made popular by Loeschke (1948). He had the idea that the acardiac twin suffered malnutrition and hypoxia because it developed in the decidua capsularis which, however, is clearly often not the case. Alderman (1973) challenged this notion and proposed a "primary failure of organ development." Köhn (1953) and Dahm (1955) also favored primary developmental problems. They suggested that "pathologic division" of the embryo and perhaps extraneous factors were responsible for acardiac development. They entertained the possibility of heritable causes. Gruenwald (1942) described a young, partially duplicated human embryo that might well have become an acardiac twin. He considered the two principal and opposing theories: (1) primary maldevelopment and (2) vascular reversal leading to suppression of cardiac development. His statement, "…an anomaly, anatomical or functional, intraembryonic or extraembryonic, may turn

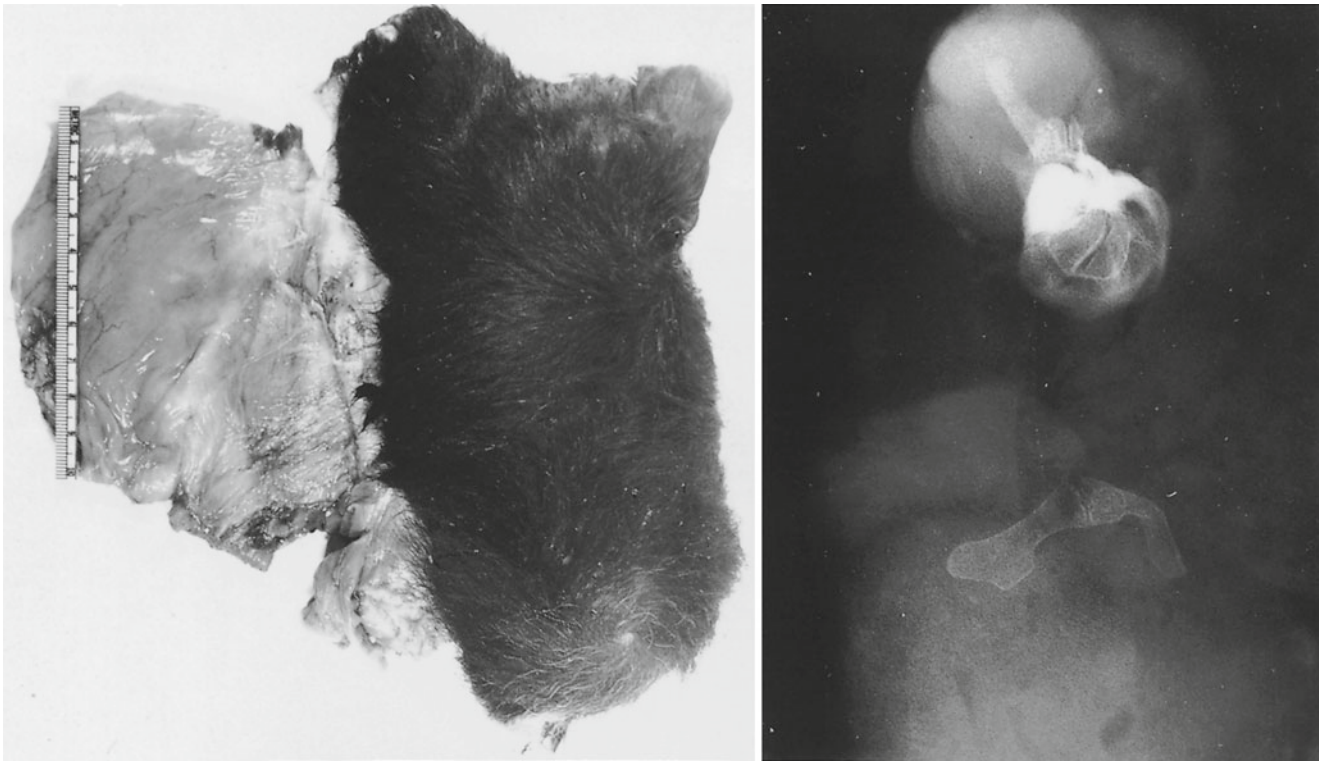


Fig. 25.92 Bovine acardiac monster attached to remnants of membranes. This 600-g elongated structure had a semblance of pelvis (*bottom right*) and even more ossified cranial structures (*top right*). Karyotype was 60,XX (From Benirschke (1970b), with permission)

one twin into an acardius if its circulation becomes dependent on that of the other embryo," probably best reflects our current thinking about the nature of these monsters. Lachman et al. (1980) have also presented reasonable theories of etiology in their discussion of a relevant case.

That vascular reversal nourishes the acardiac is without question. Much of the failure of organ systems to develop at all, or to do so in a diminutive fashion, is due to a deficient circulation. The circulating blood is not only deoxygenated but also arrives at a reduced pressure; indeed, van Gemert et al. have shown this in an exceptional modeling methodology (2005). The fact that the lower limbs of acardiacs are usually better formed than the arms has been considered to result from preferential perfusion of the legs as they are closest to the incoming reversed arterial flow. The fact that the central nervous tissue is often reasonably well developed contradicts some notions that unimpaired neural development guarantees limb development an area that has been summarized by Boulgakow (1926). Schatz (1898) suggested that there was a gradual reversal of blood flow and that, commensurate with the arrival of the reversed flow, organs would degenerate.

An important etiological consideration for the development of acardiacs is that these anomalies may occur in one of dizygotic twins of certain animals. Some species, in contrast to human twins, share anastomoses between fraternal twins. This situation is best known from the freemartin condition of cattle (Lillie 1917). Here, the male twin is responsible for atrophy of the female genitalia of the co-twin, with which he is vascularly connected, the basis of freemartinism. These connections also lead to permanent blood chimerism. Similar anastomoses are regularly present in the twins of marmosets and tamarins (Benirschke et al. 1962). In these primates, however, sexual disturbances do not occur. Schatz (1898) remarked already that there are many ruminant acardiacs. Occasionally, they are found in carnivores but not in horses. Figures 25.92 and 25.93 shows a bovine acardiac monster, and such a twin from a goat is seen in Fig. 25.94. Table 25.5 summarizes some of the literature of animal acardiacs. They are a crucial component in the considerations of the genesis of these anomalies. One may speculate that these fraternal twins were originally normal but that, because of happenstance chorionic anastomoses, they became anomalous by virtue of circulatory reversal. This speculation is supported by the hypothesis of original normality, first enunciated by Claudius (1859) and later by Ahlfeld (1879). Schwalbe (1907) sided with Schatz, in that he assumed a primary inequality of

Fig. 25.93 "Amorphus globosus" from quadruplet pregnancy of a goat (MM;F), weighing 20 g. It had a short cord with two vessels and a small amount of cartilage and muscle amid fat

the twins, and that secondary alterations (macrocardia, microcardia, SUA, omphalocele) determine its ultimate outcome.

Evidence for a primary anomaly of, at least, some acardiacs has been gathered from cytogenetic studies. In a few acardiac monsters, investigators have found abnormal karyotypes that were different from those of the co-twin. Other acardiacs have had normal chromosomal complements identical with those of the normal co-twin, as in the example shown in Fig. 25.90. These interesting findings are summarized in Table 25.6. One must caution, however, that only those studies in which the chromosome analysis was undertaken from the *solid* tissues of the acardiac specimens can be considered valid. The lymphocyte populations would be admixed a priori, and thus their karyotypic analysis is not helpful. Moreover, it is known that the lymphocyte contribution of the acardiac, who also usually lacks a thymus, may be minimal (Nigro 1977). Therefore, the new molecular studies by Fisk et al. (1996) are of importance. These authors studied the DNA of placental and fetal solid tissues in acardiacs and their placentas to find evidence of the monozygotic derivation of these unusual gestational products. Finally, it is of interest that at least two "normal" co-twins of acardiacs have had an abnormal chromosomal constitution (Table 25.6). Thus, the cytogenetic picture is complex and does not lend itself to a resolution of the question which event is primary in the etiology of acardiacs. Acardiac twins may be observed at young gestations and then already have all the characteristic stigmata (Fig. 25.95). We have concluded that, whatever happens to their anatomical development, it is an early process. Our own concept is that, in humans, perhaps unequal splitting of the inner cell mass at splitting and the reversal of circulations are the causes of the anomaly.

The characteristic vascular arrangement pertaining to most acardiacs is illustrated in Fig. 25.96. It mirrors many descriptions of former authors. In these days of acronyms, the term TRAP (twin reversed arterial perfusion) has been applied to this "syndrome" (van Allen et al. 1983). In this chapter which presents 14 acardiac cases, the spectrum of anomalies is well delineated. They described an additional specimen with chromosomal error. We have recently karyotyped two new acardiacs and their co-twins and found both to have normal chromosome complements in solid tissues. An excellent review of the origin of acardiac twins and "TRAP" can be found by Malinowski and Wierzba (1998). They also gave frequency figures for the various anomalies of acardiac fetuses. That acardiac fetuses may even have a more developed cephalic portion was presented by Mohanty et al. (2000). Likewise, Sergi and Schmitt (2000) presented an acardiac with microcephaly and discussed various CNS anomalies found in such cases. Petersen et al. (2001) even reported relative normality of development in an edematous acardiac that was thought to have been dead sonographically.

25.16 Conjoined Twins

Incompletely separated twins (conjoined, Siamese, x-pagi, double monsters) presumably take their origin after day 13 of embryogenesis. Because it has been most seriously questioned whether conjoined twins are one person or two, the reader is directed to the searching review of this topic by Gould (1982). Gould concluded that this question is not answerable, and perhaps it may even be an erroneous inquiry. The MZ twinning process is a continuum; sharp divisions do not exist, as is often the case in biologic phenomena. Schatz (1898) was the first to express this clearly; indeed, even the process of twin-twin transfusion syndrome may fall into this

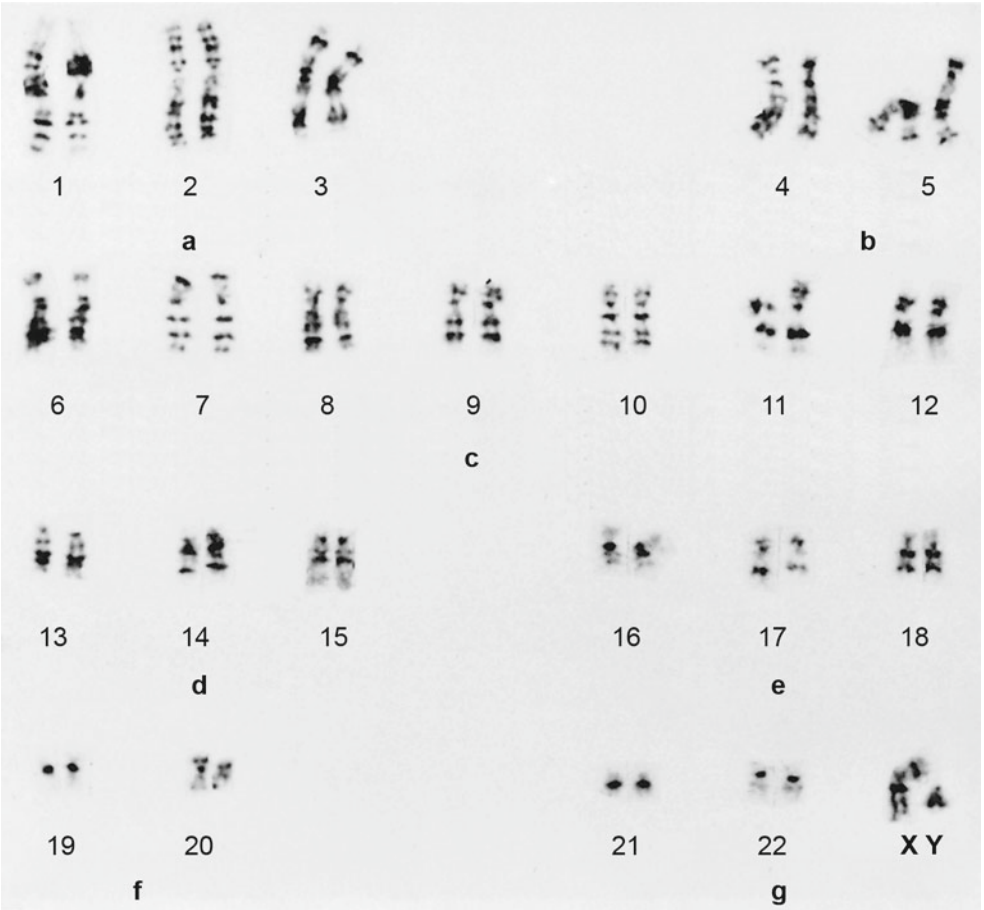


Fig. 25.94 Normal male karyotype from skin of the acardiac shown in Fig. 25.92. Giemsa banding

Table 25.5 Karyotypic studies in animal acardiacs

Source	Year	Species	Sex	Remarks
Sutton	1899	Cattle		Anidian monster
Simonds and Gowen	1925	Cattle		13 Amorphi
		Sheep/goat		3 cases
		Bird		1 case; extensive literature
Cole and Craft	1945	Sheep	Female	
Roberts	1956	Horse		
		Cattle		
Dunn et al.	1967	Cattle	Female	60,XX; 61,XX (??mosaic) male co-twin 60,XY
Neal and Wilcox	1967	Cattle		2 Amorphous twins, 1 heifer
Dennis and Leipold	1968	Sheep		1 Holoacardius acephalus
Herzog and Rieck	1969	Cattle	Female	60,XX misinterpreted
Benirschke	1970b	Cattle	Female	60,XX, normal co-twin
Dunn and Roberts	1972	Sheep	Male	54,XY (co-twin); 54,XY/53,XY
Crossman and Dickens	1974	Horse		Mass (500 g)
Höfliger	1974	Horse		Review
		Cattle		Acormus (head only)
Hein et al.	1985	Monkey	Female	DiMo; A-A anastomosis

spectrum of the monozygotic twinning process. Even more problematic is it to make clear decisions as to the classification of whole-body chimerae, as we will see below. Moreover, the precise manner of the formation of conjoined twins is uncertain. Opposing views suggest on the one hand incomplete splitting and on the other, partial fusion of embryonic precursors. The reader is referred to the searching reviews of over 1,000 cases by Spencer (1992, 2000, 2003) who has clearly had the greatest experience with this topic. Spencer's special interest has been the embryologic development of conjoined twins, and she posits as her basic tenet that fusion (rather than incomplete splitting) is the principal mechanism

Table 25.6 Karyotypic studies of human acardiac fetuses

Source	Year	Donor	Acardiac	Placenta remarks
Richart and Benirschke	1963	ND	46,XY (F)	DiMo
Rashad and Kerr	1966	46,XY (F) 47,XY (F)	46,XY (L) Extra C element	DiMo
Turpin et al.	1967	46,XX (F)	46,XX (F) 47,XX (L) extra minute element extra minute element	MoMo
Scott and Ferguson-Smith	1973	46,XY (L,F) 46,XY (L)	46,XY (L) Failed	DiMo DiMo
Machin	1974	46,XX (F)	46,XX (F)?	Triplets, 46,XX
Benirschke and Harper	1977	ND	46,XY (F)MoMo	See Fig. 25.90
Rehder et al.	1978	47,XXY (F)	47,XXY (F)	?
Kaplan and Benirschke	1979	46,XX (F,L) 46,XX (F,L)	46,XX (F) 46,XX (F)	DiMo DiMo
Deacon et al.	1980	45,X (F)	46,XX (F,L)	?
Bieber et al.	1981	46,XY (L) Genetic studies indicated acardiac to derive from polar body	69,XXX(F)	DiMo
Gewolb et al.	1983	46,XY (?)	46,XY (?)	DiMo Authors stated DiDi, but depicted DiMo
van Allen et al.	1983	46,XX (?) Nature of chromosome study unknown;	45,XX t(4;21)del(4p)	DiMo
Shapiro et al.	1986	46,XX (?) 47,XX +11(F)	46,XX ?	
Moore et al.	1987	47,XXY (?)	92,XXXXYY (?) ?	Review of the 11 previous acardiacs with karyotype
Bhatnagar etc.	1986	47,XX,tri 18	ND	?Mo
Moore et al.	1987	47,XXY (L) 47,XXY (L)	47,XXY (L) 92,XXXXYY (F,L)	DiMo DiMo
Landy et al.	1988	45,X/46,XX (A)	46,XX (A,L,F) TriMo triplets; mosaic fetus was normal female	
Wolf et al.	1991	46,XX	46,X,i(Xp)	DiMo hydropic 3,720 g
Ginsberg et al.	1992	46,XX,inv10	46,XX,inv10	MoMo normal members with same inversion
Benirschke	1992	46,XX	46,XX	Two normal acardiacs
Bolaji et al.	1992	46,XX	46,XX + 4n, +6n	TriMo triplets well-formed acardiac, Hyperdiploid cells from lymphoid aggregate of acardiac

A amnionic fluid cells, *F* fibroblast, *L* lymphocytes, *ND* not done

of their formation. The reason for her view is primarily that many cases of conjoined twins cannot possibly be explained by a fission event, although she begins the evolution of conjoined twinning by assuming a primary MZ splitting event (see also the review by Kaufman 2004). The reader is led to believe that, because the MZ twins are oriented on either an amnionic "bubble" or large yolk sac, their potential proximity leads to this fusion. It must be pointed out though that to the best of our knowledge, all conjoined twins have been of the same sex which one might not expect if fusion were the only and principal mechanism. In another contribution, Spencer (2001) suggested that conjoined twins, fetus in fetu, parasitic twins, and acardiacs really form a spectrum and that the primary abnormality is a cardiac malformation; it is of further interest that she also supported the abundance of female conceptuses and that there is allegedly often a history of familial twinning. Another detailed study from the same author discusses the rare occurrence of rachipagous conjoined twins (Spencer 1995). In addition, an encyclopedic review book was published by Quigley (2003) that addresses many of the ethical and social issues confronted by these twins; another book by Dreger (2004) is perhaps more directed to the lay public but it also discusses some serious scientific issues. Even more provocative is the observation by Logroño et al. (1997). They reported a "heteropagous" conjoined twin with male pelvis and lower extremities

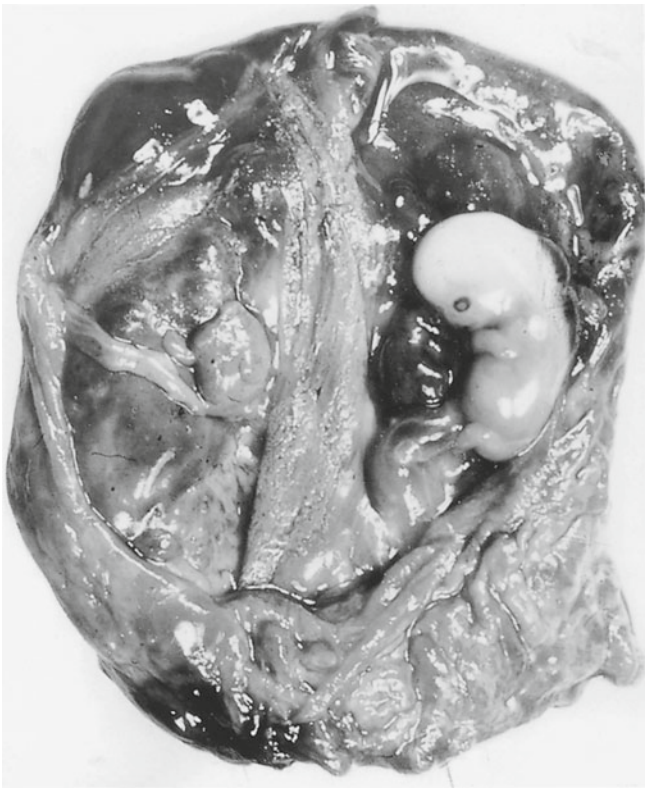


Fig. 25.95 DiMo twin abortus at approximately 9 weeks' gestation. At left is a degenerating acardiac. Note that it has a large amnionic cavity

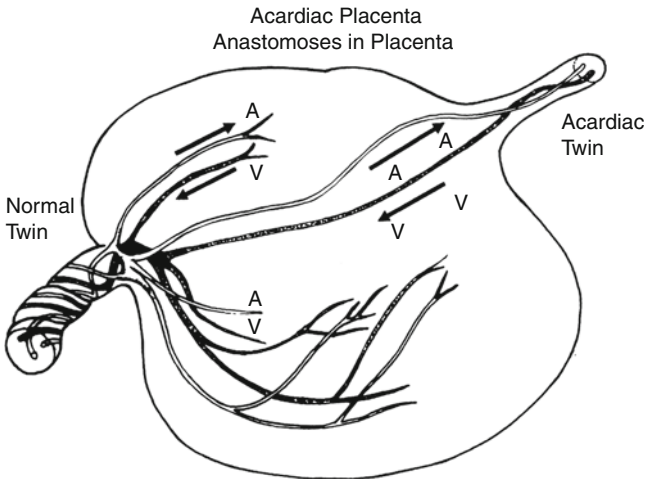


Fig. 25.96 Usual vascular relations (anastomoses) among an acardiac and co-twin

attached to the chest of a male autosite and inferred, from FISH genetic study, dizygosity of these joined parts. The autosite also had a cardiac anomaly, but the placenta was not described. The unequal craniopagi reported by Aquino et al. (1997) had two umbilical cords with velamentous insertion, one being diminutive and with a single artery. There were surface placental anastomoses. We have observed exactly the same features in one of the many acardiac pregnancies sent to us. Ozturk et al. (2007) reported another heteropagous twin that was attached to the umbilicus. It was successfully removed. Finally, there is Kim's case that involved cephalothoracopagous twins with one male and one female phenotype (2007). It was not the result of IVF or other embryonic manipulation. One-half of the twins had a penis and testes, the other had a uterus and ovaries. Lymphocyte culture yielded 46,XX, but the culture of solid tissue unfortunately did not succeed. Martinez-Frias (2009) added another historical case to this sparse literature. These observations then would generally support Spencer's notions.

Most fused twins are joined at the chest (thoracopagus), but all sorts of unions have been described (Harper et al. 1980). Numerous triplets have included conjoined twins (Koontz et al. 1985; Seo et al. 1985; Gardeil et al. 1998). In triplets, the placentas may be monochorionic (Tan et al. 1971b), with the conjoints living in their separate amnionic cavity, or they may be dichorionic (Vestergaard 1972). We have recently observed term thoraco-omphalopagous girls with a monochorionic (diamnionic) normal female co-twin. The umbilical cord to the conjoined triplets was split (two arms with artery and vein each) at the placental surface which then joined to produce a cord with two arteries and two veins. From Japan, I have received photographs of ischiopagi endowed with a forked cord that had five vessels on the placental end but two vessels after they split. More remarkably, one twin had died in utero the day before Cesarean section, and they were separated after birth. The survivor did not show evidence of DIC as one might have suspected. In yet another case we saw recently, four arteries and one vein were found in the umbilical cord, but the vein split into two as the cord entered the fetus. Another of these rare diamnionic twin placentas with omphalopagous conjoined twins has been described by Weston and colleagues (1990).

The typical placenta of conjoined twins is a monoamnionic, monochorionic one. The former speculations that fusion of fraternal twins may be a mechanism of conjoint twinning is rarely tenable. For instance, chromosome studies of the twins have usually been identical (Kreutner et al. 1963; Kim et al. 1971). In one case, the twins and their mother had a pericentric inversion of one chromosome 9 (Delprado and Baird 1984), and most have been of the same sex. Mackenzie et al. (2002) studied the "natural history" of 14 conjoined twins diagnosed prenatally; the frequency of serious anomalies thus identified allowed more definitive decision regarding potential viability. This is an important consideration for the possible future treatment of conjoined twins in whom perhaps survival of one is unlikely and where decisions of surgery are paramount. The intervention by the courts and the problems arising from their decision to seek their advice are highlighted in an excellent article by Annas (2001).As indicated, surprisingly, approximately 70% of conjoined

Fig. 25.97 Conjoined "twin" Transvaal daisy (*Gerbera jamesonii*). The stem is fused; the flowers, with their identical number of petals (55/55), are separate

twins are females (James 1980). Burn et al. (1986) used this fact to support their hypothesis that unequal lyonization is associated with MoMo twinning. MacKenzie et al. (2004) have contributed another most unusual set of conjoined twins, a fetus with a partial twin joined on the abdomen and they differentiated it from TRAP sonographically. Incompletely separated twins have been described in a wide variety of species, e.g., rat (Levinsky 1973; Mutinelli et al. 1992), swine (Selby et al. 1973), turtle (Szabuniewicz and McCrady 1967; Lewis et al. 1992), and cetacea (Kawamura 1969; Kawamura and Kashita 1971). We have seen several California king snakes, calves, kittens, and other animals with double heads. Even in plants this event occurs with some frequency (Ahmad et al. 1977) (see also Fig. 25.97) and is there referred to as fasciation. It is remarkable and not yet fully understood why MZ bird twins have all been female. Conjoined chicken twins, described by Munro (1965), shared the single yolk sac.

Conjoined twins occur in approximately 1 of 50,000 births (Schmidt et al. 1981), or in 1 of 600 twins. The figures vary substantially among surveys (Tan et al. 1971a; Bankole et al. 1972; Harper et al. 1980; Castilla et al. 1988). They are reported to be much higher in the Japanese population (Miyabara et al. 1973). Reports have also indicated that this anomaly occurs more commonly in Nigeria, and Bhettay et al. (1975) suggested a much higher rate to exist in South Africa. This statement, however, has been criticized by Hanson (1975). Difficulty of ascertainment is further discussed by Viljoen et al. (1983) in a large series of conjoined twins from Southern Africa; contrary to earlier reports, these authors found no skewing in favor of the black population. Milham (1966) analyzed 22 sets and suggested local clustering of this anomaly. That suggestion was supported by Viljoen et al. (1983). The ultrasonographic diagnosis of conjoined twins can now be made as early as at 8 weeks' gestation (Lam et al. 1997, 1998), and three-dimensional sonography is helpful in further diagnosis of their anomalies (Maymon et al. 1998). This is also important for the selective termination of such anomalous conceptuses.

The **etiology** of conjoined twinning thus remains unknown. Sporadic reports have suggested that it is due to teratogen exposure (e.g., griseofulvin) (Rosa et al. 1987), and that its prevalence may include seasonal fluctuation. The relation of conjoined twinning to griseofulvin intake was disputed by the large data collected by Knudsen (1987), however. Ingalls (1969), who applied heat and hypoxia to zebra fish, was able to observe eight conjoined fish among 5,000 specimens; he described an "epidemic" in trout. Ferm (1969, 1978) found four conjoined hamsters whose mothers were subjected to teratogens. When Kao et al. (1986) injected solutions of lithium chloride into a blastomere of 32-cell-stage *Xenopus* eggs, a second head developed. Wan et al. (1982) observed conjoined twins in 0.4% of Swiss-Webster mice and in 0.06% of triplets. Treatment with vincristine or other manipulations did not increase the yield. Whether these data are relevant to the human condition has not been decided. It is known, however, that conjoined twins frequently have other congenital anomalies, including cleft palate, anencephaly, and particularly congenital heart disease (Noonan 1978; Marin-Padilla et al. 1981; Seo et al. 1985). Newman (1931b) noted marked differences in the development of various structures. Finally, arguing against the notion that fusion is the principal mechanism of conjoined twinning, the complex case of Bannykh et al. (2001) (and other similar complex instances) needs to be reviewed. This (male) singleton had two sets of external genitalia, portions of bowel, meningomyelocele and cardiac isomerism that can hardly be explained by a fusion event.

Keeler (1929) suggested that **mirror imagery** existed in 77% of conjoined twins, compared with 22% in monozygotic, separate twins. It must be cautioned, though, that situs inversus and mirroring are complex problems (see McManus 2002). Torgersen (1949) identified it to occur in 0.01% of a large population of Norwegians studied by mass radiography.

Fig. 25.98 Thoracoabdominopagous twins with monoamnionic placenta and a single umbilical cord

Fig. 25.99 Conjoined twins (ischiopagi) with a MoMo placenta, a single velamentous umbilical cord, and SUA. They were delivered at 40 weeks' gestation. One had a cleft face and microcardia. There were two female genital tracts (Courtesy of Dr. S. Sekiya, Tokyo, Japan)

Its incidence paralleled that of twinning, and he found that it was "not much higher" in MZ twins and was "rare" in DZ twins. For further insight into situs inversus and related aspects, see Layton (1976) and McManus (2002). Hydramnios is said to occur in about one-half of conjoined twins (Wedberg et al. 1979). The frequencies of various types of conjoined twins have been given by Edmonds and Layde (1982), with thoraco-omphalopagus (28%) being the commonest form.

The placenta of conjoined twins is usually a single disk with MoMo membranes. The structure of the umbilical cords, however, varies widely; approximately 6% having two cords (Spencer 1992). This fact much supports her view of fusion. The umbilical cord of Fig. 25.98 was single and contained two arteries and a vein. It is similar to those described by Kreutner et al. (1963), de Leon (1974), and Itoh et al. (1974) who observed that the co-twins had a fused subdiaphragmatic aorta whence the umbilical arteries originated. Gilbert et al. (1972) and Tan et al. (1971b) described thoracopagi with one artery coming from one twin and the other from the second twin, who also received the single vein. The twins of Fig. 25.99 had a single umbilical artery and a velamentous insertion of the umbilical cord. SUA was also found in four of seven conjoined twins reported by Miyabara et al. (1973). Kim et al. (1971) described thoracopagi with a single cord that possessed six vessels: four arteries and two veins. Mitrani (1968) saw one conjoined set of twins with six arteries and two veins. In the cases reported by Seo et al. (1985), two placentas had single cords with four arteries and one vein (similar to one seen by us and referred to above), one other had three arteries and two veins, and three had normal cords with two arteries and one vein. Two placentas, however, were separate disks; one of them had a fused cord. Delprado and Baird (1984) reported cephalothoracopagi with two cords. One was thick, ran in the membranes, and contained one artery and one vein; the smaller cord contained only one vessel. Another thoracopagous set of twins was reported by Freedman et al. (1962). They had two separate cords that inserted 1.5 cm apart and fused 13 cm from the placental surface. The fused structure contained three arteries and two veins; the placenta was DiMo and contained a triplet of the same sex. Wiegenstein and Iozzo (1980) found

two separated cords (11 cm apart) in a conjoined twin. The cords fused after having entangled in the placental portion and ran in a tented segment of amnion. A case with similarly fused, but separately originating cords was described with a dicephalus, dibrachius (Beischer and Fortune 1968). In the thoracopagi examined by Marin-Padilla et al. (1981), the single cord split 9 cm before reaching the placental surface. One branch contained two arteries; the other cord had a velamentous insertion and contained the single vein. An interesting set of vessels was found in the umbilical cord of a thoracopagus studied by Chaurasia (1975). The smaller twin had a rudimentary heart, a large left and diminutive right umbilical artery, and no vein; the larger twin had a single large artery and vein. Reversal of circulation in the smaller twin was considered. Finally, Charles et al. (2005) described triplets following IVF and two embryo transfers in which early sonography identified omphalopagi; the placenta, however, had a diamnionic status in the omphalopagi, and a separate placenta was present.

There is thus great variety in the spectrum of cord vasculature and structure, and no clear relations emerge as to the associated type of conjoined twin. One might expect that embryonic splitting at slightly different times produces different fusion anomalies and different cord structures and insertions. Future correlations may uncover these as yet unknown parameters. It is especially noteworthy that not all MoMo placentas of conjoined twins with two umbilical cords have vascular anastomoses on the placental surface. Finally, there exist anomalous fetuses with diminutive parasitic "twins" presenting as inclusions or appendages. They represent transitions to the next topic. Four such cases were described in some detail by Drut and colleagues (1992). Since they have no relation to placental pathology, they will not be discussed further.

25.17 Sacrococcygeal Teratoma, Epignathus

Sacrococcygeal teratoma and epignathus are, in our opinion, malformed twins that represent a part of the spectrum of the monozygotic twinning continuum, and Spencer (2001) has similar opinions. Some may take exception to this concept; nevertheless, findings of perfectly formed extremities, digits, and other structures favor this view. They are occasionally combined with more disorganized tumors (Cousins et al. 1980; Tokunaga et al. 1986). Schwalbe (1907) and Willis (1958) extensively discussed this aspect with illustrative material that also supports this notion. Exelby (1972) reviewed the origin and therapy of these tumors and found them to be much more common in females (4F:1M); they also indicated that there is frequently a strong family history of twinning. In one parturient whose child had a large sacrococcygeal teratoma, an ovarian teratoma was found simultaneously (Rayburn and Barr 1982). These authors emphasized that recent genetic study had shown that these neoplasms have different genetic backgrounds.

There are also frequent concurrent anomalies in children with these tumors. Most of the neoplasms are "benign," which is different from the rare teratomas of other sites, in which prenatal metastases have been reported (Semchyshyn et al. 1982). At times, however, an apparently benign sacrococcygeal teratoma eventuates in a malignancy. Lack et al. (1993) found an eventually fatal adenocarcinoma in a man 40 years after a sacrococcygeal teratoma had been incompletely removed at age 2 months. An alternate etiological point of view is that sacrococcygeal tumors and epignathi derive from misplaced germ cells. In a study of obstetrical complications with sacral tumors, Spitzer (1932) commented on the female sex preponderance and noted that the tumors are often complicated by hydramnios during pregnancy. That point has been reiterated in more recent publications of the prenatal diagnoses of these lesions (Horger and McCarter 1979; Hallgrimsson 1981).

Placentomegaly has often been described to be a complication of sacrococcygeal teratomas (Cousins et al. 1980; Gergely et al. 1980; Kohga et al. 1980; Feige et al. 1982). The same is true of the placenta in epignathi (Kaplan et al. 1980; Chervenak et al. 1985), and yet other teratomas may be associated with hydramnios and fetal hydrops (Rosenfeld et al. 1979; Banfield et al. 1980; Semchyshyn et al. 1982; Mostoufi-Zadeh et al. 1985). The placental enlargement may be striking, and it is then usually exceptionally pale. There is severe edema of villi, which often appear to be excessively cellular, contain numerous Hofbauer cells, and are severely congested (Figs. 25.100 and 25.101). One often finds numerous nucleated red blood cells in the fetal placental vessels. Ultrastructural examination of such specimens was first undertaken by Arai et al. (1977; see also Soma et al. 1979). It showed marked alterations of the syncytium, with distension of the transport vesicles (Figs. 25.102, 25.103, 25.104, and 25.105), and unusually dense mitochondria. We believe that placental enlargement is the result of high output failure of the fetus and that it is similar to that found with large chorangiomas. This concept finds confirmation in the frequently present fetal cardiac enlargement. In effect, the teratoma acts as an arteriovenous fistula. This is further supported by the experience of Langer et al. (1989). They resected one of the tumors at 24 weeks and returned the fetus to the uterus (of three cases described). Hydrops improved and Doppler study showed a decrease in cardiac output. Nakayama et al. (1991) made similar observations when they resected the tumor in a newborn. Feige et al. (1982) unreasonably claimed that the placentomegaly represents an attempt by the placenta to compensate for the increased needs of the fetal tumor. Whenever karyotypic analysis has been done, the chromosomes of the tumors

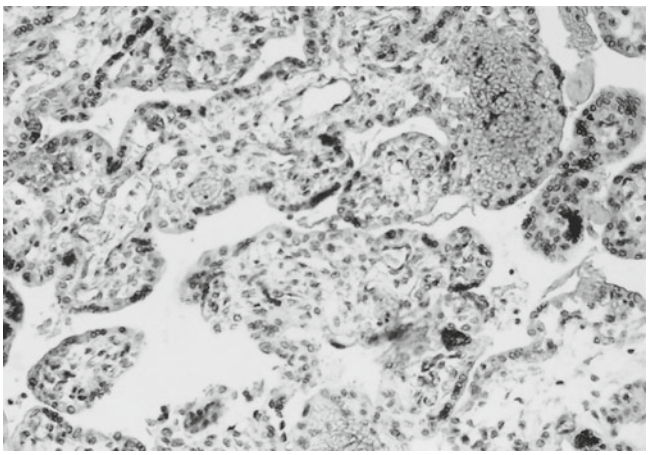


Fig. 25.100 Villi of immature placenta in a patient with a large sacrococcygeal teratoma. Placenta weighed 880 g at 31 weeks. The neonate died with extensive cerebral necroses. The villi are irregular and patchily edematous and have distended fetal capillaries. There is focal hemorrhage, and numerous nucleated red blood cells are present. The cytotrophoblast is more prominent than expected at this age. H&E, ×160

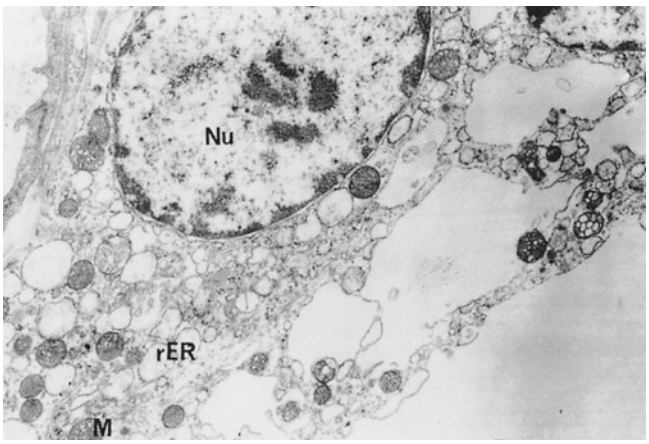


Fig. 25.101 Ultrastructural view of villi in a sacrococcygeal teratoma, showing hugely distended syncytial transport vesicles. Data: 28 weeks' gestation, hydramnios; elevated hCG levels (9,830,400 IU/L), 680 g placenta. ×5,600. *NU* nucleus, *rER* rough endoplasmic reticulum (Courtesy of Dr. H. Soma, Tokyo, Japan)

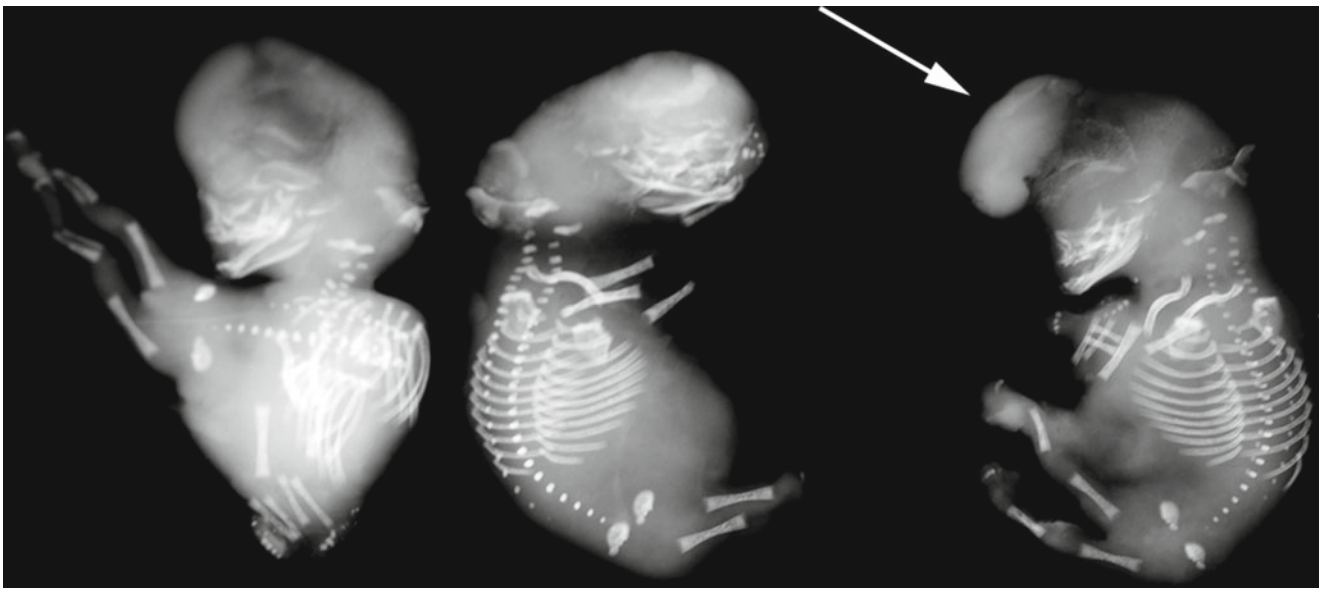


Fig. 25.102 Triplet fetus papyracei from assisted reproductive technology (ART) gestation. The triplet at right has an encephalocele that was not recognized macroscopically. The radiograph shows the value to take x-ray pictures of such fetuses

have been normal and identical to those of the host (Kaplan et al. 1979; Cousins et al. 1980). An interesting question remains regarding the "hairy polyp" removed from the throat of occasional patients (Isaacs 2002). Should it be regarded as an epignathus or teratoma? We have seen such an anomaly in a newborn with respiratory distress. The polyp impinged upon the defective soft palate. After removal, it was found to have a lanugo-covered skin, and internally, it was composed of fat, cartilage, nerve, and skin remnants.

25.18 Congenital Anomalies

Twins have congenital anomalies more often than do singletons. Hendricks (1966) evaluated the outcome of 438 multiple pregnancies and found that their perinatal mortality rate is not only "startlingly high" (14%) but also that anomalies occurred with a frequency of 10.6% (approximately three times that of singletons). In a review of anomalies of Swedish twins, Källén (1986) noted that some anomalies (?posthemorrhagic hydro-

Fig. 25.103 MoMo triplet term placenta, without entangling of cords but anastomoses among all circulations. The triplets survived (*Source*: Sinykin (1958), with permission)

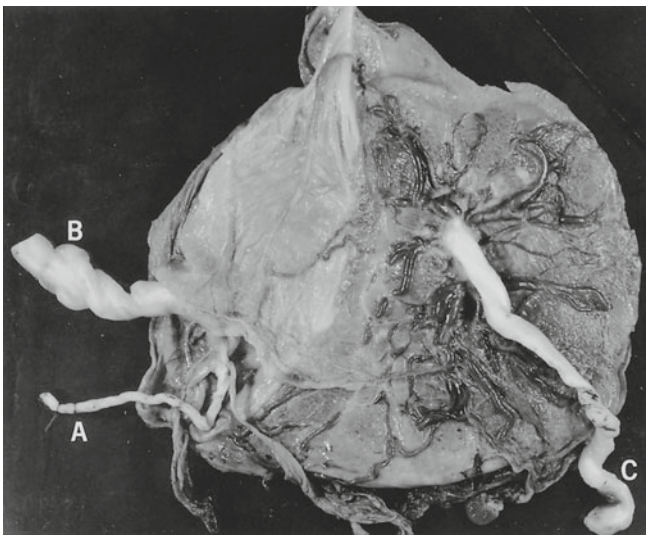


Fig. 25.104 Triamnionic, dichorionic triplets, all females. *A* is the donor of the transfusion syndrome, and *B* is the recipient in a DiMo placenta. *C* has a separate amnion and chorion, and blood groups are different from those the twins (Blood groups courtesy of Dr. F.H. Allen, New York, New York)

cephaly, patent ductus) are undoubtedly an effect of the prematurity of many twins. Other anomalies, notably those referred to as the VACTERL association [*v*ertebral *a*nal *c*ardiac *te*-fistula *r*enal *l*imb, a variant of the VATER (*v*ertebral *a*nal *te*-fistula *r*enal) association] and anencephaly were overrepresented in twins. A new international study of malformations in twins was authored by Mastroiacovo et al. (1999). Of 260,865 twins, 5,572 malformations were identified, affecting virtually all organ systems. The associations previously already known to exist were confirmed, although higher rates were found. James (1976) found that anencephaly occurs in DZ twins with the same frequency as in singletons, but that its incidence is increased in one or both of MZ twins. When it occurs in dichorionic twins, expectant management is advocated (Lipitz et al. 1995), although hydramnios may occur. In contrast, when it is found in monochorionic twins, "…expectant management is associated with a high rate of intrauterine lethality of the normal twin" (Sebire et al. 1997a). Of 11 such pregnancies, these authors observed fetal demise of both twins in 3 pregnancies.

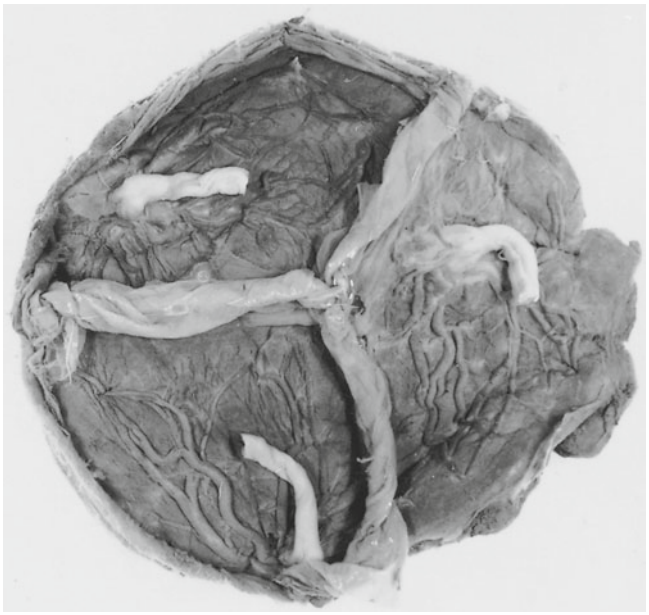


Fig. 25.105 Triamnionic, monochorionic triplet placenta at term. Many large anastomoses are present

Schinzel et al. (1979) studied the structural defects of MZ twins in greater detail. They considered that some of these anomalies are related to the MZ twinning process *per se*. This concept is certainly true for the acardiacs, the conjoined twins, and probably also for those defects that arise as the result of vascular anastomoses, e.g., porencephaly, intestinal occlusions. When twin abortuses were studied, it was found that the incidence of twinning, particularly MZ twinning, is much higher than expected (1 in 35 abortions). The rate of associated anomalies was not significantly different from the rate in the total population (Livingston and Poland 1980). Livingston and Poland (1980) found that 35 of 53 pairs were monochorionic MZ, 2 were opposite sex (DZ), and 16 were same sex and dichorionic. Uchida et al. (1983) found 7 of 15 to be opposite sex. In other situations, monozygotic twins apparently react differently to environmental teratogens, as was the case of the MoMo twins of Reitnauer et al. (1997).

A striking increase in twinning was found in infants with sirenomelia (symmelia). Usually, only one of the twins had that anomaly. Only rarely have both of MZ twins been concordantly affected by anomalies in general and symmelia in particular (Roberge 1963). Davies et al. (1971) gathered 327 cases of sirenomelia from the literature and found that there is a 100-fold increase of this anomaly in MZ twins when compared with singletons. We have previously discussed that the hypoplasia of sirenomelics' lungs, the Potter syndrome features, and amnion nodosum are prevented by the presence of the normal amnionic environment, guaranteed by a normal co-twin. This idea is beautifully demonstrated in the case described by Kohler (1972), and McNamara et al. (1995) added two more cases. Klinger et al. (1997) found additional support for this idea. They reported absence of "Potter" features in a MoMo twin with absent kidneys, genitalia, anal atresia, and SUA. Kapur et al. (1991) described sirenomalia in one twin, the other (dichorionic) having vanished.

Discordance for major anomalies in MZ twins seems to be the unexplained rule rather than the exception. It has been the topic of numerous publications, e.g., Fogel et al. (1965; Benirschke and Masliah 2001). Machin (1996) has summarized all known or hypothesized facts and theories of such unusual cases. Imaizumi (1989a) found that concordance of congenital hydrocephalus in Japan was only 15% for all twins (21% in like-sex twins), but that the corresponding figures from the literature were 4.6% and 7.8%, respectively. They also saw two like-sex sets with anencephaly and hydrocephaly. Hernandez-Johnstone and Benirschke (1976) cited much of the relevant literature. This concept, however, has been considered to be a "tautology" (Boklage 1987b). Boklage suggested that most surveys of anomalies in twins employ the Weinberg formula for the assignments of zygosity. We cannot agree with this statement. In numerous studies, the chorionic status was the method that decided the presence of MZ twins. Boklage was also critical of the concept that MZ twinning and anomalies are related processes; he favored the interpretation that, because such features as non-right-handedness and familial twinning are overrepresented in these anomalous twins, the relation between MZ twinning and anomalies does not hold. His concept was that many such twins derive from "polar body" fertilization, which he considered to be tertiary oocytes. That twinning and cardiovascular anomalies may have common origins was detailed in a large study by Berg et al. (1989). Most remarkably, Hamasaki et al. (1998) found discordance of the expression of the mutated prion that leads to Gerstmann–Sträussler–Scheinker disease in identical twins. Both had the mutation, but only one twin expressed the symptomatology.

In some cases, major disruptions of fetal structures can be explained by amnionic bands or adhesions of fetus to large sheets of amnion (Khudr and Benirschke 1972; Donnenfeld et al. 1985). Boulot and colleagues (1990) proposed that the anencephaly-like anomaly they observed may have resulted from injury at "embryonic reduction." It is of parenthetic interest to point out that the presence of placental anastomoses in DiMo twins, one being anencephalic, has served to better understand the regulation of fetal adrenal development (Kohler and MacDonald 1972).

In most of these anomalies, there is no evidence of a genetic component. It is perhaps even more surprising to learn that anomalies with a strong genetic etiology, e.g., cleft lip and cleft palate, are frequently discordant in MZ twins. Metrakos et al. (1958) reviewed 108 twin pairs and found the concordance in MZ twins to be 31%; in DZ twins, it was 6.3%. These authors and others proved monozygosity for some pairs by means of exchange skin grafts. Discordance of facial clefts is unusually common in MZ twins. Their evidence and that from many other studies clearly indicates a familial disposition of cleft lip/palate. Murray et al. (2004) searched for gene abnormalities in twins discordant for clefts and detected none. They concluded that this "…supports the hypothesis that non-etiologic post-twinning mutations are rare." Most recently, Segal (2009) reported male monochorionic triplets all of which had some cleft lip in all and cleft palate in one triplet. Studies of twins for other defects (e.g., club foot, dislocated hip) have led to the concept of causation by "polygenic genetic predisposition interacting with additional unknown intrauterine environmental triggers" (Carter 1968; see also Kato et al. 2005). This concept of a quasicontinuous variation or a threshold character with anomalies of multifactorial etiology (Fraser 1970) is currently the best way to interpret these seemingly contradictory findings. It remains to be elucidated as to what the prenatal factors are that place the affected twin beyond the critical threshold. It could be adverse placentation (e.g., velamentous insertion of cord or SUA), as we have championed, or it could be one of many, as yet undetermined, other factors. It may relate to unequal splitting. Too little is known of the placental conformation of most such twins to allow us to come to any definitive conclusion. More data must be collected on the precise placentation of twins with discordance for defects. The relative frequency of intestinal atresias reported may have a more direct relation to monochorionic twinning as they are overrepresented in like-sex twins. Perhaps it is caused by periods of hypotension, so-called vascular disruptions (Cragan et al. 1994). Discordance of twins, one with the Beckwith–Wiedemann syndrome, is definitely more frequent in monochorionic twins. In one relevant case that we observed, there were calcified thrombi in superficial placental veins of both twins, aside from massive enlargement of the affected twin's umbilical cord. Other MZ twins discordant Beckwith-Wiedemann syndrome (BWS) were reported by Weksberg et al. (2002) who suggested that this imprinting abnormality (on chromosome 11p13–15) perhaps predis-

poses to MZ twinning. Much other work on the imprinting abnormality in BWS and Angelman's syndrome has recently been conducted, and at least some findings suggest that there is a higher incidence when ART is performed for conception (Maher et al. 2003; DeBaun et al. 2003; Gicquel et al. 2003). The BWS is especially relevant here. Not only are female newborns more commonly affected, numerous monozygotic twins, discordant for the BWS, have been described (Weksberg et al. 2002). While these authors studied the imprinting discrepancies in great detail, both from lymphocytes and fibrous tissue cells, unfortunately, the placentas were not available, and thus the exact timing of the twinning event was not determined, although the possible unequal partitioning of cells (Machin 1996) was addressed. Most recently, ear lobe anomalies were shown to be discordant in well-characterized MZ twin (Artunduaga et al. 2009).

Two major reviews of discordant anomalies in twins were undertaken in an effort to delineate the prognosis of such gestations (Malone et al. 1996; Alexander et al. 1997). Both authors came to the conclusion that this constellation significantly increases the risk of premature delivery. Malinowski and Biskup (1997) found two sets of monochorionic twins in whom the survivors had gastroschisis, and they related this anomaly to possible ischemia of the abdominal wall occurring at the time of fetal demise of their co-twins.

25.19 Cytogenetics and "Heterokaryotypic MZ Twins"

Twins may have the same chromosomal errors as singletons. Rohmer et al. (1971) described a set of DZ twins with Down syndrome and collected 200 cases of trisomy 21 in the twin literature. One of these twins was a pure trisomic; the other had a small, subsequently diminishing population of trisomic cells; it had a normal phenotype. They speculated that blood chimerism might exist but were unable to verify it; the DiDi placenta contained no anastomoses. Most commonly, MZ twins are concordant for a particular aneuploidy (e.g., 48,XXXY in Simpson et al. 1974). Mosaicism has been observed on occasion, as in the MZ twins with trisomy 21 described by Shapiro and Farnsworth (1972).

A number of unusual so-called heterokaryotypic twins have been reported. They were monozygotic by various criteria, but their chromosome number differed. The list of these heterokaryotypic MZ twins reported has become so large that it is impractical to summarize all the reports here. Reasonably, complete reviews may be found in the contributions by Dallapiccola et al. (1985) and by Machin (1996). The former authors described a heterokaryotypic triplet and summarized, in table form, the 25 cases reported prior to their publication. Monteiro et al. (1998a, b) investigated the X-inactivation of the X chromosome in twin girls and found that different inactivation patterns occurred only in dichorionic twins. From a comparison of blood and buccal cell X-inactivation patterns, they reason that splitting of the MZ twins occurs at the time of this chromosomal inactivation, around day 4 (see also Machin 1996; Goodship et al. 1996). Cantú et al. (1998) did an interesting study of the segregation of X-chromosomal variants of the fragile X gene in a set of MZ triplets. The **paternal** gene was identical in all, but the **maternal** gene was different in all three triplets. This effectively eliminated their prior hypothesis of a single chromatid mutation **before** ovulation but also indicated that, despite physical similarity of these MZ triplets, their genetic disposition was different. The authors went so far as to state: "genomically speaking, there are no identical twins."

The commonest chromosomal variant is discordance associated with the Turner syndrome. The 45,X genotype is prone to abort during early gestation. Of the relatively few survivors, most had mosaicism for cells composed of 45,X and 46,XX (or XY) genotypes. Mosaicism results from the simultaneous occurrence of twinning and somatic nondisjunction of chromosomes. If the Y-chromosome of a 46,XY embryo is lost by nondisjunction during early development, male and female (45,X) MZ twins may be the outcome (e.g., Schmid et al. 2000; Wachtel et al. 2000). This formerly inexplicable situation, MZ twins of different sex, has in fact been recorded in several instances to have resulted in this fashion, as, for instance, by Gonsoulin et al. (1990a). The 45,X MZ twin of their report was additionally hydropic. Shevell et al. (2004) ablated such an abnormal MZ twin with 45,X by using radiofrequency obliteration of the umbilical cord. Investigators have more often documented MZ twins with various degrees and types of mosaicism, of X,XX, and XXX, or Y chromosomes. There is a wide spectrum. Kurosawa et al. (1992) have reported a set of MZ twins who were mosaic for two populations of cells, 45,X and 47,XYY, in lymphocytes and fibroblasts. One twin had a greater proportion of male-determining cells and had a male, the other a female phenotype. The fact that often both twins are mosaic may betray the influence of monochorionic placentation with anastomoses (when the mosaicism is confined to lymphocytes). Alternatively, when the fibroblasts of only one twin are mosaic or have a different complement from the karyotype of the co-twin, it may suggest the loss of one chromosome in one twin after splitting has occurred. Such is likely to have occurred in the two sets of mosaic monozygotic twins (45,X/46,XY) reported by Costa et al. (1998), who also reviewed the entire literature of this unusual phenomenon. Most of the placentas associated with this phenomenon have been DiMo, but an occasional twin has had a MoMo placenta. Precise studies of placenta and of lymphocyte, fibroblast, and chorionic karyotypes will enhance our knowledge as to the timing of this unusual event.

Prenatal diagnosis of such errors was once difficult because the intentional sampling of individual amnionic cavities was impractical. Young et al. (1974) introduced a feasible method to sample the individual cavities for the surveillance of Rh-sensitized pregnancies. It has now been reported successfully accomplished for 79%, 94%, and 98% of cases, respectively (Librach et al. 1984; Taylor et al. 1984; Tabsh et al. 1985). This methodology has not only allowed precise diagnosis but has led to fetal transfusions, now practiced routinely (Bowman 1985; Pijpers et al. 1988). An alternative method for aspirating the two cavities was advocated by Jeanty et al. (1990). They were nearly uniformly successful, but the possibility of destruction of the dividing membranes exists with this technique. Selective feticide can then be undertaken when fetal trisomy is diagnosed by any of these techniques (Kerenyi and Chitkara 1981; Chitkara et al. 1989; see also Donnenfeld et al. 1989). Pijpers et al. (1988) studied 83 pregnancies and obtained karyotypes of both twins in 77 cases (93%). They found elevated AFP levels (in both sacs) in two cases that were due to renal abnormalities. This finding suggested to them that AFP diffuses through the membranous partition. Unfortunately, the types of placenta present in these cases were not recorded. Franke and Estel (1978) had previously found that AFP permeates the membranes.

25.20 Chimerism, Mosaicism

It is not uncommon in cytogenetic studies to identify cell lines with different chromosome number or different complements. This has most recently become a problem in amniocentesis and placental cell cultures. The latter aspects will be considered in Chap. 21; here, it is essential to make the differential diagnosis of mosaicism and chimerism. Whole-body chimerism may develop when, in very early stages of development, dizygotic twin embryos fuse to form a single individual. The resulting genetic chimera, a "whole-body-chimera," is an individual that is composed of two populations of cells whose origin are two genetically completely different fertilization products. In addition to this mechanism, the possibility exists that two spermatozoa fertilize an ovum **and** a polar body and that these structures then make up a single embryo. This second explanation is the mechanism that is favored by most investigators for the production of chimeras. Chimeras differ from mosaics, and they should be clearly distinguished.

Mosaics are individuals composed of different cell lines but derived from a single embryonic precursor. Because of the process of "lyonization," all females are considered to be mosaics. Not only mosaics may have different cell lines with different chromosome numbers, but because of mutations, they may also have lines of cells with different phenotypic expressions. An individual with cancer, for instance, could be a mosaic; one line of cells would be the normal body constituents, the other would be those cells that form the neoplasm. Healey et al. (2001) examined lyonization in monozygotic twins genetically and deduced from their findings of 20 discordant female twins that adult height was not correlated with different lyonization patterns. It is convenient and important to distinguish two pathogenetically different types of chimeras: (1) blood chimeras (also called "Twin chimeras" by Tippett 1984) and (2) whole-body chimeras ("dispermic chimeras").

Blood chimeras have long been known to occur in cattle. In bovine fetuses, the placentas often fuse, the fetal blood vessels join, and blood is exchanged between the embryonic twins. Because embryonic blood is largely like bone marrow, there is seeding of the other twin's marrow space with genotypically different hematopoietic elements and lymphocytes. It results in life-long admixture because these cells are not rejected by the immunologically impotent embryo; the foreign cells are subsequently regarded as "self." When male and female bovine fetuses are thus joined, it is easy to identify clones of male lymphocytes in the female and vice versa. This phenomenon is restricted to motile hematopoietic system cells. The fixed tissue cells do not participate.

The fact that chimerism first was recognized in cattle results from the masculinization of the female twin in heterosexual bovine co-twins. The female becomes a "freemartin" (Lillie 1917) an animal that has external masculinization, an absent uterus, atrophied ovaries, and female genotype. The degree of masculinization does not depend on the percentage of chimeric male hemopoietic cells (Herzog 1969). Complex chimerism may be detected when triplets or quadruplets are thus admixed (Basrur et al. 1970). Although long known, the virilization of female artiodactyl twins has not yet been satisfactorily explained. Lillie (1917) and most subsequent investigators have presumed that it was the result of embryonic hormone action, secreted by the male gonads. Such an obvious hypothesis proved facile when it was discovered that marmoset monkeys of South America not only always have DZ twins but also regularly have fused placentas and that they are all blood-chimeric. Although 50% are XX/XY chimeric, the females are not sterilized in analogy with the freemartin effect (Benirschke 1971; Gengozian 1971). Currently, no rational explanation exists for this discrepancy among species. One might speculate that there are differences in the Mullerian inhibiting substance or the receptor because they are not subject to hormonal influences. We have always assumed that these are analogous in different taxa, but perhaps this is an error to make such an assumption. Niku et al. (2004) showed that among the hematopoietic precursors are some remarkably multipotent cells that are irregularly distributed throughout the body and that become especially prominent in granulation tissue. From the same

laboratory comes evidence of the variable percentage of B- and T-cells. These systems are currently of particular interest as the role of circulating "stem cells" is central to our understanding of chimerism (Pessa-Morikawa et al. 2004). Freemartinism occurs in other artiodactyla, in birds, and in a few other species. We used to believe that some primitive germ cells might also travel through embryonic intertwin anastomoses to take up residence in the opposite-sex host; findings by Gengozian et al. (1980), however, have made this unlikely. In addition, many investigations have addressed issues of immunological tolerance in chimerism (Porter and Gengozian 1969; Tippett 1984).

In contrast to marmosets and cattle, anastomoses between DZ twin placentas of humans are rare indeed. One dichorionic twin placenta with an anastomosis has been described by Cameron (1968) and is depicted in Fig. 25.22. Genetic study of the twins, however, showed them to be MZ. More recently, Lage et al. (1989) presented a dichorionic twin placenta with anastomoses that was also accompanied by a mild form of the transfusion syndrome. The hematocrits of the twins were 43% and 59%, respectively. Molnar-Nadasdy and Altshuler (1996) saw a similar case at autopsy of macerated immature fetuses. The female stillborns possessed dichorionic dividing membranes (with velamentous cords) and had marked discrepancy in heart weights and coloration. Quintero et al. (2003a) reported TTTS in DiMo twins that were dizygotic (XY/XX), and at a later time (2010), they found TTTS in a DiDi placenta that needed to be laser-treated. Ekelund et al. (2008) showed that this may occur in patients who had ART (Chap. 27). Another unusual set of twins is that recorded by King et al. (1995). These presumably MZ twins had DiDi placentation, with ink injection–confirmed anastomoses. While blood exchange had occurred, the typical TTTS was absent; one fetus had died with hydrocephaly before the other was aborted. More recently, Souter et al. (2003) reviewed the topic and presented a set of monochorionic, heterosexual twins conceived by IVF and who also had blood chimerism. The chimerism must have resulted from the "fine arterial-to-arterial anastomoses" that were identified by fluid injection. Redline (2003) who made editorial comments on the case reviewed the development of twin embryos and also entertained the possibility that the IVF manipulation could have been a factor in the genesis of these unusual twins. As has been indicated earlier, the occurrence of monochorionic twins after IVF and embryo transfer is not uncommon now, and the dogma that monochorionic twins *must be* MZ twins is no longer tenable. In order to prove the existence of such unusual placentas, it is necessary that injection of the vessels be done. Therefore, another report, anastomoses in a dichorionic twin placenta of twins with CMV infection, is more difficult to interpret (Foschini et al. 2003). The anastomotic arrangement was suggested only by stereomicroscopy of formalin-fixed placentas and described as being "subchorial." Since there are generally never any subchorial anastomoses in any placenta, we reserve judgment on this case. More challenging still is the report by Quintero et al. (2003a) on a set of heterosexual twins with TTTS (unsuccessfully treated with laser ablation of A-V anastomoses) and DiMo placenta; this is truly exceptional but points to the need for full genetic and pathological study.

These cases are truly exceptional. In addition to these observations, it must be recorded that spontaneous "blood chimerae" have been observed in a few other occasional human fraternal twins. They have had no sexual abnormalities and are like marmosets in that respect. When their *fixed* tissue has been studied, it was not found to be admixed. The chimerae must, therefore, have received the foreign clone of blood cells either through placental anastomoses or, less likely, transplacental. Kadowaki et al. (1965) reported the transfer of maternal lymphocytes to the fetus. They described a phenotypically normal male with XY/XX blood chimerism and apparent graft-vs.-host rejection disease. Such transplacental exchange of lymphocytes, however, must be uncommon (Olding 1972). Only on rare occasions have prospective studies shown minor transplacental lymphocyte chimerism. This transplacental traffic of cells is discussed in Chap. 17; it may affect singletons as well as twins and has recently been of great interest because the resulting microchimerism of blood and stem cells finds correlation with maternal "autoimmune" diseases (Johnson et al. 2001b; Srivatsa et al. 2001; Nelson 2001; Adams and Nelson 2004).

The occurrence of blood chimerism in human DZ twins was first demonstrated by Dunsford et al. (1953). Since then, more than 30 cases have been described (Tippett 1984). They are usually detected when blood group tests have peculiar results that necessitate full genetic investigation; it usually happens long after birth. The associated placenta of such a chimera has been fully studied only in the case of Nylander and Osunkoya (1970). Hartemann et al. (1963) suggested that placental study of twin placentas would more often identify anastomoses among fraternal twins. This has not been our experience, despite the fact that we have tried on many occasions to verify anastomoses among DiDi twins by use of dye injections. Anastomoses that become apparent by radiographic examination of injected twin placentas, and those discovered by corrosion casts made following plastics injection (Scipiades and Burg 1930; Pérez et al. 1947) give unreliable results. Crookston et al. (1970) described the unusual and complex immunological breakdown of tolerance that rarely occurs in such twins. On occasion, most unusual situations are encountered with chimerism; thus, O'Donnell et al. (2004) found blood chimerism for 47,XY and 47,XY + 21 in a monochorionic set of twins that was naturally conceived. Genetic analysis revealed monozygosity; how the trisomy then developed in a DiMo placenta is a

bit speculative. "Trisomy rescue" is often assumed but not easily compatible with a DiMo placentation. A similar case of chimerism for Down's syndrome in male twins with a diamnionic monochorionic twin placenta and A-A anastomosis was terminated by Shalev et al. (2006); there was no visible evidence of trisomy 21 in either abortus. Perhaps more readily explicable is the 45,X/46,XY blood chimerism in a set of twins (DiMo placenta) reported by Tho et al. (2007) who followed the twins to age 21. The normal male had then oligospermia while the "female" twin had some testicular development. Clearly, one Y-chromosome must have been lost in early development.

25.21 Whole-Body Chimerism

In whole-body chimeras, the entire body consists of cells with two or more genetic lineages that are derived from separate fertilization products. Most common among them is probably the fertilization of an ovum and a polar body by two spermatozoa, with the maternal contribution being similar. Such individuals represent, genetically speaking, fraternal twins fused into one body. They are not necessarily clinically manifest and may be fertile, even when XX and XY lineages coexist. The topic was discussed in great detail by Yu et al. (2002) because of the discovery of a fertile 46,XX/46,XX woman who was tested for transplantation antigen. It is accompanied by excellent drawings and discussion. Boklage (2006) has reviewed the topic in great detail, although a number of considerations are missing in that discussion. The condition most closely resembles the famous statement of Faust written by Goethe: "Zwei Seelen wohnen, ach! in meiner Brust, Die eine will sich von der andern trennen…"

Most total body chimeras are discovered when the two populations of cells have different sex chromosomes (XX/XY), which frequently results in gonadal abnormalities, most common among which is true hermaphroditism (see also Kim et al. 2002). The diagnosis was initially made by amniocentesis in a detailed report by Lawce (1985). The male neonate was entirely normal and had an overall 48/98, XX/XY cell admixture. Remarkably, the ratio was 40/8 in placental membranes but 1/39 in placental tissue. Other cytogenetic errors with multiple karyotypes are also known (Moreno and Sanchez 1971). Whole-body chimerae may also be discovered during routine blood grouping tests. Still others may be found because of unusual phenotypic features, such as heterochromia, eyes of different color. Some such cases may even possess "striping" of skin, or they may have abnormal patches of the skin, resulting from the irregular distribution of melanocyte precursors that are derived from different genotypes (Zuelzer et al. 1964; Corey et al. 1967). An especially striking case of chimerism was published by Karam and Baker (2004). The neonate had a vertical pigment difference, right-sided male genitals and left-sided female genitals and was 46,XX/46,XY on karyotyping. This skin coloration is particularly obvious in the rare male tricolored (tortoiseshell) cats because the colors black and orange are allelic on the X chromosome in felines. Tricolored cats must all be female, or else they have chimerism (rarely are they endowed with 39,XXY chromosomes) as the basis for their abnormal coloration (Centerwall and Benirschke 1975). It is thus important to clearly distinguish between mosaicism and chimerism, something often not duly considered in the literature. The placentas of these individuals never seem to have been examined, but then there is no reason to believe that they would be unusual.

The question of how spontaneous whole-body chimerism originates is not yet completely answered. It is readily achieved experimentally by fusing morulae of experimental animals after their zonae pellucidae have been removed (Tarkowski 1961). How this happens in vivo is speculative. The finding of diploid/triploid chimeras (e.g., Van den Berghe and Verresen 1970) was taken as evidence that fertilization of a large polar body (common in mice) produced such abnormal individuals (dispermic chimeras). Other proposed mechanisms, such as secondary nondisjunction of whole haploid sets (Jenkins et al. 1971), are much less likely. De la Chapelle et al. (1974) have suggested, as did other investigators, that early fusion of two embryos may be the way that whole-body chimeras are produced spontaneously, much as in the experimental model. This idea has subsequently been disputed because of the paucity of markers available. These concepts and the wide complexity of chimerism and hermaphroditism are topics of the review by Tippett (1984). Finally, an interesting true hermaphrodite (46,XX/46,XY) was described by Strain et al. (1998). It resulted most likely from fusion of two early fertilized ova and was the result of in vitro fertilization and implantation of three fertilized ova; a male singleton resulted with inguinal hernia that contained an ovary tube and uterine horn. Whole-body chimerism was elegantly proved by DNA study, and the occurrence suggests that manipulation of early ova may have such undesirable result. Since that report, other cases of abnormal blastocyst behavior following in vitro fertilization have been reported, especially the increased frequency of MZ twins among multiples, when smaller numbers of ova were transferred than babies born.

25.22 Triplets and Higher Multiple Births

The frequency of spontaneously conceived higher multiple births is customarily estimated with the help of Hellin's rule, which was discussed earlier. Because of ovulation induction with hormones, many higher multiple births have occurred; nonutuplets hold the record, but they did not survive. Survival of septuplets was first observed in the USA in 1997, and surviving, prematurely delivered octuplets were delivered in

Houston in 1998. For reasons of widespread hormone usage in assisted reproduction, it is presently difficult to ascertain the real and spontaneous occurrence of higher multiple births in any population. Many excessive numbers are reported only in the newspapers, and they are usually artificially induced. The patient who aborted the nonutuplets during the 12th week of pregnancy was not further described. Octuplets, born prematurely to a Mexican woman who had taken contraceptives until 8 months earlier, all died from complications of prematurity (Anonymous 1967), but a more recent set survived and is referred to below and in Chap. 27. The frequency of higher multiple births has increased significantly in recent years because of the practice of "assisted reproduction." Thus, Collins and Bleyl (1990) were able to summarize results of 71 quadruplet pregnancies. They advocated delivery by the 34th week of pregnancy because of the growth deficit occurring thereafter. Elliott and Radin (1992) reviewed their own 10 quadruplet pregnancies and made specific management recommendations. They had no bad outcomes, even though their gestations terminated at about 32.5 weeks. Interestingly, the older the mothers of quadruplets and quintuplets, the better were the outcome (Salihu et al. 2004a). Kiely et al. (1992) surveyed the trends of higher-order multiple births from 1972 to 1989. There had occurred a 113% increase among White and a 22% increase among African American mothers, with a 50% reduction in perinatal mortality. We have recently had surviving sextuplets (six chorions) at 28 weeks with three separated placentas on each anterior and posterior portions of the uterus. They were conceived after hormonal superovulation and survived. At the same time, sextuplets were born at 32 weeks in Pennsylvania, also after hormonal medication usage.

When Allen (1960) applied the Weinberg formula to higher multiple offspring, he observed for triplets that the proportion of MZ/DZ/TZ (TZ = trizygotic) was 1:3:2 among African Americans and 1:2:1 among Whites; quadruplet Whites were 2:6:5:4. In Japan, with different rates of multiple births, the ratios for triplets were more like 2.5:1:1, reflecting the lower DZ twinning rate of this genetically different population (Imaizumi and Inouye 1980). The high DZ rate of Nigerians is reflected in their distribution of zygosity in triplets, approximately 1:4:6 (Nylander 1971b). The frequent admixture of monozygotic and dizygotic twins in plural births is well reflected in their placentation. They may all be monochorionic or they have mono-, di-, and trichorionic placentation. Nylander and Corney (1971) found in the Yoruba population of triplets, 1 monochorionic, 10 dichorionic, and 29 trichorionic specimens. Most other reports are of single gestations or are from smaller series, than those collected by Nylander and Corney (1971). Boyd and Hamilton (1970) had the following placentation in their eight triplet pregnancies: four monochorionic, three dichorionic, and one trichorionic; they were thus different from that in African women, and this reflects the different causes of twinning in the populations studied. Not all dichorionic triplets are polyzygotic. Thus, the dichorionic triplets described by Komai and Fukuoka (1931) were shown to be monozygotic.

Triplets and higher plural births are not only smaller than expected for their gestational age (McKeown and Record 1952), they also commonly deliver much earlier than twins or singletons. The perinatal mortality of 59 triplet pregnancies was 23% in the study of Itzkowic (1979). This investigator emphasized that "cervical incompetence" was not a significant factor in their premature deliveries. Others (Gabos 1972) reported that cervical failure may require surgical intervention in these higher multiple gestations. O'Sullivan (1968) even advocated it routinely in multiple pregnancies with hydramnios. Michlewitz et al. (1981) found a perinatal mortality of 13% past 20 weeks and 7% when 15 triplet pregnancies past 28 weeks were studied. A very large experience of the outcome of assisted reproduction from Norfolk (Seoud et al. 1992) found that there was the expected progressive increase of perinatal complications and prematurity with higher-order births. Keith et al. (2002) edited a book on all aspects of triplet deliveries.

Lipitz and his colleagues (1989) have shown that the outcome of triplet pregnancies has improved in recent years. They studied 78 triplet pregnancies between 1975 and 1988, with 88% occurring after ovulation induction. Their finding was that elective cerclage neither improved fetal loss nor enhanced the length of gestation. Of the babies they were able to follow, 10.5% had severe neurological handicaps. Some triplets have been delivered with long time intervals. Simpson et al. (1984) had the first infant born at 23 weeks' gestation (neonatal death with 505 g weight, congenital infection), and 99 days later (with Shirodkar stitch, antibiotics, and isoxsuprine), a Cesarean section was done at 37 weeks. One triplet was macerated, and the other lived (2,580 g); the placenta was a fused TriTri organ. Cardwell et al. (1988) described the survival of one triplet, with the first being born at 23 weeks (hyaline membrane disease); the second was born 4 days later and died with hyaline membrane disease. The third triplet delivered 16 days after the first and survived. Chorioamnionitis complicated this pregnancy as it does in many plural pregnancies. A pregnancy with one triplet aborting during the 16th week of pregnancy and the other triplets surviving to delivery at 35 weeks was reported by Banchi (1984). The aborted triplet had a separate chorionic sac; the survivors had a DiMo placenta. A most remarkable case of triplets in a uterus didelphys was described by Mashiach et al. (1981). The clomiphene-induced pregnancy resulted in triplets: two in one horn and one in the other. One was found dead at 22 weeks; and at 27 weeks, uterine contractions expelled a macerated triplet from the right horn, but Cesarean section was done to deliver its cotwin who later died. The left horn did not go into labor. At 37 weeks, a normal triplet was delivered by Cesarean section. Gonen et al. (1990a) reported on five triplet gestations

Fig. 25.106 Triamnionic, trichorionic term placenta. There are no anastomoses, and despite intimate fusion, no blood chimerism. Note the velamentous cord insertion of No. 3

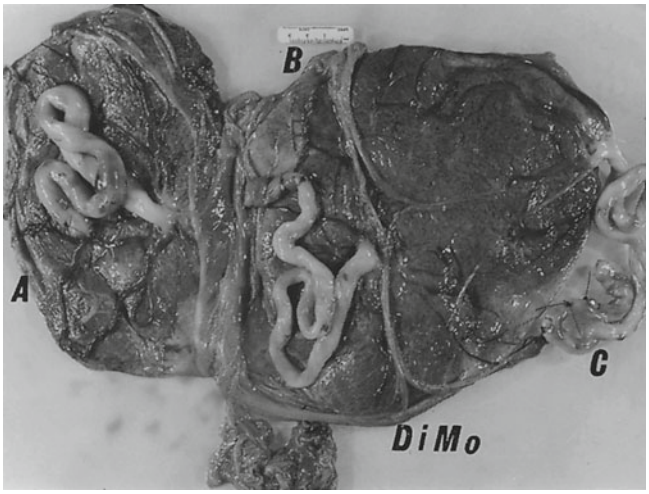


Fig. 25.107 Triamnionic, dichorionic triplet placenta at 36 weeks' gestation, all males. The diamnionic set of twins are at right with a single A-V anastomosis from *C* to *B*. All survived. The slightly separated dichorionic placenta of triplet *A* (at *left*) has an area of circummargination at *top*, where the membranes of the right triplet were pushed the membranes away

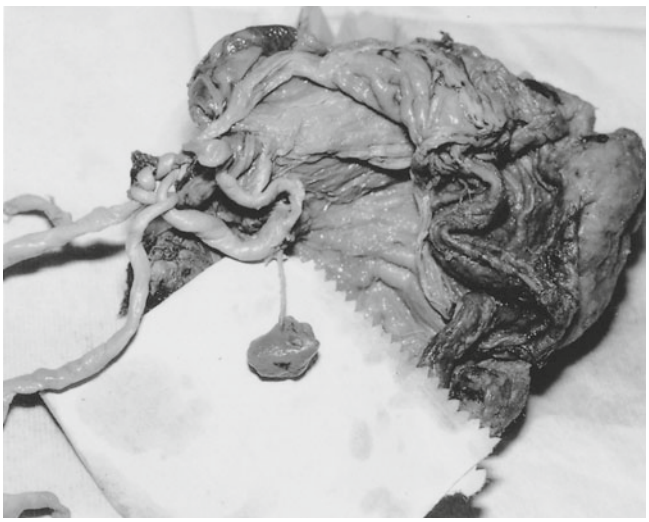


Fig. 25.108 A MoMo triplet placenta from a spontaneous abortion. Note the entangling of all umbilical cords. One was a normal fetus and one an anencephalic; the small fetus, placed separately on the piece of paper, was an acardiac

with fetal death of one or two fetuses. Four of these were monochorionic and delivery took place 30 (±26) days after the diagnosis of fetal death. Blickstein et al. (2003) found frequently large discrepancies in birth weight and implied "exhaustion of fetal growth potential." Salihu et al. (2004b) compared survival of triplets in white and black populations, finding substantially higher mortality in the black population, being highest postnatally. Al-Kouatly et al. (2003) commented on the high frequency of thrombocytopenia in triplets and inferred that its commonest cause was preeclampsia. Luke et al. (2002) found that outcome of 178 sets of triplets was most favorable when there was a prior gestation with good outcome, adequate weight gain, and greater length of gestation.

The various types of triplet placentations are shown in Figs. 25.103, 25.104, 25.105, 25.106, 25.107, and 25.108, and they have been investigated in considerable detail by Machin and Bamforth (1996). In addition to these three variants, the placentas of DiDi triplets may be separate. This is relatively uncommon, however, as the uterine surface area available for the implantation of multiple placentas is not large enough for them to remain separate. The live-born monozygotic triplets whose placenta is shown in Fig. 25.103 were monoamnionic and monochorionic (Sinykin 1958). Triplet pregnancy does not always prevent entangling of cords when they are monoamnionic, as in the case shown in Fig. 25.104, although entangling is less common in triplets than in twins. In this case, one anencephalic and a tiny acardiac fetus were associated with a normal triplet. All were aborted because of cord entanglements. Kohler and MacDonald (1972) reported triplets, one of whom was anencephalic and who had a normal DiMo cotwin. There was a normal separate chorionic triplet. The DiMo twins of the TriDi placenta shown in Fig. 25.104 had suffered the typical transfusion syndrome, with A being the runted donor and B the recipient who died neonatally. All were females, with C representing a separate zygote, as established by blood grouping (courtesy of Dr. F.H. Allen, New York). Another TriDi set of triplets is seen in Fig. 25.107.

It has long been known that an admixture of MZ and DZ multiple births is more common than would be expected by chance, but the reason is not clear. In addition to these examples, we have seen a DiMo triplet pregnancy abort with two monoamnionic pygopagous twins, a term DiMo triplet placenta with one set of thoracopagi, as well as a TriTri triplet pregnancy with two fetus papyracei, the other fetus coming to term and being normal. The prenatal death of the two

fetuses may therein have been due to their velamentous cord insertions. A triplet pregnancy produced by in vitro fertilization is reported in Chap. 6. Five ova had been transferred, three implanted, and one became a placenta percreta that had to be removed from its interstitial implantation during the second month of pregnancy. The two remaining fetuses were delivered by Cesarean section near term, one having amnionic bands. We have witnessed yet another triplet placenta percreta. Thus plural pregnancies can present multiple problems with many anomalies of placentation alone.

It has often been asked how triplets or quintuplets (e.g., the famous Dionne quintuplets) can be MZ, as one might expect even numbers to result. Uneven numbers of monozygotic multiples may be explained by assuming that, on occasion, one embryo may not have survived or that "…one division may set back development of the daughter products so that secondary division can occur at the same stage or even an earlier stage than did the primary division…or… three or more embryonic centers might arise simultaneously instead of two" (Allen 1960). Allen presented a graphic demonstration of the genesis of multiple embryos, assuming binary divisions as the principal modus operandi. Monochorionic, tetraamnionic quadruplet girls have been recorded by Steinman (1998); born by Cesarean section, they weighed between 940 and 1,440 g and did well.

Quadruplets and quintuplets have also become more common in recent years. Whereas in the past most had not been induced by hormone administration, such treatment is clearly now a factor. We have met a diabetic patient who had three sets of fraternal triplets and then a set of fraternal twins, and her uterus finally had to be removed when it ruptured with a quadruplet pregnancy. Sinclair (1940) depicted the QuaTri placenta of a set of surviving quadruplets. A similar placenta from three-egg quadruplets was described by Ryan and Wislocki (1954). Hamilton et al. (1959) reported the quadrichorial placenta depicted in Fig. 25.109. They found in the 16 cases of the English literature that "…every possible combination of ovulation had occurred except for double monozygous, often stated never to appear." Diddle and Burford (1935), however, described just such a case in stillborns. Atlay and Pennington (1971) observed a quadruplet pregnancy after ovulation induction with pituitary gonadotropins. It was composed of a set of monoamnionic twins, the others all having their separate amnion, and they were of different sexes. The 30 weeks' gestation quadruplets had a good outcome. In this contribution, Atlay and Pennington provided much hormonal data that may be helpful in the surveillance of plural pregnancies. McFee et al. (1974) reported on two sets of quadruplets, among which only one of the eight premature newborns succumbed. The authors gave detailed and helpful instructions as to preparations needed by staff and family for the anticipated delivery of plural births. Williams (1926) described the quadruplet pregnancy of a 38-year-old woman whose offspring all died. The placenta was TriTri and fused.

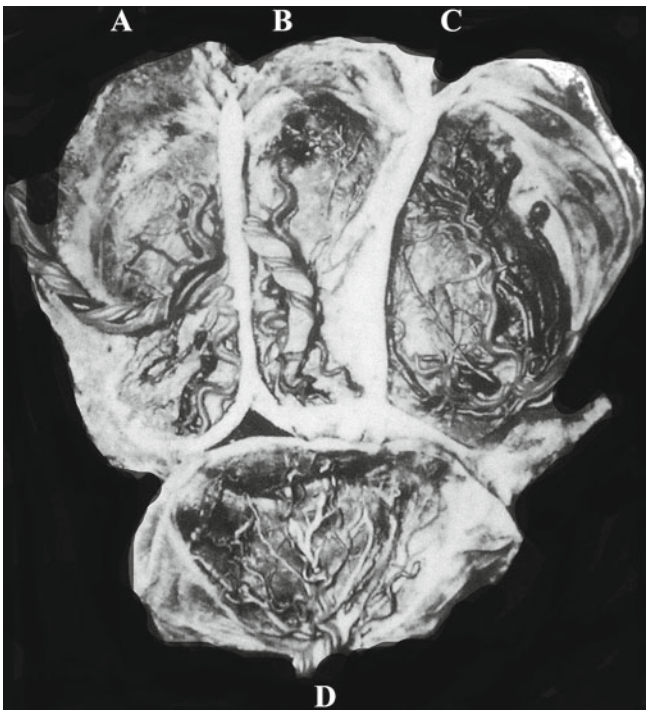


Fig. 25.109 Quadruplet placenta with four chorionic sacs, all surviving (*Source*: Hamilton et al. (1959), with permission)

Fig. 25.110 Quadruplet placenta (QuaTri), with DiMo MZ twins at *bottom left*, one having marginal insertion of the umbilical cord (35 weeks, 920 g)

He also reported on the fact that 24% of the 280 sets of twins observed at the Johns Hopkins Hospital were monochorionic; of four triplets, three were TriDi, and one was TriTri. We have seen several quadruplet placentas with four chorions and one with four amnions and three chorions (Fig. 25.110). Imaizumi (1989b) reported on 16 sets of quintuplets from Japan. Three sets were live-born, eight were stillborn, and five were live- and stillborn, with 51 of 80 offspring being stillborn. The mean weight of 40 quintuplets was 1,048 g.

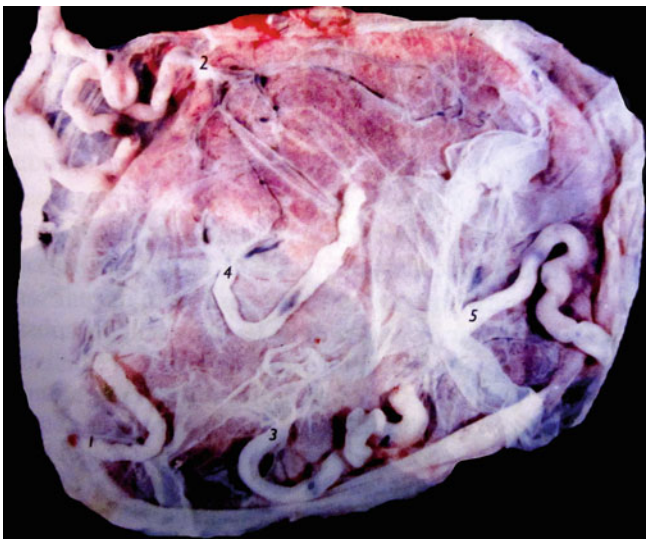


Fig. 25.111 Monochorionic (quint-amnionic) quintuplet placenta, immature. All infants died from hyaline membrane disease; No. *5* had SUA. Large anastomoses are present (From Gibbs et al. (1960) and Neubecker et al. (1962), with permission)

Fig. 25.112 Sextuplet placenta with six chorionic sacs and a male fetus papyraceus (Courtesy of Dr. M.A. Fletcher, Washington, DC)

Nichols (1954) published a list of 17 quintuplet births in the United States and two in Canada, as well as five sextuplets in the United States. An editorial (Anonymous 1968) estimated spontaneous quintuplets to occur as rarely as 1 in 8 million to 54 million births. The combined weights for four surviving sets were 10.61, 14.08, 12.11, and 23.52 lb. We have seen surviving quintichorial quintuplets, conceived after clomiphene citrate (clomid) induction and delivered at 31 weeks. Their combined weight was 8,200 g (1,420–1,820 g). Three of the umbilical cords had marginal insertions. As can be imagined, such enormous uterine distension gives rise to maternal dyspnea, hydramnios (?), excessive weight gain, preeclampsia, edema, varices, and cardiac failure. In another editorial (Anonymous 1963a), 50 sets of quintuplets were listed as having been reported in the entire medical literature. It is interesting to note that several of the well-described quintuplet placentas were diagnostic of MZ quintuplets, as were the Dionne quintuplets. The fact that one of the latter gave birth to a set of male twins is presumably a random occurrence.

A monozygotic quintuplet placenta was superbly studied by Gibbs et al. (1960); it is depicted in Fig. 25.111. This placenta had a single chorion and five amnions. There were many vascular anastomoses on the chorionic surface; several cords inserted marginally, and that of No. 5 had a single umbilical artery. All these extremely immature infants succumbed from hyaline membrane disease. The placenta was redescribed by Neubecker et al. (1962). Quintuplets reported by Berbos et al. (1964) were QuiQua (quint-amnionic, quadrichorial); a quintuplet pregnancy induced with gonadotropins and studied by Aubert (1960) resulted in three male and two female infants, with QuiQua placenta, and the successful quintuplet pregnancy reported by Liggins and Ibbertson (1966) had five chorionic sacs (QuiQui). Bender and Brandt (1974) studied a quintuplet placenta by morphometry. It was induced by hormones and had QuiQui membranes. These authors drew attention to the "irregular chorionic fusion" of the dividing membranes, discussed earlier and depicted in Figs. 25.51 and 25.52. G. Altshuler (1975, personal communication) also observed a QuiQui placenta that, when injected with milk, exhibited no anastomoses. Finally, the monochorionic quintuplets (QuiMo) with one acardiac fetus reported by Hamblen et al. (1937) are shown in Fig. 25.90.

No sextuplet placentas had been described as far as we can ascertain from the literature, and few sextuplets have been reported to have occurred. Figure 25.112 shows such a specimen from a patient treated with "fertility drugs" that was provided by Dr. M.A. Fletcher from a delivery in Washington, D.C. in 1983. It was a fused placenta with six amnions and six chorions. It also contained a fetus papyraceus, estimated to have died at 20 weeks' gestation. That fetus had a normal skeleton, but its cord had velamentous insertion, and this insertion was the presumed reason for his demise. Three other fetuses had marginal cord insertion. Two cords had a left, and three a right spiral; that of the fetus papyraceus was not spiraled at all. One specimen of a septuplet pregnancy, induced by gonadotropins and prematurely delivered (Turksoy et al. 1967), was depicted by Boyd and Hamilton (1970). The sacs each had their own chorion and amnion; one was separated, and the others were fused. The cords were mostly marginal, and one had SUA. A new set of septuplets was recorded by Suvalsky et al. (2005) with an excellent description of the placenta. The pregnancy was the result of superovulation; seven surviving neonates were born at 30.5 weeks' gestation; two umbilical cords had a velamentous insertion, and seven chorions were found. Now, because

of the practice of ART, a set of octuplets has been witnessed with IVF and six blastocyst transfers. Two of these bastocysts must have "split" and resulted in MZ sets of twins (Minkoff and Ecker 2009), a practice that was commented upon critically by Chervenak and McCullough (2009).

Because plural gestations generally have poor outcomes, their early diagnosis and "selective reduction" of some cases is currently being advocated. By ultrasonography, Campbell and Dewhurst (1970) diagnosed hormone-induced quintuplets as early as at 19 weeks' gestation. The pregnancy went to 31 weeks. Labor ensued, and the healthy quintuplets were delivered by Cesarean section. Kanhai et al. (1986) punctured the hearts of three quintuplets at 10 weeks' gestation (one was repeated at 11 weeks). The mother subsequently delivered full-term healthy twin girls. The placenta had only one 2.5-cm embryonic rest. Various authors have addressed fetal reduction of multiple gestations in recent years, primarily, we believe, because of the poorer outcome of multiples and because so many more large "litters" are being produced. Thus, Miller et al. (2000) addressed the fiscal aspects of hospitalization and those occurring in later life. Stone et al. (2002) found that additional fetal losses occurred mostly in sextuplets, less so with other multiples and found an overall loss rate of 5.4% in 1,000 (!) consecutive cases. Fetocide was performed for a variety of reasons, and its frequency had been steadily increasing in these authors' experience, with more mothers now opting to retain a singleton rather than twins. Their previous publications on this topic are referred to in this chapter as well, and the rate is compared to the findings of other institutions. In the second chapter of this institution (Eddleman et al. 2002), the authors reviewed 200 terminations for anomalous multiples and caution that dichorionicity needs to be established sonographically before an attempt at potassium chloride injection is done. It is also interesting to note that, when Dickey et al. (2002) studied the *spontaneous* reductions of multiples, they found that more than 50% of triplets had IUFDs before 12 weeks (36% of twins, 53% of triplets, 65% of quadruplets). Similar findings come from La Sala et al. (2004). Heyborne and Porreco (2004) used reduction in three cases of severe preeclampsia complicating twin gestations with discordance and found that PIH resolved in all three and allowed lengthening of gestation. Most commonly, this reduction is accomplished by cardiac injection of KCl, but on occasion, this is dangerous, as the maternal cardiac arrest (resolved) in a patient reported by Coke et al. (2004) describes. They reviewed the usage of KCl injection in general. Another hormone-induced quintuplet pregnancy was managed by Farquharson et al. (1988). At 9 weeks, two embryos had intracardiac injection of hypertonic saline. Five days later, the procedure was repeated with another embryo. The maternal serum human chorionic gonadotropin levels declined substantially, and at 37 weeks, heterosexual twins were delivered vaginally. Their placenta was DiDi. In the membranes, a plaque of atrophied villi and a cavity (but no fetuses) were found.

Evans and colleagues (1988) presented four such cases of therapeutic intervention. They also discussed the legal and other implications that attend this novel therapy. Their first case had nine gestational sacs at 7 weeks. Three fetuses were "needled" at 8 weeks and three additional ones at 9 weeks. The patient delivered two healthy males at 35 weeks. Their second case was a hormone-induced quadruplet pregnancy with elimination of two sacs by cardiac puncture at 10 weeks. Two healthy children delivered at 36 weeks. In the third case, in vitro fertilization led to implantation of four embryos; two embryos were eliminated at 10 weeks. One remaining fetus was then found to have Potter's syndrome. The other died in utero. In their fourth case, four fetuses had been induced with hormones, and two were eliminated at 11 weeks. The remaining twins were aborted because of "cervical incompetence." They delivered, despite cerclage, at 19 weeks; the placentas were not described by these authors. They emphasized ethical issues and the need for regulated hormone induction of pregnancy for infertile patients, an aspect that was further elaborated on in discussion by Weiner (1988). It might be mentioned parenthetically that there has been much discussion as to whether cerclage is indicated in multiple pregnancy because of the frequently observed cervical dilatation. Michaels et al. (1991) recommend that it not be used routinely but used ultrasonic criteria to select those patients who might benefit from this operation. Their results suggest that some patients' twin pregnancy is lengthened when cerclage is done. Berkowitz et al. (1988) reported their experience with selective embryocide in 12 multifetal pregnancies (2×6; 1×5; 5×4, 4×3). They reduced the number to two fetuses in 11 pregnancies and to three fetuses in one pregnancy. The surgery was undertaken between 9 and 13 weeks. Seven healthy twins were born. One produced a healthy singleton, and four had only fetal deaths. Later, these authors reported on 200 multifetal reductions (Berkowitz et al. 1993), and Boulot et al. (1993) concluded that the reduction reduces but does not prevent preterm labor. The difficulty and rationale for the procedure were highlighted in an editorial by Hobbins (1988). One problem is the development of unforeseen complications in the survivor. Mahone et al. (1993) had such an experience. They described a twin transfusion syndrome at 23 weeks' gestation where the selective feticide of the hydropic recipient was followed quickly by hydrops in the remaining donor. They speculated that perhaps one mechanism of cardiac failure in the donor was the additional blood loss into the plethoric donor. Their photograph of the twins supports this notion. It also suggests to us that the best therapy for this ominous syndrome is the interruption of the anastomosing vessels, as practiced by De Lia (1996).

Since these earlier reports on "embryo reduction," there have been numerous reports that should be consulted. Thus,

Wapner et al. (1990) reviewed 46 cases with 80 fetuses remaining; 94% of these survived. Lynch et al. (1990) discussed 28 triplet, 47 quadruplet, four quintuplet, four sextuplet, one septuplet, and one nonatuplet pregnancies with reductions, usually to twins. Their outcomes were excellent. Tabsh (1990b) reviewed 40 cases, and Melgar et al. (1991) suggested that their results from the reduction of quadruplets indicated marked improvement in outcome, while that for triplets remains controversial. The intentional delivery of a 710-g acardiac fetus at 22 weeks' gestation by Robie et al. (1989) is also relevant in this regard. It was followed by delivery of a normal girl. The case is of special interest because the acardiac had a penile structure, yet possessed ovaries. She also had a normal female karyotype, and the co-twin was a normal girl. Itskovitz et al. (1989) and Gonen et al. (1990b, c) elected to use a transvaginal ultrasound approach for "selective embryo reduction." The latter authors used intrathoracic KCl injection and had one case of chorioamnionitis follow the procedure. They considered the procedure to be not without significant risk. Tabsh (1993) reported the result of 131 transabdominal reductions done by one practitioner, with 103 deliveries ensuing. He had a 7% pregnancy loss rate from the intervention that occurred within 4 weeks and concluded that this is a safe procedure. Macones et al. (1993) showed that reducing triplets to twins markedly improves fetal survival. A large international experience was summarized by Evans et al. (1994), with the majority of infants being born after 33 weeks when reduction had been done. The procedure was judged to be safe. Other studies to be consulted are those by Lipitz et al. (1994, 1997), Berkowitz et al. (1996), Lynch et al. (1996), Haning et al. (1996), and Smith-Levitin et al. (1996). Sebire et al. (1997b) reported less fortunate results when reducing triplets to twin pregnancies, while Albrecht and Tomich (1996) and Lipitz et al. (1996) suggested to have had better successes. Finally, Evans et al. (1995) reported that, despite increased triplet and quadruplet pregnancies, higher multiple conceptions have declined because of better management of the superovulation techniques.

25.23 Twins in Abortion and Ectopic Pregnancy

Multiple pregnancies occur also as abortions and in ectopic gestations, but they are not often reported or perhaps they are frequently overlooked. Many specimens from spontaneous abortions do not contain an embryo, many are chromosomally abnormal, and many are fragmented when they are observed in the laboratory. Javert (1957) reviewed most of the relevant literature. He found citations of twin frequencies ranging from 6% to 20%. In his own material of 2,000 abortuses, he had an incidence of only 1.2%. Our own observations have yielded a still lower figure (0.3%) (Benirschke and Driscoll 1967). There is general agreement, however, that monochorial twins are overrepresented in abortion material. Numerous MoMo twins, for instance, vanish during early development (Figs. 25.43 and 25.88); and still other twins succumb from the transfusion syndrome or because they are acardiacs (Fig. 25.91). It is impossible to give accurate figures. The great student of twinning, Guttmacher (1937), believed that twins were twice as common in abortions as in births (1 in 37 vs. 1 in 86.5), and the investigations of Livingston and Poland (1980) and Uchida et al. (1983) pointed in the same direction.

It should be easier to identify ectopic twin gestations, as they are generally better preserved. Indeed, many such cases are on record (e.g., Starks 1980). The exceptional case of a tubal triplet gestation was reported by Forbes and Natale (1968), who believed it to be only the fourth case published. It was TriMo, and only a single corpus luteum cyst was found. Fujii et al. (1981) described a unilateral tubal quadruplet pregnancy with QuaMo placenta and unequal development of the embryos. Twin ectopics have been seen more often. Considering the frequencies of ectopic pregnancy and twinning, it is surprising that Storch and Petrie (1976) found only 87 reported cases of ectopic twins. More astonishing still is the fact that most tubal ectopics are monochorionic. This finding is much out of proportion to the general distribution of twin placentation, and the topic is discussed in detail by Neuman et al. (1990). They proved with RFLPs the dizygosity of tubal aborted twins and suggested that the alleged common monozygosity of ectopic twins may be in error. Arey (1923a, b) was the first to report that ectopic twins have a 15 times greater frequency of monochorionic placentation than do intrauterine gestations. He reported MoMo twins, quintuplets, three triplets, and one thoracopagus and, in an earlier publication (Arey 1922), suggested that these findings argued in favor of "chorionic fusion." The proof of this contention, the occurrence of monochorial heterosexual twins, has not been reported. Later, Arey considered the possibility of an environmental insult that produced MZ twins in this abnormal location. It is our opinion that most case reports are incomplete and too superficial; thus, usually they do not allow a clear decision on this interesting point. Perhaps monochorial gestational sacs are larger *ab initio* and have more difficulty passing through the tube. Even less commonly described are the twin ovarian ectopic pregnancies. Kalfayan and Gundersen (1980) reported a case of DiDi ovarian gestational sacs in a patient wearing an intrauterine device. They found three other reported cases.

"Heterotopic pregnancy is defined as a coexisting, intrauterine, and extrauterine pregnancy" (Goodno and Gentry 1962). It is apparently more common than is usually assumed. Gamberdella and Marrs (1989), who described a much higher frequency in "assisted reproductive technology," considered heterotopic pregnancies to occur 1/30,000 pregnancies. It

often involves an interstitial (cornual) and an intrauterine gestation. Sotrel et al. (1976) suggested that more than 600 cases had been reported in the literature. They identified a case that occurred after ovulation induction. These pregnancies are often complicated by placenta accreta/increta (Starks 1980), and they are usually dichorionic. Because they were able to make the diagnosis early, Porreco et al. (1990) electively eliminated the ectopic fetus and allowed the intrauterine gestation to proceed to term. Laband et al. (1988) who reported four such cases suggested that the incidence of this unusual, dangerous gestational complication may be greater than 1 in 30,000. Payne et al. (1971) have seen triplets in this situation after ovulation induction. A similar case is reported in Chap. 6 with interstitial placenta percreta, removed during the second month, with twins remaining in the uterus.

It is also surprising how many cases of twin gestation have been described in uterus didelphys and how frequently they have been delivered at different times. Laird et al. (1957) reported on a miscarriage from one side, 6 months before the delivery of a normal twin from the other. Dawson and Ainslie (1958) saw premature twins delivering from a bicornuate uterus in short succession. Kennedy (1959) delivered an asphyxiated infant from one side, and 3 weeks later, the other twin was born from the other uterus. Mingeot and Keirse (1971) delivered such twins within 9 h of each other. Brown and Nelson (1967) reported that a patient with completely split genital tracts intentionally became pregnant on separate occasions in each uterus, with live infants resulting. A complex case was seen by Zervoudakis et al. (1976) in which curettage emptied an aborting pregnancy, but the patient remained pregnant in a blind uterine horn. Six weeks later, the horn was surgically emptied when a chemical interruption failed. There were no apparent connections, although Loendersloot (1977) later suggested that a perforation may have been present from first curettage. Nhân and Huisjes (1983) induced the second uterine horn after delivery of a normal child from one horn. Finally, Ahram et al. (1984) delivered twins from both horns of a bicornuate uterus. They, as many before, had to initiate labor of the second horn before delivery could be effected. In most of these cases, the placenta is not described. When it is discussed, the twins are usually considered to be binovular.

In a review of the obstetrical performance of 150 cases with uterine anomalies (with 325 pregnancies), Jones (1957) noted that twinning was not more common in these women. It may also be noted that delivery of twins at different times has been described in women with normal uteri. Thomsen (1978) reported a case where the first twin was delivered at 27 weeks and the second at 31 weeks. We have seen twins deliver 4 weeks apart, with the placenta of the first twin remaining in utero and becoming atrophied. The second twin survived. Previously, the maximum interval of 65 days was reported by (1960), but Feichtinger et al. (1989) have described an even longer interval: The patient delivered one twin at 21 weeks' gestation, followed by tocolysis and cerclage. She delivered a healthy 1,750-g twin 12 weeks later; the placenta was dichorionic and had an infarcted portion. The survivor had a velamentous cord insertion. There was no inflammation. The most recent report on delayed delivery of second twins comes from Vancouver (Wittmann et al. 1992). They observed four cases with delivery intervals ranging from 41 to 143 days and then reviewed 21 cases from the literature. The overall salvage rate was 84%; careful management protocols are suggested by these authors.

25.24 Morbidity and Mortality

An abundant obstetrical literature discusses the causes for the excessive mortality of twins and the frequent obstetrical complications encountered during their delivery. Relatively rare but easy to understand is the phenomenon of "locked twins." Khunda (1972) discussed 37 such cases and estimated that it occurs with a frequency of 1 in 1,000 twin deliveries and that it has a high stillbirth rate. Breech/vertex presentation of twins is the commonest factor; also common are primigravidity and large pelves. Cohen et al. (1965) had previously reported similar figures. In their experience, interlocking was present once in 817 twin deliveries and once in 87 breech/vertex presentations of twins. It is a particularly serious event when it occurs at or below the pelvic inlet, with death of twin A quickly ensuing. Amniotic sac dystocia has been described once, by Nickerson (1967). The membranes from twin 2 then prolapsed in front of the first delivering twin. This abnormality was easily corrected, and delivery accomplished.

Of the numerous maternal complications that attend multiple gestations, Seski and Miller (1963) listed in descending order: premature delivery, preeclampsia, hydramnios, placenta previa, abruptio placentae, cord prolapse, uterine inertia, and postpartum hemorrhage. Placental abnormalities often mirror these events. Hydramnios in twin pregnancies is most commonly due to the transfusion syndrome; good evidence exists that the amnionic fluid index of normal twin gestations is the same as in singletons (Hill et al. 2000). Next most frequently, hydramnios results from fetal or placental anomalies. It has been debated as to whether preeclampsia is more common with DZ twins than with MZ twins; that it is more frequent in twin gestations is not disputed. We have seen numerous dizygotic twin placentas in which only one placental half was affected with infarcts and decidual atherosis. It suggests that fetal and maternal interactions of respective genotypes are critical in the determination of pregnancy-induced hypertension (PIH – preeclampsia). Campbell et al. (1977) have studied this subject in greater detail and reviewed the literature. They analyzed 343 twin

Table 25.7 Perinatal mortality of twins

Source	Year	No. of twins	Toxemia (%)	Breech (%)	Mortality (%)
Powers	1973 (review)	794	33		18.8
Europe and Africa		2,012	25	18.4	12
		98	20.4	30	16
		944	24		11
		706	35.4	36.8	12.2
		510	24.4	32	18.8
		210	31		6
		992	32	20	14
		2,000	10.1	32.1	16.1
		412	26.2	24.5	10.9
		358	34		12.3
		3,152			9.5
Tow	1959	408			12.3
de Paepe	1959	108			8.8
Farrell	1964	1,000			16.1
Scholtes	1971	200			11.8
Bleker et al.	1979	1,655			14
Powers	1973 (review)	666	21.3	26.6	13.8
USA and Canada		270	16	30.5	28.6
		750	5	33	18.5
		504	21	28.3	15.6
		384	29.2		14
		1,000	28.2	21.2	9.8
		834			9.2
		384	27	31.3	14.1
		406	10.8	33	10.1
		17,168			9.9
		2,654	4.9	29.9	13.3
		986	37.5	24.4	9.9
		1,744	5	9.8	14.4
		2,798	14		11.8
		206	4.8	25	10.3
		1,046	16.5	31	10.8
		758			14
		1,054			13.4
		104			17.3
Ferguson	1964	3,238			9.3
Robertson	1964a	496	32		12.2
Myrianthopoulos	1970a	1,230			17.3
Ho and Wu	1975	177			10.7
Medearis et al.	1979	3,594			11.7
Keith et al.	1980	588			14.6
Hawrylyshyn et al.	1982	177			13.2
Laros and Dattel	1988	206			13.3
Fowler et al.	1991	41,554 White			4.71
		10,062 African American			7.93

pregnancies, with exact zygosity determination, and found that DZ and MZ twin pregnancies had the same incidence of mild and severe toxemia of pregnancy. Skupski et al. (1996) found that the rate of PIH is higher in triplet gestations conceived by in vitro fertilization than if conceived spontaneously and when reduced to twins. Maxwell et al. (2001) found no difference in the risk for PIH with twin zygosity.

Perhaps the most debated topic in the management of twins is the manner in which the second twin is to be delivered and how rapidly it must be accomplished. Increased

fetal mortality for the second twin has often been suggested but was also frequently not confirmed by studies in detail (Adam et al. 1991). In almost all respects (Apgar score, pH, and weight), twin A is said to be favored (Young et al. 1985). The higher mortality of twin B was particularly evident in Spurway's report on the management of twin deliveries (1962). Others have not found such dramatic differences, particularly when cases in which prenatal deaths (macerated stillborns, acardiacs) and infants weighing less than 1,500 g were excluded from such analyses (Thompson and Johnson 1966; Rayburn et al. 1984; Adam et al. 1991). Nevertheless, the mortality of twins is much greater than that of singletons, and reports from the American, European, and African literature are summarized in the thoughtful review by Powers (1973). Those reports are shown in Table 25.7, as are more recent surveys. In general, the perinatal mortality of twins hovers around 10%, but the statistics are largely influenced by inclusion or exclusion of twins from early gestations and also depend on the date of study, as marked improvements have been achieved. Thus, in a case-control study of Spellacy et al. (1990), the overall mortality of twins more than 500 g in weight now was 4.88% for twin A and 6.41% for twin B. As in this study, there is little doubt that prematurity, often the result of hydramnios, is the most important factor in determining outcome. Rouse et al. (1993) related fundal height measurement to preterm delivery. They decided that a single measurement of an excessive fundal height does not predict premature labor. This was to be expected, as excessive size alone cannot be the trigger for labor rather it is the rapidity of increase in uterine size (as occurs in hydramnios from the transfusion syndrome) that has this effect. At times, preterm labor is heavily influenced by the presence of the "amnionic fluid infection syndrome" (chorioamnionitis). Thus, Naeye et al. (1978), who recorded a 13.8% twin perinatal mortality, found that infection was the cause of twin deaths in 2.3%, in contrast to 0.6% in singletons. It was much higher (13.0% vs. 1.8%) in Ethiopia. Premature rupture of membranes occurred more commonly in twins than singletons, but its outcome (latency to labor, infection) did not differ from singleton pregnancies (Mercer et al. 1993). These authors remarked on the paucity of abruptio occurring in multiple gestations. No significant differences between twins were found in the occurrence of the "respiratory distress syndrome" (Arnold et al. 1987) or cerebral hemorrhages (Pearlman and Batton 1988). Most impressive, however, is the difference of perinatal mortality between monochorial and dichorial twins. Monochorionic twins have a significantly higher mortality, and that of monoamnionic twins is the highest (Benirschke 1961; Cameron 1968; Fujikura and Froehlich 1971). On occasion, it may be necessary to delay delivery of a second twin after the premature birth of one. This topic was addressed by Arias (1994) who found it possible to occasionally significantly delay the birth of a second twin with cerclage and other modalities.

Early bed rest has been proposed to improve twin survival (Anonymous 1963b). The cost of this measure is formidable (Powers and Miller 1979), however, and careful appraisal with random trials has shown that it is inefficacious. In fact, with early admission and bed rest, the prematurity rate is increased. Robertson (1964b) had earlier sought statistical improvement from early admission and did not find it; he thought that random trials would be unethical. One study of the possible benefits comes from Rydhstrom (1988). Pregnancy outcome for 78 twin-bearing women who were prescribed prophylactic leave of absence from work to prevent preterm delivery was compared with a group of 78 twin-pregnant controls who did not take prophylactic leave. Gestational duration and birth weight did not differ between the two groups. The results indicated that prophylactic leave of absence from work did not improve the outcome of a twin pregnancy. Crowther et al. (1989) and MacLennan et al. (1990) also found that bed rest had no beneficial outcome in twin survivals. Indeed, "…evidence is accumulating that rest may even increase premature labour" (Thornton and Rout 1990; see also Andrews et al. 1991). Although Cesarean section rates have increased from 3% (1963–1972) to 51% (1978–1984), Bell et al. (1986) were unable to show that even this modality of care improved the condition of twins at birth (see also Saunders et al. 1985, and Greig et al. 1992). Only attendance at prenatal twin care clinics seemed to have had a beneficial effect on outcome (Ellings et al. 1993).

The excessive mortality of multiple offspring has been given as one reason for "selective reduction" during early pregnancy. Layzer (1988) noted that a 16% perinatal mortality exists in triplets, and another 15% does not survive infancy. The figures for quadruplets and quintuplets are 21% and 22%, respectively; for sextuplets, the respective figures are 41% and 50%. At the other end of this spectrum, large twins have also been recorded. Leonard (1957) has reviewed this topic and reported twins weighing 4,075 and 5,180 g (20.4 lb together). They were, of course, dichorionic (male/female) and are the largest recorded in the literature.

25.25 Hormones in Twin Pregnancy

In efforts to predict twin pregnancies, various serological parameters have been studied for better surveillance. Halpin (1970) found excessively high hCG titers in a twin pregnancy, and Thiery et al. (1976) determined that hCG titers in twins were 2.5 times higher than in singletons. This increase was confirmed by studies of Jovanovic et al. (1977). Thiery et al. (1976) also reviewed the literature on the elevation of

chorionic gonadotropin levels in pregnancy and simultaneously studied the human placental lactogen (hPL) levels. The latter were found to be 1.5 times higher than in singleton pregnancies. Other investigators have made similar observations (Gennser et al. 1975; Grennert et al. 1976a; Mägiste et al. 1976; Daw 1977). In general, the values are 1 SD above those for singletons, and when one twin dies, a noticeable fall has been recorded (Kenney et al. 1976). It has also been shown that, following elective embryocide, there is a marked fall in chorionic gonadotropin levels, but that progesterone and estradiol levels remain stable (O'Keane et al. 1988). α-fetoprotein was found to be elevated in seven of ten twin pregnancies reported by Ishiguro (1973), as was the level of cystylaminopeptidase (Einerh and Jacobsson 1976). Because of the considerable scatter of hPL values in pregnancy, Dhont et al. (1976) suggested that simultaneous determination of hCG and hPL values gives more reliable results in the anticipation of twins (see reply by Grennert et al. 1976b).

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