8.
TWIN STUDIES AND CHRONOGENETICS

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CONTENTS

MAJOR FETAL HAZARDS IN MULTIPLE PREGNANCY

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Fetal risk in twin pregnancy is recognized as being about 2 to 4 times higher than in singletons. The main factors of this increased mortality are reviewed. Pathological effects associated with MZ origin are mainly due to the " third circulation " occurring in monochorial twins. Three situations can be distinguished: (a) *hemodynamic equilibrium resulting in fetal growth impairment*, (b) *strong hemodynamic imbalance inducing fetal death*, (c) *moderate imbalance as the cause of "intertwin transfusion syndrome". The acardiac and to some extent the papyraceus fetus can be considered as particular cases of the same problem. Other risks associated with MZ twins are the higher rate of malformations and umbilical cord entanglement in monoamniotic twins. The conjoined effects of prematurity and intrauterine growth retardation are undoubtedly the main cause of fetal death in multiple births. Therefore, some consideration is given to the underlying physiopathogenic factors. Prevention of twin weight defects demands early diagnosis of multiple pregnancy. As little can be expected from classical clinical methods, the obstetrician has to rely on more sophisticated techniques such as fetal ultrasonography. Even with an early diagnosis, at the present time there is no satisfactory treatment capable of preventing prematurity and retarded fetal growth. In this specific context, bed rest would appear as a fallacy.*

INTRODUCTION

The human species is certainly no exception to the general rule of reproductive biology according to which multiplicity of embryos, whether characteristic of the species, whether occurring haphazard in isolated individuals, leads to increased fetal wastage. Although the higher mortality rate observed in multiple births is therefore quite understandable, the obstetrician is nevertheless faced with a risk running about two to four times higher for twins than for singletons.

Table 1 gives the relative importance of the various causes of perinatal mortality which we have found among a series of 338 twin pregnancies delivered in our department. It should first be specified that the rather high mortality due to hemolytic disease is artificial since our clinic used to drain perferentially this kind of pathology. Since we have already dealt elsewhere in some detail with delivery problems (Leroy 1974), we shall restrict ourselves in the present paper to the two main causes of twin mortality, i.e., weight defect and homozygotic pathology. It is even probable that most of the " undetermined " cases also belong to one or the other of those two etiologies.

MONOZYGOTIC PATHOLOGY

Identical twins are known to be endowed with a mortality rate which is about twice or three times higher than observed in fraternal pairs (Benirschke 1972). In our series, MZ pathology and associated malformations accounted for about one fourth of the fatalities.

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Vascular Anastomoses

In relation with MZ origin it should first be stressed that in about 66% of twins arising from one egg, the placenta and membranes are found to be monochorial (Strong and Corney 1967). Such twins sharing the same placenta present a higher mortality rate and have also an average weight defect of 250 g as compared with members of dichorial pairs (Bulmer 1970, Benirschke 1972). This aggravated prognosis owes to a remarkable anatomical peculiarity. As indicated in Table 2, about 90% of mo-

Table 1. *Relative importance of mortality causes in 338 pairs of twins (% values)*

Weight defect	53.5
Homozygotic pathology & associated malformations	25.3
Rh hemolytic disease	8
Obstetrical trauma & pathology	7
Undetermined	6

Table 2. *Vascular anastomoses in monochorial twin placentae.* (Benirschke 1961, Strong & Corney 1967)

Type	N
Art — Art	21
Ven — Ven	3
Art — Ven	9
Art — Art + Ven — Ven	4
Art — Art + Art — Ven	28
Ven — Ven + Art — Ven	5
Art — Ven + Ven — Art	5
Art — Art + Ven — Ven + Art — Ven	4
Art — Art + Art — Ven + Ven — Art	4
Art — Art + Ven — Ven + Art — Ven + Ven — Art	3
Without detectable anastomoses	13
Total	99

nochorial twin placentas present different types of vascular anastomoses between both fetal circulations. The most frequent types are the isolated arterio-arterial communication and the combination of arterio-arterial with arterio-venous anastomoses. In most cases there are arterio-venous channels which are to be considered as the determinant pathogenic feature. These arterio-venous communications are almost always localized at the capillary level in so-called "common villous districts" or "shared cotyledons". Such areas are centered on a placental artery of one fetus and a vein arising from the other which ramify and communicate into the depth of the placental tissue. On the contrary, arterio-arterial and veno-venous channels are readily visible since they concern bigger caliber vessels, communicating directly on the fetal surface of the placenta (Fig. 1).

Although this situation of "intrauterine parabiosis" raises a series of yet unsolved problems, we may try to give it a simplified interpretation based on the correlation between anastomotic types and the corresponding clinical observations. Grossly, five different situations can occur.

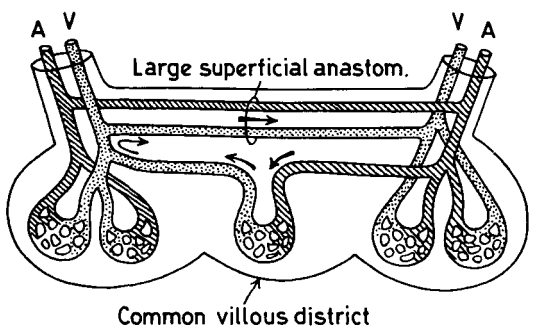

Fig. 1. Schematic representation of vascular anastomoses in monochorial twin placenta. (After Aherne et al. 1968).

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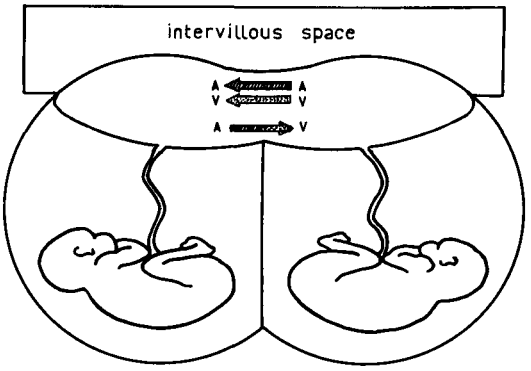

Fig. 2. Monochorial twins 3d. circulation. Hemodynamic equilibrium.

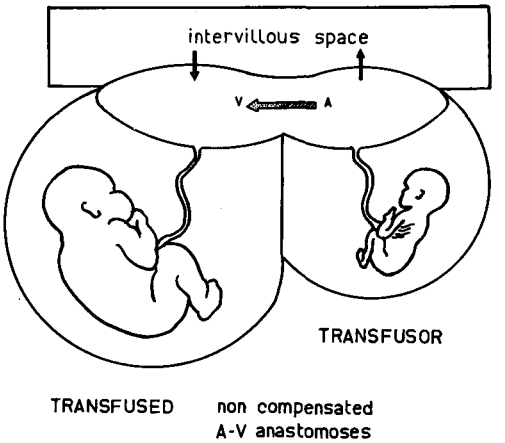

Fig. 3. Monochorial twins 3d. circulation. Hemodynamic asymmetry.

1. *Equilibrium status.* In placentas where only arterio-arterial and/or veno-venous communications are present, blood can only circulate in those channels if pressure is different on each side. If such a gradient occurs blood pressure will readily be equilibrated in both fetuses since these vessels are of big caliber. This amounts to say that any hemodynamic disturbance occurring in one twin will immediately be transmitted to this partner and that all other things being equal, their intrauterine growth will be solidary.

But in most cases big caliber anastomoses will be associated with arterio-venous communications. Under such conditions the arterio-venous gradient is continuously compensated through a reverse blood flux occurring in arterio-arterial or veno-venous channels (Fig. 2). The latter situation is also one of hemodynamic equilibrium but in which a " third circulation " will permanently operate. It is likely that the corresponding blood volume diversion and reduction of effective placental tissue are often responsible for fetal growth impairment since common villous areas can represent as much as one fifth of the total placental volume (Kloosterman 1963). At any rate it seems that this situation is not the most dangerous since it has been found that monochorial twins mortality is reduced by one half in the group with superficial compensating anastomoses involving big caliber vessels (Benirschke 1961).

2. *Strong hemodynamic imbalance.* In contrast, dramatic consequences will arise from arterio-venous channels which are not compensated for (Fig. 3), since under such conditions one twin (perfusor) will empty his blood into the other (perfused) until his arterial pressure becomes equal to his partner's venous pressure. Therefore, the transfused twin will perish from cardiac failure due to exaggerated plasmatic load, whereas the transfusor will die from hypoxia arising from blood depletion. For the same reasons there will be hydramnios on one side and very little amniotic fluid on the other. This is why sometimes the obstetrician comes accross a case of very premature stillborn twins, one of which is hydropic while the other appears to be hypotrophic. In a few cases the perfusor only, will be able to survive to this situation whereas the other one never does.

3. *Moderate hemodynamic imbalance.* However, in most cases of the " intertwin transfusion syndrome " hemodynamic asymmetry will be discrete, owing to arterio-venous communications of which the output is imperfectly compensated through similar channels operating in the opposite direction. The transfusion from one fetus to the other is then very slow and pregnancy will therefore be able

to proceed closer to term and give birth to living babies. The perfusing twin will nevertheless be pale and small. Besides important anemia, his plasmatic proteins are depleted and his blood contains many immature red blood cells as a sign of bone marrow reaction to anemia. For still unknown reasons (Aherne et al. 1968) the corresponding placental territory is very much swollen with villous edema. On the other hand, the transfused fetus will often be much heavier than his partner. He will also appear plethoric because of marked polycythemia which is responsible for a high level of blood bilirubin. This increased destruction of red blood cells will in turn be responsible for liver and spleen enlargment which are often found in such infants.

4. *Foetus papyraceus.* Sometimes one will be able to witness the birth of a twin who after intrauterine death, becomes completely dried-out and flattened by his normal partner's growth. This *foetus papyraceus* is often explained as arising from intertwin transfusion. However, in half of such cases the placenta would be dichorial (Benirschke and Driscoll 1967), whereas it is known that in such placentae vascular anastomoses are very rare. The only truly authenticated case has been published by Cameron in Birmingham (1968). Therefore, it is believed that a *foetus papyraceus* can occur because of a series of different etiologies causing intrauterine death around mid-pregnancy, among which intertwin transfusion is only a special example.

5. *The acardiac monster.* Another curiosity relating to the twins 3rd circulation is the profoundly malformed fetus known as acardiac monster. Such fetuses have no heart and very often lack the upper part of the body as well, as if cut at the waist level. The growth of such a monster up to the end of pregnancy is made possible through the existence of two large vascular anastomoses linking both fetal circulations and through which the malformed twin is being perfused by the heart of his normal partner. One of the linking channels is arterio-arterial, the other is veno-venous. It is quite clear that inder such conditions the circulation in the acardiac is running opposite to the normal direction. He receives lowly oxygenated blood through an ombilical artery from his cotwin, the blood returning to the normal partner through the venous anastomosis. This malformed fetus is thus permanently lacking oxygen.
According to one theory, those very abnormal hemodynamic conditions would be responsible for the absence of heart and cephalic development. This, however, requires that vascular anastomoses would have played their teratogenic role at an early stage of development. Therefore, there is an alternate explanation which would be that this anomaly results from another yet unknown cause. Accordingly, the association with a normal twin would be fortuitous but still necessary to allow the acardiac fetus to survive and grow.

Malformations

We will not dig very far into the problem of twin congenital defects since their etiology remains obscure. MZ twins are endowed with a rate of malformations which is about twice as high as in singletons (Bulmer 1970). In our series of 338 twin pairs they were responsible for 3% of the fatalities.
The curious thing is that in more than 50% of cases the defect will be present in only one member of a MZ pair, the other being normal (Metrakos 1951). Such discordant malformations when occurring, as is often the case, at the level of cardiovascular organs, can eventually be understood through hemodynamic disturbances arising from early vascular anastomoses. The situation is much more puzzling when it comes to anomalies such as cleft lip and palate known to have some type of hereditary background and which are still most of the time discordant.

Monoamniotic Twins

Twins contained in a single amniotic pouch represent only a small percentage of identical pairs and this is fortunate since such twins appear to be most threatened. Not only are they exposed to the

hazards of intertwin transfusion and to a 10% rate of malformation, but very often will their umbilical cords become entangled or knotted, causing intrauterine death of one or both fetuses. As a consequence the rate of double survival in such cases is only about 30% (Leroy 1962).

BIRTH WEIGHT DEFECTS

Birth weight defect is undoubtedly the major risk run by multiple pregnancy babies. In the group which we have studied this factor was responsible for more than 50% of fatal cases resulting in such complications as asphyxia, cerebral hemorrhage, hyaline membrane, hypoglycemia and hemorrhagic pneumonia.

The first cause of this weight defect is of course prematurity. As an average the delivery of twins occurs around the 37th week of pregnancy, its duration being reduced respectively to 35 and 34 weeks for triplets and quadruplets.

Although we do not yet understand the intimate mechanism of labor onset in the human, it may be

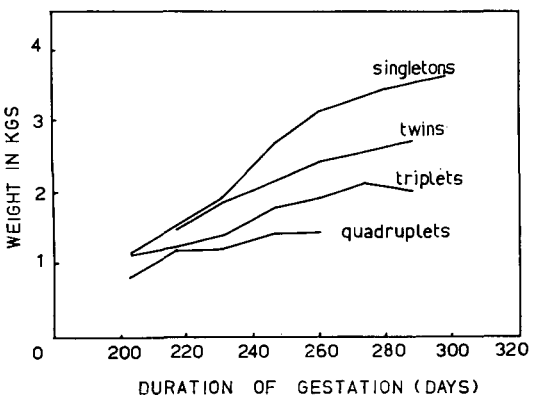

Fig. 4. Mean birth weight in multiple births by length of gestation. (After Mc Keown & Record 1952).

assumed that uterine overstretching plays a role in the premature termination of multiple pregnancy. But it is likewise possible that some humoral factor arising from the placenta (Csapo 1961) or from fetal adrenals (Comline et al. 1973) could reach a threshold level much sooner than in single pregnancies and therefore be the cause of early onset of uterine contractions. Nevertheless, the mean birth weight of multiple pregnancy babies remains much lower than that of singletons at identical gestational age. It can be seen in Fig. 4 that their intrauterine growth is definitely slowed down during the last months of pregnancy. In twins this weight reduction versus singletons amounts to about 20%. Multiple pregnancy babies are therefore not only premature but also small for date.

If one ponders over the causes of this intrauterine growth retardation the first explanation coming to mind is that in multiple pregnancy overcrowding of the uterus could limit the extension of normal placental development. It is true for instance in twins, that placental weight and volume at all ages of gestations are definitely less than double of what is observed in single pregnancies (Mc Keown and Record 1953). However at equivalent relative placental weight twins are still lighter than singletons even when allowance is made for gestational age. In other words the percentage of placental weight reduction in twins is less than their relative body weight defect; these two figures being respectively of about 12% and 20% (Bulmer 1970). Therefore impaired placental development cannot account entirely for fetal growth retardation in multiple pregnancy.

There is evidence pointing to insufficient uterine vascularisation as the additional factor of twin growth retardation. It has been found that in multiple pregnancy utero-placental circulation is much slower than normal (Morris et al. 1955) and that twins have increased hemoglobin and red blood cell levels

Table 3. *Fetal birth weight according to parity in 338 twin pairs*

Birth weight (g)	Primiparas n	Primiparas %	Multiparas n	Multiparas %
< 2,000	78	41	118	24
> 2,000	122	59	368	76

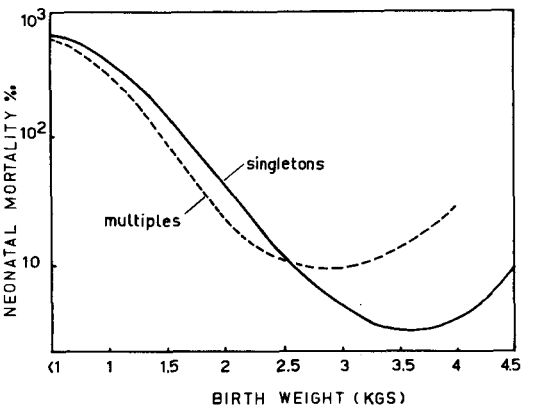

Fig. 5. Neonatal mortality by birth weight. (After Montagu 1952).

at birth, which can be interpreted as a consequence of intrauterine anoxia (Walker and Turnbull 1955). In this context it should be mentioned that the risk of fetal weight deficiency is greater in multiple pregnancies occurring in primigravidas although their average gestation length is not shorter than in multiparas (Guttmacher 1939). Therefore it is not surprising to find an increased mortality rate among twins born from first pregnancies (Kurtz 1955, Donnelly 1956, Tow 1959 Gaves et al. 1962, Spurway 1962). In our series the number of twins weighing under 2000 g was likewise significantly higher in the group of primiparas (Table 3). It would thus seem that the human uterus will improve its deficient fitness to the needs of multiple gestation through successive pregnancies.

It is of some interest to compare the evolution of perinatal mortality rate in multiple pregnancy babies and in singletons as a function of birth weight (Fig. 5). At first sight it may seem paradoxical that below 2500 g twins should die less often than single babies of equal weight. This is firstly due to their retarded growth which makes them have a better visceral maturity and consequently a better resistance and adaptation to extrauterine life than premature singletons of identical weight. It appears moreover that the premature birth of a singleton is often linked to some serious complication such as congenital malformation, placenta previa or toxemia which predispose to intrauterine death, whereas these pathological factors are not especially associated with low weight twins.

Above the 2500 g limit the relationship of both curves is reversed since at this stage weight defect is no longer a problem. The higher mortality in multiple births at this level owes mainly to delivery complications such as obstetrical trauma and anoxia of the second twin. The terminal rise of both curves should be ascribed to such factors as overmaturity and diabetes which are often associated with large fetuses running considerable risk. It will be noticed that this type of pathology does not mask the retarded growth of multiple pregnancy fetuses since their mortality curve rises at a lower weight level than that of singletons.

PROPHYLACTIC CONSIDERATIONS

Clearly, the early diagnosis of twins is a prerequisite to any effort aiming at reducing fetal loss in such cases. Nowadays it has become possible to fulfil this goal by the use of ultrasound scanning on a large scale. Provided that almost all multiple pregnancies would be discovered at an early stage, what can be done to diminish their high perinatal mortality?

As we stated in a previous paper (Leroy 1974), most labor and delivery problems can efficiently be dealt with by the simple observance of some methodical rules. But it must be remembered that obstet-

rical trauma is only responsible for a small part of twin mortality. Therefore better obstetrical management is not likely to affect much the overall fetal loss in multiple pregnancy.

It is quite obvious that for the time being there is unfortunately no way to avoid the hazards associated with intertwin transfusion or congenital malformation which account for about 25% of fatal cases. For what concerns prevention of prematurity and intrauterine growth impairment, several authors would put much emphasis on the usefulness of bed rest (Bender 1952, Russel 1952, Tow 1959). This

Table 4. *Mortality according to the moment of diagnosis in 338 twin pairs*

Diagnosis	Mortality rate n	%
Before 34th week	23	10.1
After 34th week	17	9.5
During labor	57	23.3

Table 5. *Twin birth weight according to the moment of diagnosis in 338 pairs* (% values)

Diagnosis	Birth weight	
	< 2,500 g	> 2,500 g
Before 34th week	50.4	49.6
After 34th week	52.8	47.2
During labor	72.9	27.1

assumption mainly stems from the observation that perinatal mortality is lower when the diagnosis of twins has been made early and from the subsequent whishful belief that early and better care of such pregnancies is bound to be determinant. In our series it did indeed appear that twins discovered before the 34th week of pregnancy are endowed with a significantly lower mortality rate than when diagnosis was not made until labor (Table 4). We also found that early diagnosis correlates with higher birth weight (Table 5).

In our opinion such data are best interpreted as a consequence of the fact that only the biggest and therefore the most resistant twin pairs can be diagnosed by clinical methods at an early stage of pregnancy. A work by Dunn (1961) indirectly confirms this conclusion. Dunn performed a study where women carrying a double pregnancy were randomly put at rest or left to their usual occupations. His study concerns 158 future twin mothers half of whom were submitted to hospital bed rest for an average duration of 3 to 4 weeks before delivery. The results were that fetal weight gain and lengthening of gestation attributable to this treatment were insignificant since they respectively amounted to 85 g and 3 days. Therefore bed rest aiming at preventing fetal weight defect in twins would appear as a fallacy. However it can not be excluded that complete rest from the very beginning of pregnancy could be more beneficial but this is obviously difficult to obtain from patients. At any rate such a method of prophylaxis would be mainly advisable to primigravidas since not only do they more often deliver smaller twins but they are also more likely to accept the inconvenience of prolonged inactivity. The arrest of premature labor through drug therapy is likewise bound to be disappointing. Once contractions have started we can only hope to gain a few days of pregnancy as is observed in single gestations. One approach which has not yet been carefully evaluated and should be tried, would be to give high prophylactic doses of progestational hormones, such as for instance caproate of hydroxyprogesterone at 5 to 6 g per week, from the moment of twin diagnosis in order to prevent premature labor. Added to some experimental arguments (Csapo 1961) there is evidence that such a treatment is at least useful in the prevention of repetitive premature delivery in single pregnancies (Rosa 1967). As a conclusion, our opinion is that the best prophylaxis of the high perinatal mortality in multiple births would be, if ever feasible, the prevention of multiple gestation itself, since it seems that the human uterus is particularly ill-adapted to such a situation.

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