ADVANCES IN HUMAN GENETICS 14

Edited by

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and

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Chapter 1

Cytogenetics of Pregnancy Wastage

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INTRODUCTION

During the last two decades, the important progress that has been made in the control of human reproduction, in medical care during pregnancy and the neonatal period, and more recently in *in vitro* fertilization (Schlesselman, 1979; Biggers, 1981) has focused interest on the understanding of the causes of the high mortality rate among human conceptuses before, during, and shortly after birth. It has been recognized that chromosomal abnormalities are among the most important causes of this high mortality rate, and thus couples with a history of pregnancy wastage are now frequently referred to a geneticist for counseling.

ESTIMATION OF PREGNANCY WASTAGE

For a given couple, it is difficult to estimate the probability of conception of a living newborn. Thus, demographers have defined "fecund-

ability" as the probability of producing a full-term infant per menstrual cycle during which intercourse occurred. Different demographic studies collected by Short (1979) show that at the age of 20–30 years, fecundability ranges from 21 to 28%. Thus, human fecundability is very low when compared to the fertility of domestic mammals.

From the results of studies using different methodological approaches it has been shown that this low fecundability can be explained by a high rate of intrauterine mortality occurring in the period from fertilization until delivery.

Using a statistical model, Roberts and Lowe (1975) postulated a 78% loss of all human conceptions, most of them occurring before the first missed period.

A 4-year followup study of 3084 pregnancies in the Hawaiian island of Kauai from the first missed menstrual period showed that 23.7% of these presumed conceptions failed to result in a live birth and that the mortality was largely concentrated in the early months of pregnancy (French and Bierman, 1962).

The detection of elevated human chorionic gonadotropin (hCG) by RIA for the β subunit of hCG allows the diagnosis of early pregnancy after implantation 8–9 days after fertilization. In a prospective study of normal women (Edmonds *et al.*, 1982) 118 pregnancies were diagnosed on biochemical criteria, 67 of which had increased hCG levels but no clinical pregnancy; of the remaining 51 pregnant women, six had clinical abortions. Thus the postimplantation pregnancy loss rate was 62%.

Prior to these studies, the work of Hertig had shown not only the high rate of early embryonic mortality, but also that a high percentage of these embryos were abnormal. Thus the causes of early embryonic wastage were mainly linked to zygotic defects and not to maternal factors. In

Table I. Simple Morphological Results of an Analysis of 1000 Consecutive Spontaneous Abortions[a]

Pathological ova with absent or defective embryos	489
Embryos with localized anomalies	32
Placental abnormalities	96
Anatomically normal ova with macerated embryos	146
Total	763
Anatomically normal ova with nonmacerated embryos	74
Uterine abnormalities	64
Others	99
Total	237

[a] From Hertig and Sheldon (1943).

Table II. Incidence of Morphological Abnormalities in Relation to the Developmental Age of the Abortus

Study		Incidence of abnormalities at given developmental age		
		≤4 weeks	5–8 weeks	9–12 weeks
Mikamo (1970)	Number of abortuses	48	61	81
	Number of abnormal abortuses	48	40	10
	Percent abnormal abortuses	100	65.6	12.3
Miller and Poland (1970)	Number of abortuses	83	122	177
	Number of abnormal abortuses	73	71	56
	Percent abnormal abortuses	88	58	32

a study of 34 early fertilized ova from 1 to 17 days, 13 showed some degree of abnormality (Hertig and Rock, 1949). In a morphological study of 1000 spontaneous abortions about three-fourths showed abnormalities (Hertig and Sheldon, 1943) (Table I).

Other pathological studies on abortuses (Mikamo, 1970; Miller and Poland, 1970) confirmed the findings of Hertig and showed that the frequency of abnormality was related to the developmental age, approaching 90–100% in early specimens arrested during the first month after fertilization (Table II) and decreasing when developmental arrest occurred later.

These studies showed that intrinsic zygotic defects are the main causes of early embryonic losses and spontaneous abortions. The discoveries that congenital malformation syndromes may result from chromosome anomalies led to cytogenetic studies seeking the etiology of fetal wastage.

EVALUATION OF THE INCIDENCE OF CHROMOSOME ABNORMALITIES

The main problem has been the collection of specimens allowing cytogenetic surveys at different stages of development. Investigation of human abortions (spontaneous or induced) have provided the largest

amount of data, followed by surveys of perinatal deaths and more recently by the analysis of some data of prenatal diagnosis. Unfortunately, the collection of embryonic losses of the first 2 weeks of development is nearly impossible.

Spontaneous Abortions

Most spontaneous abortions (about 90%) occur during the first trimester of pregnancy. In these abortions the developmental age of the embryo is generally less than 8 weeks, and a prolonged *in utero* retention follows embryonic death.

A large number of publications have reported chromosome abnormalities in spontaneous abortions. Most of the studies published in the 1960s were analyzed by Carr (1971*b*) in his article in the second volume of this series. Since then, surveys based on the cytogenetic analysis of hundreds of specimens have been published, and these furnish the basis of this chapter (J. Boué and Boué, 1973*a*; Carr and Gedeon, 1978; Creasy *et al.*, 1976; Hassold *et al.*, 1980*a*; Kajii *et al.*, 1980; Lauritsen, 1976; Warburton *et al.*, 1980*a*; Meulenbroek and Geraedts, 1982).

The manner in which specimens are collected is an important factor that is sometimes difficult to clarify. It can be estimated that the number of induced abortions included in the large surveys is low, which is not the case in some of the earlier studies.

Many spontaneous abortions (especially the earlier ones) occur at home and do not necessitate hospitalization (Stevenson *et al.*, 1959). Specimens collected either at home by the patient or in the hospital reflect different ways of sampling.

There are also differences in the distribution of gestational ages at abortion and especially in the percentage of older fetuses in some studies. From the followup studies after amniocentesis for prenatal diagnosis, which are usually performed at the beginning of the second trimester pregnancy (16–17 weeks gestational age), the incidence of late spontaneous abortions is low, 1.5–2% of the pregnancies in progress at the time of amniocentesis. In some abortion surveys, the number of abortuses with a gestational age of 18 weeks and more exceed 20% of the specimens collected, which is far more than expected from clinical studies.

This may explain the differences in the total frequencies of chromosome abnormalities among the studies. In order to minimize the bias in

selection, different criteria were used to calculate the incidence of chromosome abnormalities.

Abortions During the First Trimester

In some surveys in which pathological examination of abortuses was performed, the incidence of chromosome abnormalities was evaluated according to the developmental age (Mikamo, 1970; J. Boué and Boué, 1973*a*). Anatomical studies have demonstrated that the duration of development is a reliable criterion for the classification of specimens. An estimation of the stage of development attained by the specimen is based on pathological examination, which comprises a detailed macroscopic description of the abortus and a microscopic study of the placenta (Philippe, 1974).

When embryonic formation exists, the age of the embryo is estimated by the stage of embryogenesis it has attained, rather than by its size, which is usually modified by maceration.

Detailed histologic examination of the placenta, including an appreciation of the degree of maturity of the villi and their blood vessels, permits the determination of the stage of development (Philippe and Boué, 1969).

Table III shows that the incidence of chromosome abnormalities is greater than 60% in abortuses of a developmental age less than 7 weeks and then decreases.

In other studies the incidence of chromosome abnormalities was evaluated in relation to the gestational age of the abortus calculated as the time from the first day of the last menstrual period to the day of abortion. This age is usually easy to determine but is highly dependent on the long and variable time of *in utero* retention, which in many cases is longer (mean time 6–7 weeks) than the developmental age of the embryo (mean age 4–5 weeks).

Table IV gives the results of four surveys (Creasy *et al.*, 1976; Kajii *et al.*, 1980; Hassold *et al.*, 1980*a*; Warburton *et al.*, 1980*a*) that showed that in abortuses of 8–16 weeks gestational age the incidence of chromosome abnormalities was about 50% and then decreased.

The rate of abnormalities in the earliest abortions (less than 8 weeks) is surprisingly low. These results are in contradiction with the increased incidence observed in studies based on developmental age either in spon-