Chromosome Abnormalities and Repeated Abortion: A Preliminary Report

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The role of chromosome aberrations in the etiology of early spontaneous abortions has been well established (1). Various investigators have found that 25–35% of all such abortions are the result of cytogenetic abnormalities (2, 3). The great majority of these aberrations are believed to be the result of *de novo* errors in meiosis and only rarely can early mitotic mistakes account for these events (3). In a minority of cases, one of the parents may harbor a transmissible chromosome anomaly. The carrier is apparently physically normal and has a balanced genetic make-up compatible with life. During gametogenesis, however, unequal gametes may be formed, resulting in development of a nonviable zygote. This may predispose the carrier to recurrent early abortion of his or her offspring.

Recently, a number of studies have attempted to find such a correlation between recurrent pregnancy loss and parental chromosome anomalies (3, 4, 5, 6). An investigation of this type was initiated at the Medical College of Virginia in the fall of 1973. Letters were sent to obstetricians in eastern Virginia requesting referrals of patients with histories of two or more spontaneous abortions. Blood was drawn from both the husband and wife and karyotype analysis was performed according to conventional methods. Five anomalies have been ascertained in the 25 couples studied so far. A discussion of the significance of these findings is considered below.

A 28-year-old white female was found to have a modal chromosome number of 47. The patient was intelligent and physically normal with a history of two spontaneous abortions and no live births. Karyotype analysis, banding studies, and buccal smears showing two sex chromatin bodies in 31% of 800 cells analyzed confirmed that the patient was a triplo-X female. The incidence of 47,XXX females is believed to be about one per 1000 in the normal population (7). Due to wide phenotypic variability, a clearly defined triplo-X syndrome has not been established. Fertility is thought to be unimpaired (8). There is, however, a slightly increased risk of sex chromosome anomalies in the offspring.

Chromosome polymorphism was detected in a 30-year-old white female with a history of two early spontaneous abortions. Satellites on chromosome 17 were seen consistently in all preparations. A polymorphism of this type is not believed to contribute to repeated fetal wastage (4), although the possibility cannot be ruled out until prospective studies are done. The patient was in the seventh month of an uneventful pregnancy when the study was done.

Another structural polymorphism was discovered in a husband whose wife had experienced three spontaneous abortions and no live births. The husband's karyotype was 46,XY with an enlarged #16 chromosome. The clinical significance of this finding is not known at present, and the patient's chromosomes are being studied with banding techniques.

One of the most interesting findings was the ascertainment of two families with balanced D/D

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translocations. In the first family, the husband was the carrier and exhibited a 45,XY t(DqDq) cell line. His wife had experienced three spontaneous abortions, had given birth to a normal female, and a hydrocephalic female who died in infancy. In a pedigree study, the patient's mother, brother, sister, and sister's son were all ascertained as carriers (Figure 1).

In the second family, the wife was found to have the same type of D/D translocation. The patient had two normal sons and three early spontaneous abortions. One of the patient's sons is a carrier. Pedigree studies are incomplete in this family as of this writing.

Translocations in patients selected for investigations of this nature may be as frequent as one in 53 (6). Thus, about 1 in 26 couples with a history of habitual abortion may be found to exhibit a translocation. The frequency of t(DqDq) in the normal population is believed to be one per 1000 (9). As in our study, this specific rearrangement is the single most frequent finding reported in cytogenetic evaluation of couples experiencing recurrent abortion (3).

Since both t(DqDq) patients in our study have produced normal offspring, both must harbor heterologous translocations. Analysis is continuing in both families to detect which D group chromosomes are involved and to locate other carriers in relatives.

The major question in this investigation is whether observed chromosome anomalies are causally related to repeated fetal wastage. Based on previous reports, there does not seem to be an increased risk of abortion in a triplo-X female or patients with satellites on chromosome 17 (4, 7, 8). Due to the increase in sex anomalies in offspring of triplo-X females, however, amniocentesis at 14-16 weeks of pregnancy is indicated in these cases. Wide phenotypic variability in both male and female offspring with an extra X chromosome makes counseling difficult, but families need to be advised of the potential risks involved. In this particular patient with a triplo-X karyotype, the extra chromatin material appears to be innocuous in terms of her own physical manifestations. In the case of the large #16, chromosome banding techniques should shed light on the structural polymorphism involved. In all three cases, only prospective studies will give more precise counseling information.

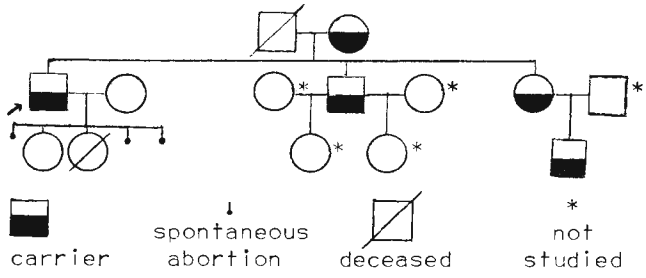

FIG. 1—Pedigree of a family showing inheritance of a D/D Robertsonian translocation.

In the two couples with D/D translocations, we believe the rearrangements are related to recurrent spontaneous abortion. Amniocentesis is indicated in any future pregnancy due to the increased risk of an offspring with D-trisomy.

A study is currently in progress to examine, with recently developed banding procedures, karyotypes of all patients seen to date. In this way anomalies unrecognized with the standard procedure may be detected. These hidden aberrations may be responsible for repeated fetal wastage in certain cases.

In view of the increased frequency of chromosome rearrangements demonstrated in these couples and the importance of counseling for future pregnancies, it would be wise to consider cytogenetic evaluation when all other probable causes for recurrent abortion have been ruled out.

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