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Parental Chromosomal Abnormalities in 50 Couples with Recurrent Spontaneous Abortions†

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= **Abstract** =Although the etiology of repetitive fetal wastage is unknown in many instances, parental chromosomal rearrangements represent a well-established cause of repetitive spontaneous abortions. And the frequency of parental translocations with recurrent spontaneous abortions varies widely in reported series (4.7%-19.3%).

From January, 1980 to December, 1985, fifty couples with histories of two or more recurrent abortions were evaluated cytogenetically with a GTG(G-band with Trypsin using Giemsa) technique.

The results were as follows:

1. In five (10%) of the couples with balanced translocations, four balanced carrier partners (8%) were identified in husbands and one another (2%) in wives.
2. Pericentric inversion of the ninth chromosome were identified in two male partners (4%).

A high incidence (14%) of cytogenetic abnormalities were found in couples with recurrent abortions. Chromosome analysis is advocated as a primary tool in the evaluation of couples with repetitive fetal wastage.

Key words: ***Chromosomal abnormalities, Parental, Recurrent abortion***

INTRODUCTION

The causes of spontaneous abortion are probably multiple, including abnormalities of placentation, systemic diseases, endocrine disturbances, immunologic factors, anatomic defects and genetic errors. With exception of Müllerian abnormalities, the precise contribution of each of these factors to recurrent abortion and early fetal wastage remains ill-defined. The contribution of chromosomal rearrangements in parents, as predisposing to recurrent abortion, is gradually coming into focus.

Between 40% and 60% of spontaneous abortions were to be the result of numeric or structural chromosomal abnormalities. (Kajii *et al.* 1973; Boue *et al.* 1975) The majority of these abnormalities are sporadic and therefore nonrepetitive. Nature thereby efficiently reduces the incidence of chromosomal anomalies in the general population. Awareness of this fact can help women to overcome the emotional impact of a single abortion, since the prognosis for future pregnancies is the same order as for nulligravidas. However we know, from retrospective studies, that the chances of carrying an infant to term are significantly reduced after two or more abortions, indicating that there is a specific and recurrent cause in some couples in this category.

An increased incidence of chromosomal translocations in couples who are "habitual aborters" has been reported. (Lucas *et al.* 1960; Lillian *et al.* 1972; Kajii *et al.* 1973; Khudr *et al.* 1974; Kim *et al.* 1975; Lauritsen 1976; Sutherland *et al.* 1976; Byrd *et al.* 1977; Mennuti *et al.* 1978; ThiTho *et al.* 1979; Simpson 1980; Ward *et al.* 1980; Simpson *et al.* 1981; Blumberg *et al.* 1982; Davis *et al.* 1982; Holzgrave *et al.* 1984) This incidence ranges from 4.7% to 19.3% (average 10.1%) and has suggested to some that cytogenetic analysis be utilized as a primary tool in the assessment of recurrent

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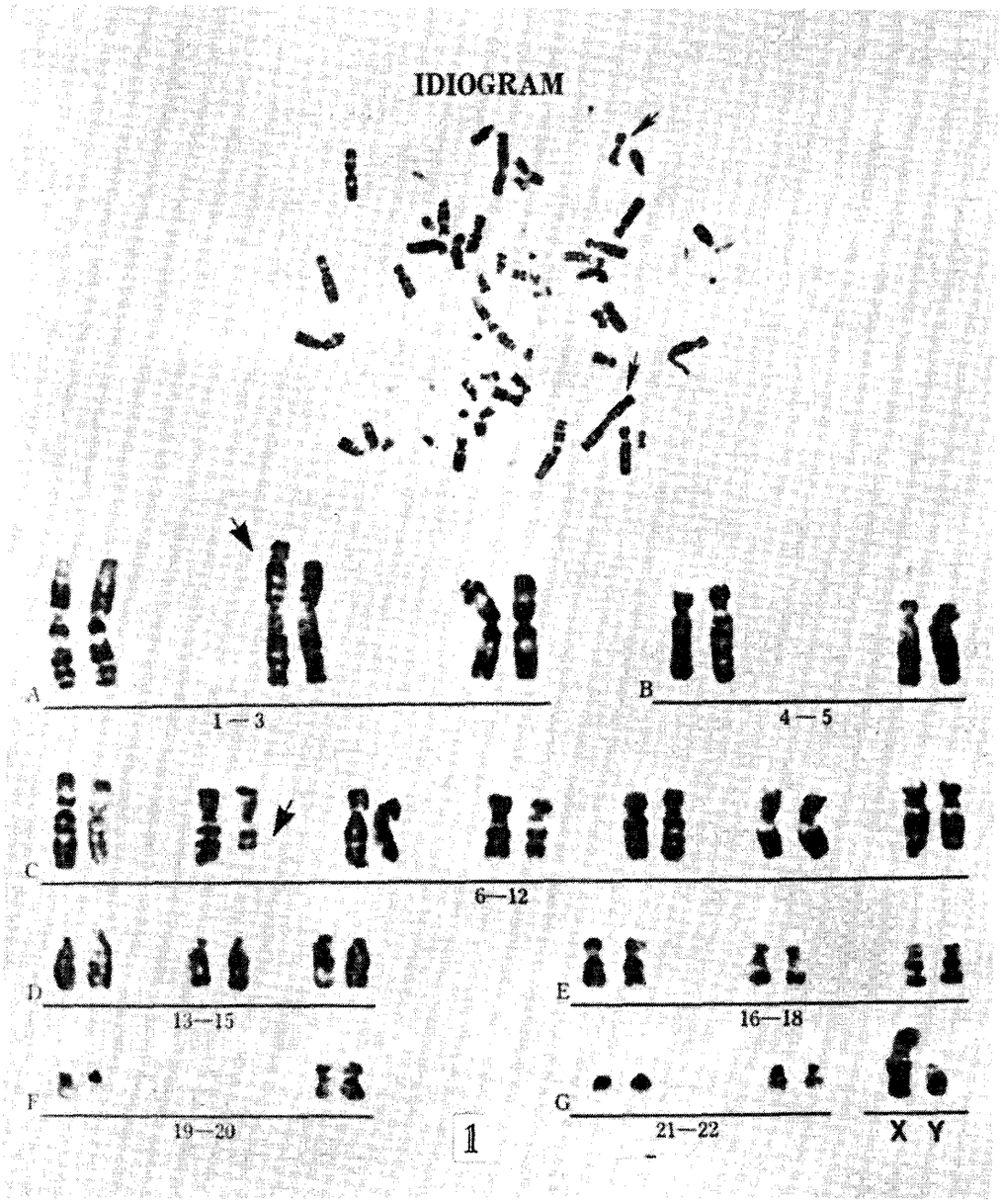

Fig. 1. Husband with balanced 2/7 translocation 46, XY, t(2:7). Three abortions and one child with skeletal malformation.

pregnancy wastage. (Mennuti *et al.* 1978)

The purpose of this study was designed to present cytogenetic data of 50 couples who have histories of recurrent spontaneous abortions and to determine the necessity of cytogenetic study for those couples.

MATERIALS AND METHODS

From January, 1980 through December, 1985, 50 couples (100 individuals) were investigated cytogenetically because of habitual abortions. From each couple a detailed family and medical history was obtained. Only 4 couples whose history included at least two spontaneous abortions were reported, and more than 92% of the couples had three or more abortions (Table 1). Spontaneous abortion was defined as an embryo or fetus expelled spontaneously from the uterus before the 20th week of gestation, weighing less than 500g, or measuring less than 25 cm. The individuals were studied regardless of pregnancy order or the presence of previous live or stillbirths (Table 2). The mean age was 28.8 (± 3.7) years for the women and 33.2 (± 2.5) years for the men. Only 5 of the couples had had one or more liveborn children, whereas 39 couples had experienced only spon-

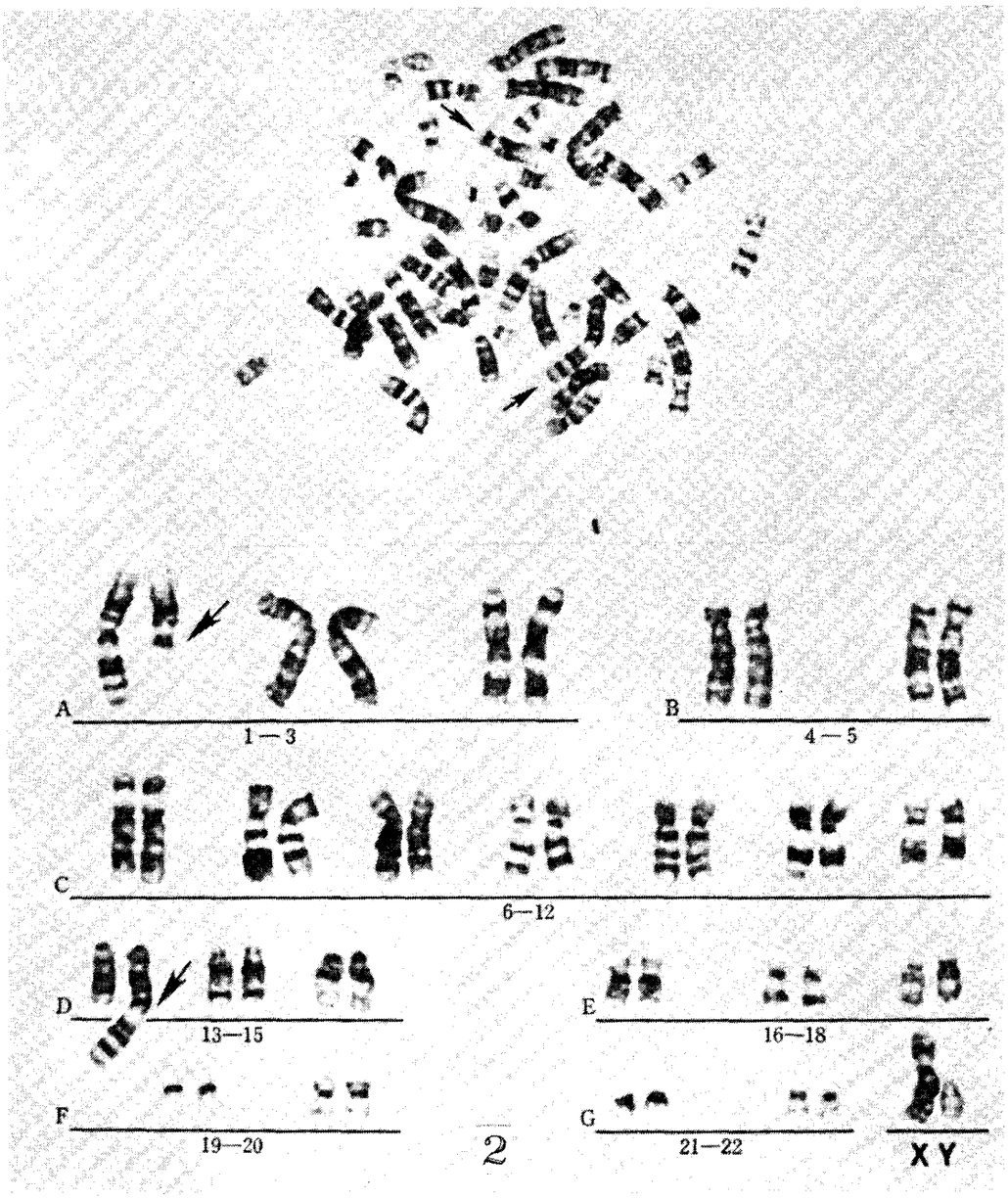

Fig. 2. Husband with balanced 1/13 translocation 46, XY, t(1:13). Three abortions.

Table 1. Number of spontaneous abortions in couples studied

No. of spontaneous abortions	No. of couples (N = 50)
2	4
3	23
4	12
5	6
>5	5

Table 2. Previous obstetric history in couples with multiple spontaneous abortions

Obstetric history	Mean (± SEM)	Range
Spontaneous abortions per couple	3.8 (0.23)	2-10
Therapeutic abortions per couple	0.12(0.01)	0 - 3
Stillbirths per couple	0.16(0.01)	0 - 2
Live births per couple	0.10(0.01)	0 - 2
Offspring with congenital malformations per couple	0.04(0.01)	0 - 1

taneous abortions. Both partners had been available for cytogenectic studies, and in neither were there other obvious reasons for the multiple spontaneous abortions (hormone abnormalities, im-

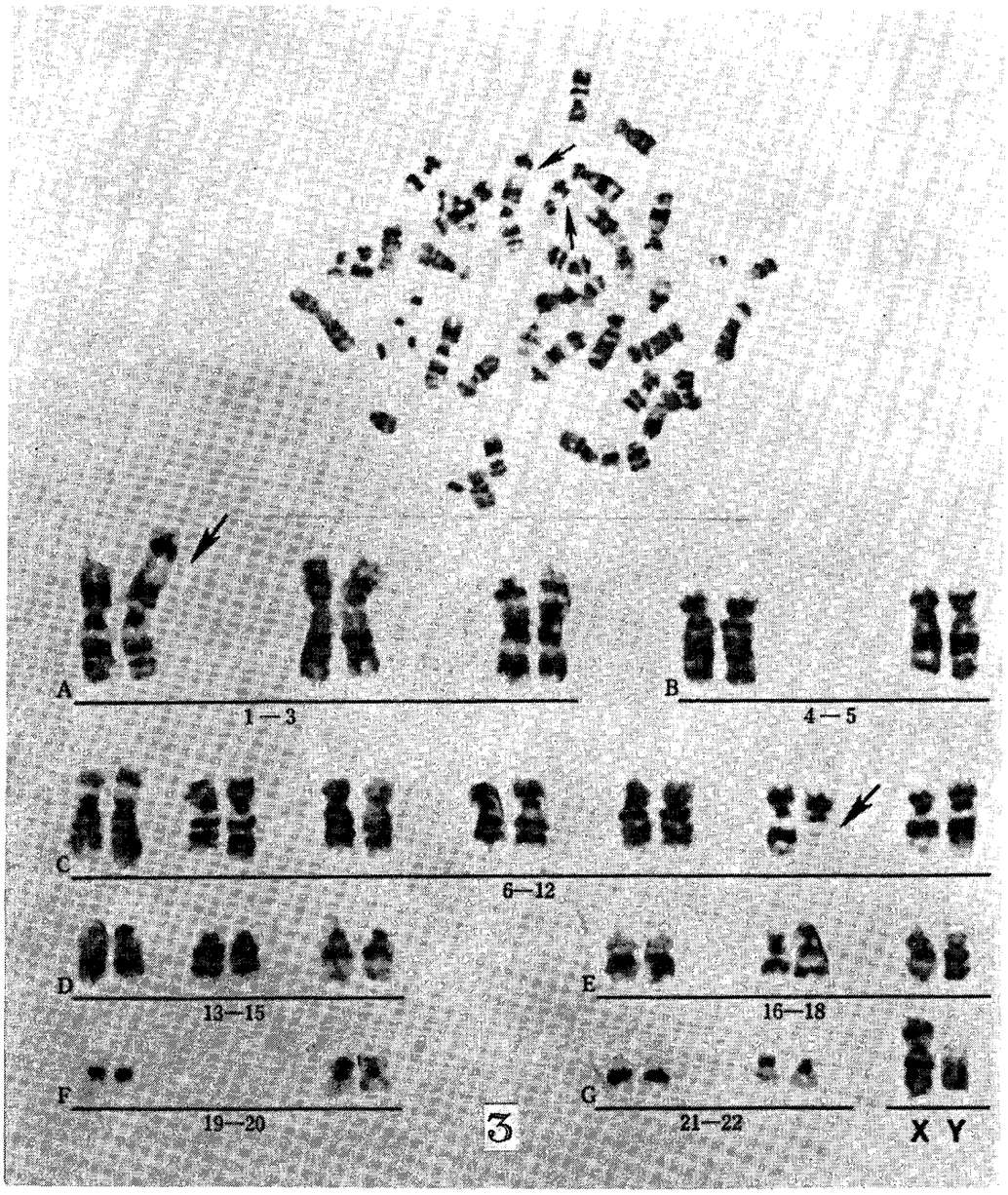

Fig. 3. Husband with balanced 1/11 translocation 46, XY, t(1:11). Three abortions.

munologic factors, anomalies of the reproductive tract, infections, etc) found during the medical workup.

Cytogenetic studies of peripheral blood lymphocytes of both partners were carried out after routine cell culture and processing for Giemsa banding. (Priest 1977) After incubation at 37°C for 66 to 72 hours, add colchicine (Colcemid) for 1 hour at 37°C. Critical steps are: (1) Hypotonic KCl (0.075 M) for 10 minutes at room temperature (2) Fixation in 1 part glacial acetic acid: 3 parts absolute methanol (twice) and keeping overnight (3) Slide preparation by standard air drying technique (4) Aging for 3 days (5) Place slide in Coplin jar containing 0.125% trypsin at room temperature and leave for 30 to 60 seconds (6) Stain 10 minutes with 10% Gurr Giemsa (7) Air dry and Microscopy. At least 25 metaphases were studied microscopically and five were fully analyzed: one karyotype was prepared for each patient. In cases of a suspected chromosomal rearrangement or mosaicism, 50 metaphases of peripheral lymphocytes were analyzed.

RESULTS

Chromosomal aberrations found in 7 (14.0%) of 50 couples who had cytogenetic studies are summarized in Table 3. There were 5 translocation

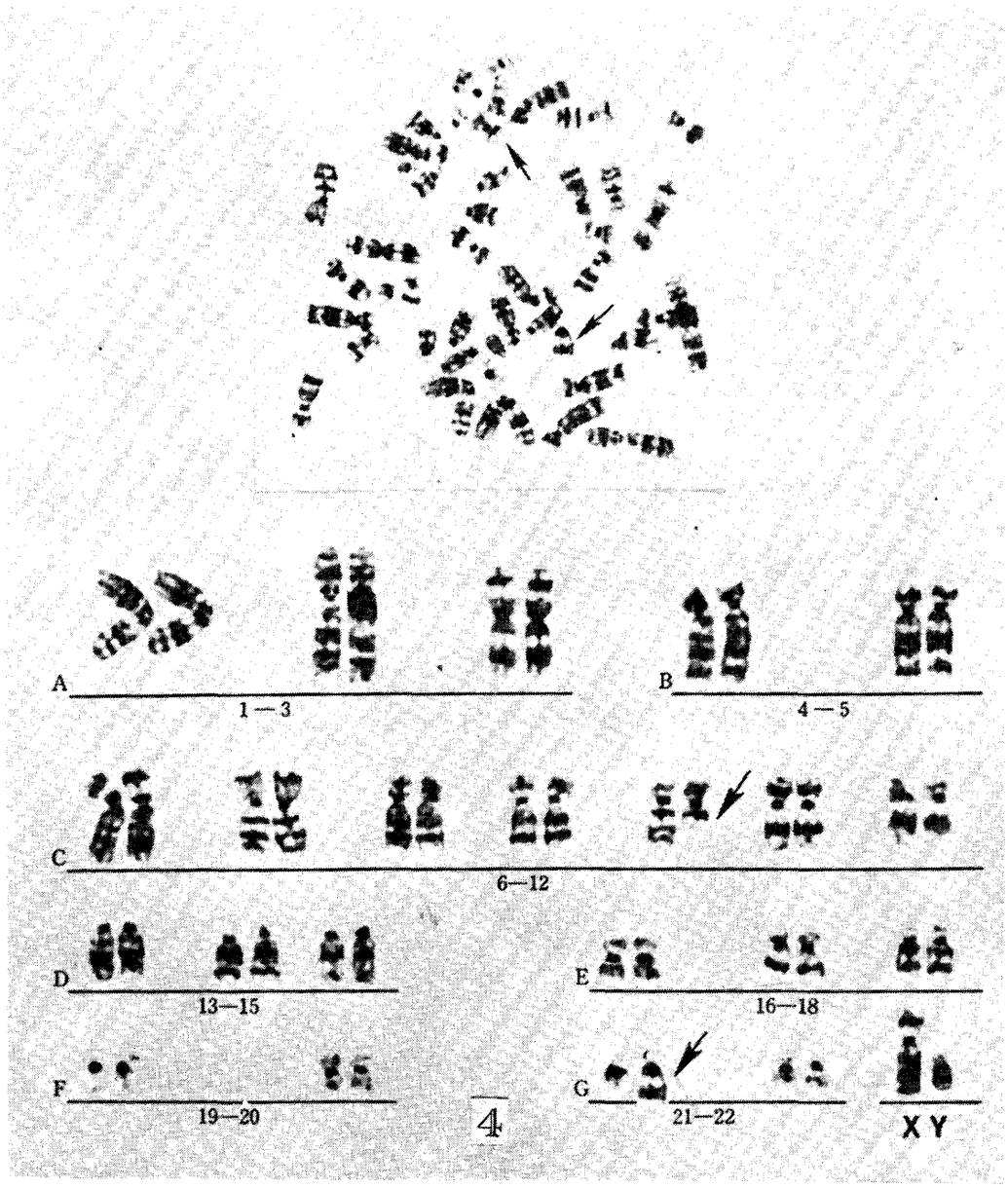

Fig. 4. Husband with balanced 10/21 translocation 46, XY, t(10:21). Three abortions.

(2:7, 1:13, 1:11, 10:21, 5:11) (10%) and 2 inversions (9) (4%). All translocations were balanced translocations. There was neither Robertsonian translocation nor reciprocal translocation. And two inversions were pericentric.

In contrast to other studies, (Lillian *et al.* 1972; Khudr 1974; Simpson 1980; Holzgrave *et al.* 1984; Sach *et al.* 1985) there was neither X-hyperploidy nor X mosaicism. Among 7 aberrations, six were found in male partners and only one was in female partner.

Chromosomal polymorphism in the form of enlarged satellites, secondary constrictions, other heterochromatic segment or other non-systematic anomalies, for instance, a slightly increased frequency of chromosome breakage, were not considered to be of importance and were therefore not reported here.

DISCUSSION

About 50% of all spontaneous abortions are caused by chromosomal aberration of fetus. This means that up to 10% of all fertilization result in a chromosomally abnormal zygote. Since most of these cases are aborted, only 0.5% of chromosomal aberrations are observed in a newborn population. (Boue *et al.* 1975)

Most of chromosomally aberrant fetuses are of

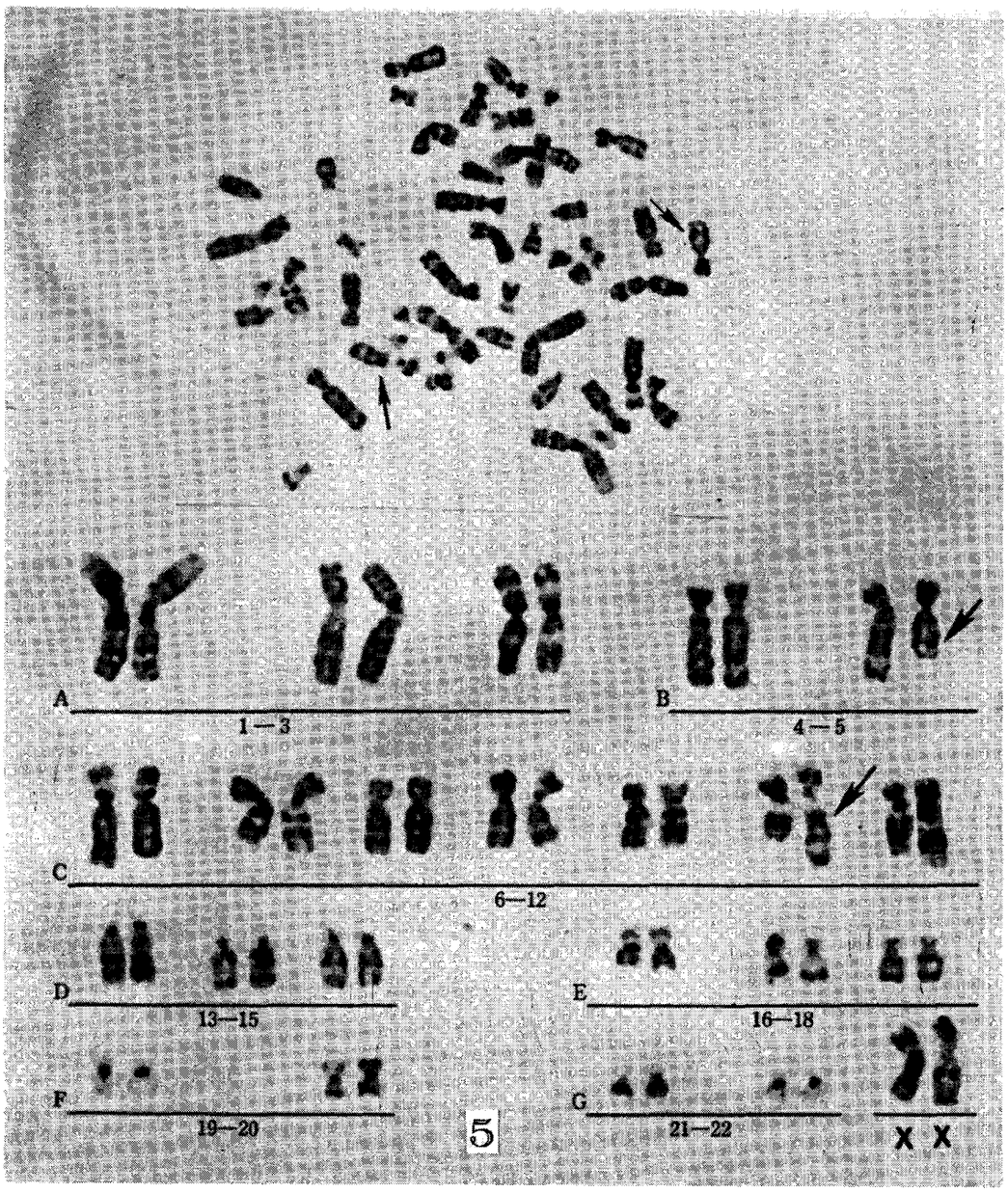

Fig. 5. Wife with balanced 5/11 translocation 46, XY, t(5:11). Four abortions(1st trimester).

spontaneous origin, with no abnormality detectable in either parent. In a certain proportion of cases, one partner is found to be carrier of a chromosome aberration that, although not harmful to him, causes recurrent fetal wastage. (Husslein *et al.* 1982) Other data of frequency of chromosomal aberrations in couples with recurrent fetal wastage are shown in Table 4. In our study, the proportion of chromosomal aberration in recurrent spontaneous abortion is slightly higher than other data (Table 4).

The relationship between a balanced translocation in a parent and abortion has been definitely established. Abortuses of such parents often show the unbalanced forms, as demonstrated by Lauritsen. (Lauritsen 1976) In addition, it is generally accepted that the balanced rearrangement leads to increased nondisjunction of other chromosomes during meiosis, a relation that might also hold true for inversion. (Husslein *et al.* 1982) The diversity of types of balanced translocations in these series is striking of 71 translocations in other studies in Table 4, every autosome is involved, and they are predominantly unique in different exchange chromosomes and size of exchanged segments. (Davis *et al.* 1982)

In our study, chromosomes of A,B,C,D and G group are involved in translocations. Unlike other

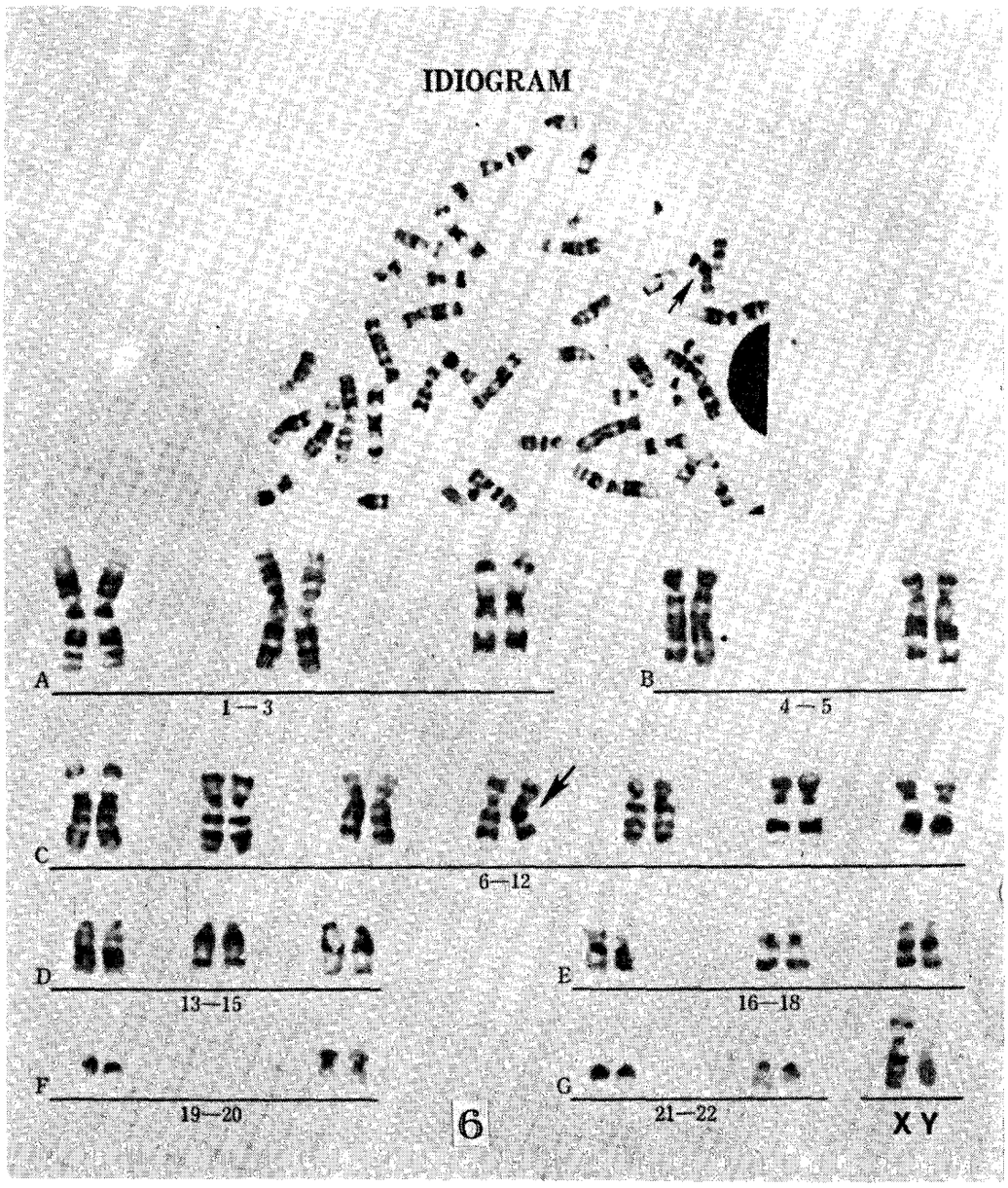

Fig. 6. Husband with 9 pericentric inversion 46, XY, inv(9). Five abortions(3rd or 4th months).

studies, we had neither Robertsonian nor reciprocal translocation.

An association of pericentric inversions of chromosome 9 and reproductive failure has been suggested. The rate of pericentric inversion of chromosome 9 in our study (4.0%) is higher than reported for general population and for the rate observed in control group of Ward *et al.* (1.1%). (Ward *et al.* 1980)

Individuals with chromosomal inversions are also phenotypically normal, but like those with translocations are predisposed to unbalanced gamete. Gamete of individual carrying inversion may be abnormal if crossing over occurs within inverted loop. (Simpson 1981) The likelihood of crossing over occurring within the rearranged segment and, hence, the likelihood of unbalanced gametes, is believed to depend directly upon the length of the inverted segment. If an inversion is detected in a parent, the likelihood of live born offspring being abnormal has been estimated to be about 10-15%. (Sutherland *et al.* 1976) In contrast to other studies, (Lillian *et al.* 1972; Khudr 1974; Simpson 1980; Holzgrave *et al.* 1984; Sach *et al.* 1985) we had neither mosaicism nor X-hyperploidy. This can be accounted for by the number of cases, hence we will find mosaicism if many cases are studied from now on.

Table 3. Cytogenetic data in seven couples with chromosomal abnormalities

Case	Chromosomal aberration and history
1	Husband with balanced 2/7 translocation 46, XY, t(2:7) 3 abortions and one child with skeletal malformation
2	Husband with balanced 1/13 translocation 46, XY, t(1:13)(q21:q34) 3 abortions
3	Husband with balanced 1/11 translocation 46, XY, t(1:11) 3 abortions
4	Husband with blanced 10/21 translocation 46, XY, t(10:21) 3 abortions
5	Wife with balanced 5/11 translocation 46, XX, t(5:11) 4 abortions (1st trimester)
6	Husband with 9 pericentric inversion 46, XY, inv(9) 5 abortions (3rd or 4th months)
7	Husband with 9 pericentric inversion 46, XY, inv(9) 4 abortions (3rd or 4th months)

We feal that chromosomal analysis should be considered as an integral part of the evaluation of patients who have had recurrent spontaneous abortions because of the clear relationship between chromosomal aberration in a parent and subsequent abortions (14.0% in our study and 10.1% of recent other studies). The detection of couples with chromosomal aberrations can undoutedly help to prevent the births of malformed infant.

In future studies of reproductive failure, the correlation of a careful clinical history with selective studies may identify those chromosomal rearrangements which are specifically linked to infertility, early abortion, or fetal malformation.

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Table 4. Reported series tabulating the frequency of chromosomal aberration in recurrent fetal wastage

References	Frequency	Cases of each aberration			
		Translocation	Inversion	Mosaicism	Others
Husslein *et al.*	7/150 (4.7%) F:M = 5: 2	5 (4:1)	1 (0:1)	1 (1:0)	
Sach *et al.*	50/500 (10.0%) F:M = 36:14	22 (16:6)	3 (1:2)	24 (19:5)	1 (0:1)
Byrd *et al.*	7/ 55 (12.7%) F:M = 5: 2	7 (5:2)			
Blumberg *et al.*	7/ 81 (8.6%) F:M = 5: 2	6 (4:2)	0	1 (1:0)	
Lucas *et al.*	5/ 42 (11.9%) F:M = 4: 1	4 (4:0)	1 (0:1)	0	
ThiTho *et al.*	12/ 62 (19.3%) F:M = 10: 2	11 (9:2)	0	1 (1:0)	
Kim *et al.*	4/ 50 (8.0%) F:M = 4: 0	3 (3:0)		1 (1:0)	
Davis *et al.*	11/100 (11.0%) F:M = 8: 3	8 (5:3)		1 (1:0)	2 (2:0)
Mennuti *et al.*	5/ 34 (14.7%) F:M = 1: 4	5 (1:4)			
Total	108/1074(10.1%)	71	5	30	3
Moon *et al.* (S.N.U.H.)	7/ 50 (14.0%) F:M = 1: 6	5 (1:4)	2 (0:2)		

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= 국문초록 =

반복 유산력이 있는 50쌍의 부부에 있어서 양친의 염색체 이상에 관한 연구

서울대학교 의과대학 산부인과학교실

문신용 · 신희철 · 장윤석

습관성유산의 원인은 내분비이상, 해부학적 결함과 염색체 이상 등을 포함하여 여러가지가 알려져 있다. 특히 양친의 염색체 이상은 습관성 반복유산의 잘 알려진 원인중의 하나로 알려져 있다. 하지만 반복유산력이 있는 부부의 염색체 이상의 빈도는 발표된 논문마다 다양하다(4.7%-19.3%).

저자들은 1980년 1월부터 1985년 12월까지 서울대학교 의과대학 부설 인구의학연구소 유전학 연구실에 의뢰된 반복 유산력이 있는 50쌍의 부부를 대상으로 말초혈액 임파구를 배양하여 핵형분석을 실시하였다.

1) 5쌍의 부모(10%)에서 평형전좌가 나타났으며 이중 4명(8%)은 평형전좌부부의 남편에게서 발견되었고 1명(2%)은 평형전좌부부의 아내에게서 발견되었다.

2) 2쌍의 부모(4%)에서 역위가 나타났고, 모두 9번 염색체의 중심절(中心節)주위 역위였으며, 모두 역위부분의 남편에게서만 발견되었다.

3) 이상에서 반복유산력이 있는 부부에 있어서 이상염색체의 빈도는 14%의 고율을 나타내었다. 그러므로 이러한 경우 염색체의 핵형분석은 필수적인 검사중의 하나라고 결론 지을 수 있다.