

Contribution of parental chromosomal abnormalities to recurrent spontaneous abortion: A cytogenetic study on Iraqi couples

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Abstract:

The main objective of this research study the parental chromosomal abnormalities to recurrent spontaneous abortion. Parental chromosomal rearrangements account for more than 50% of RSA. So, it became necessary in this study to determine whether chromosomal factor is involved in RSA in Iraqi population. Related to that reason, blood samples from couples were collected and chromosomal abnormalities (structural or numerical) were detected by cytogenetic studies. Results from this examination indicated that increased chromosomal abnormalities in couples with advanced age and these abnormalities include translocation and deletion as follows: 46 XY,9qh+ ; 46 XX,21pss ; 46 XY, t(14,15) ; 46XY,14 pstk ; 46 XY ,15 pstk ; 45 XY, 3del. One can expect that, when these abnormalities are transferred to the fetus it can cause disturbance of the chromosomal structure of the fetus which resulted in abortion.

Keyword: G-band, chromosomal abnormalities, recurrent spontaneous abortion

Introduction:

One of the most frequent reproductive events is recurrent spontaneous abortion (RSA) that occurs in women in reproductive age with a frequency of 1–3 % (1). It is defined as two or more repeated pregnancy losses before the 20th week of gestation (2). The etiology of RSA is often unclear and may be multi factorial, with much controversy regarding diagnosis and treatment. Reasonably accepted etiologic causes include, genetics, anatomical, placental anomalies, hormonal problems, infection, hereditary thrombophilia, immunologic factors, nutritional and environmental factors (3).

Chromosomal abnormalities in the conceptus are usually the characteristic findings in cases of SA occurring due to problems with the Chromosomal heteromorphism is considered a variant of a normal karyotype, but it is more frequent in couples with RSA (4). Common cytogenetic polymorphisms detected by G-banding are considered heteromorphisms. They have heterochromatic regions of chromosomes 1, 9, 16, and Y, with prominent acrocentric short arms, satellites and stalks. Such heteromorphic chromosomes have been

observed since the early studies of cytogenetics and are believed to have no impact on the phenotype (5, 6) . In recent studies, however, patient groups with RSA have been found to have higher rates of chromosome heteromorphism compared to the rest of society and to control groups, which may not be merely an incidental finding (7).

Translocations involve breaks in two different chromosomes with an exchange of segments. In human, there are two major types of translocation: reciprocal translocations in which there is no visual loss of chromatin and Robertsonian translocations in which the long arms of two acrocentric chromosomes are joined with loss of the two short arms. Ascertainment of both reciprocal and Robertsonian translocations is often through multiple miscarriages, unbalanced progeny or infertility (8).

Subject and methods:

The study included 30 couples of those who suffered miscarriages repeatedly, after they were diagnosed at Iraqi Center for Cancer and Medical Genetics Research during July 2012 to June 2013, primarily for their need to examine genetic where they underwent tests other causes and results were negative. Clinical diagnostic indications for chromosome analysis included recurrent abortion (at least two) intrauterine fetal deaths or stillbirths and abnormal children.

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Chromosome analysis was performed on cultures of peripheral blood lymphocytes according to standard methods(9). For each patient at least 30 well-spread metaphases were analyzed by G- banding staining.

Result:

Of the 30 couples, six cases (2 females and 4 male) showed the major chromosomal abnormalities. Chro-

mosomal abnormalities were found in 6 subjects including (2) females and (4) males. Among (6) subjects (3) showed structural aberration and (3) individuals were found to have chromosomal variants.

The first couples have average age of 30.5 years and have normal deliveries. The chromosomal structure of these two couples revealed that both have normal karyotype; 46 XX for female and 46 XY for male. These couples were kept as control for our study.

Table 1: Karyotype Findings between the Couples with History of Reproductive Failure.

Number of cases	Female karyotype	Male karyotype	Age		Number of abortion	Number of gestation
			♂	♀		
1	46,XX,21pss	46,XY,9qh+ & 46 XY,3del	37	30	6	0
2	46,XX	46,XY,14pstk	33	30	3	2
3	46,XX	46,XY,15pstk	36	32	5	1
4	46,XX	46XY,t(14;15) (q32.1,q24)	31	26	3	0
5	46,XX,7del	46,XY	35	33	3	1

Case1 These couple has average age of ~ 29.5 years old and had 6 times recurrent abortion. The chromosomal karyotype of these couples showed a male karyotype with 46, XY, 9qh+

(increased heterochromatin on chromosome 9) and he had deletion in chromosome 3 . And a female chromosomal karyotype 46, XX, 21pss (double satellite on chromosome

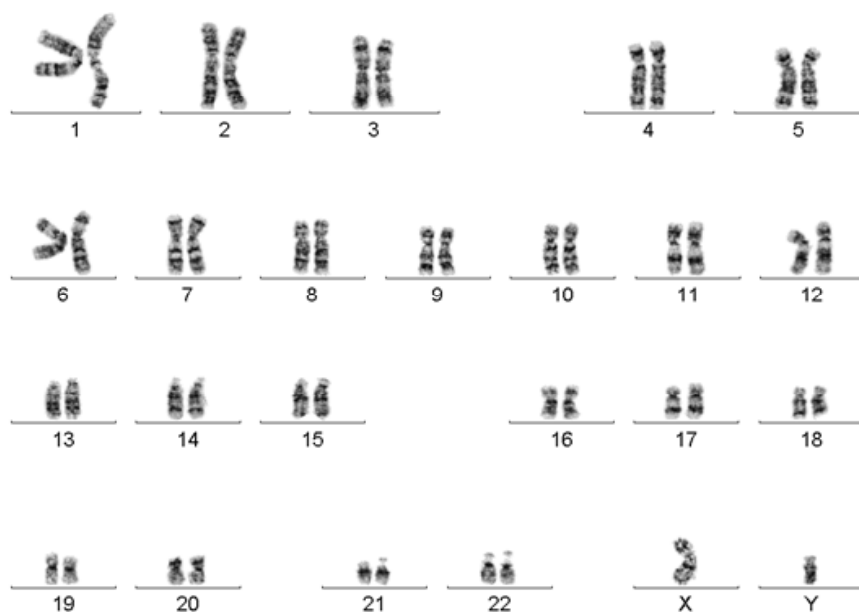


Figure 1: karyotype of the male with 46, XY, 9qh+ & del 3. Showed a male karyotype with 46, XY, 9qh+ (increased heterochromatin on chromosome 9) and delete in chromosome 3. (X100) by G- banding

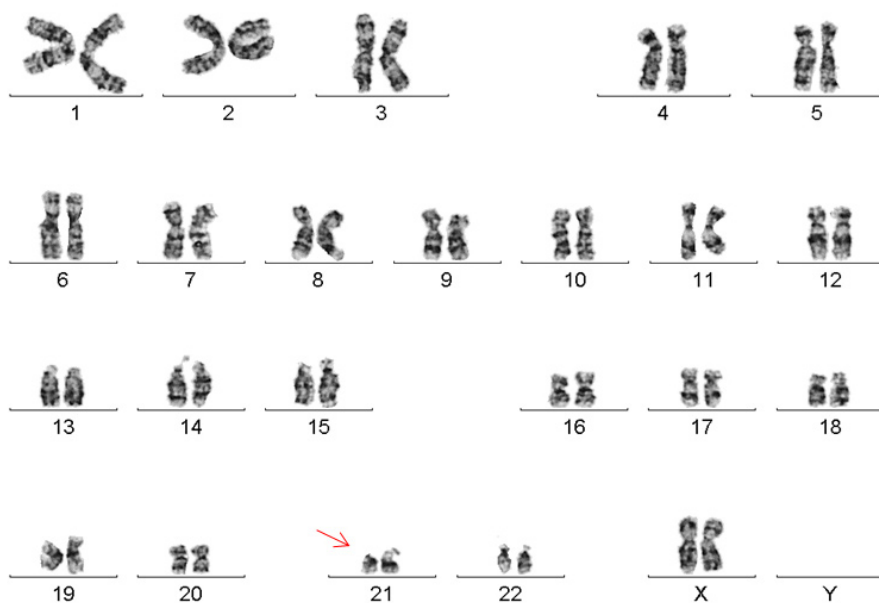


Figure 2 : A female chromosomal karyotype 46,XX,21pss (double satalite on chromosome 21) . (X100) by G-banding

Case 2 A couple was referred for chromosomal analysis because three pregnancies had ended in first trimester abortions. Karyotype of wife (30 years) was normal 46 XX . But hus-

band (33 years) was found to have 46 XY,14 pstk (increasing length of satellite threads on chromosome 14) [Figure 3]

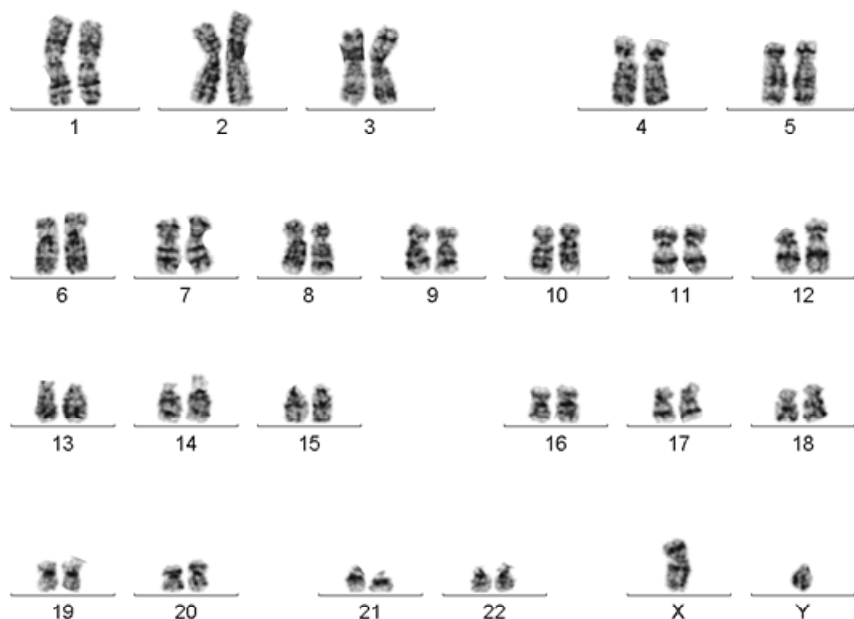


Figure 3 : karyotype of the male with 46 XY,14 pstk . Results showed abnormal male karyotype have 46 XY,14 pstk (increasing length of satellite threads on chromosome 14) (X100) by G- banding

Case 3 Other couples were at average age of 32 years old and have 5 abortions. They were found to have a chromosomal karyotype 46,XX (normal Female Karyotype) and

46,XY,15pstk (increasing length of satellite threads on chromosome 15) [figure 4]

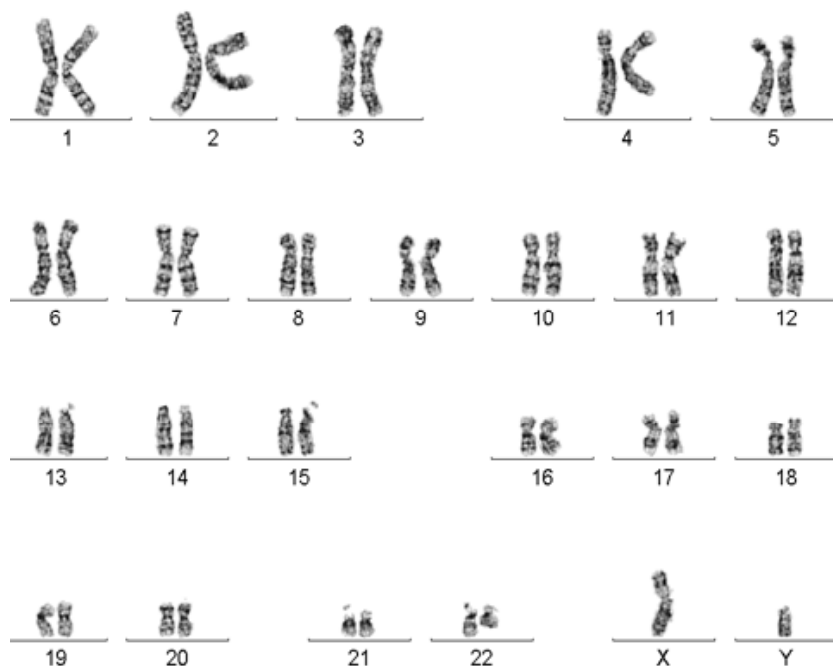


Figure 4 : karyotype of the male with 46 XY,15 pstk . Results showed abnormal male karyotype have 46 XY,15 pstk (increasing length of satellite threads on chromosome 15) (X100) by G- banding

Case 4 A 26 year old female was referred for karyotyping with history of three abortion in first trimester. Karyotype was found to be 46 XX and no anomaly was seen. Her husband's

karyotype was found to have 46XY,t(14;15) (q32.1,q24) translocation [Figure 5]

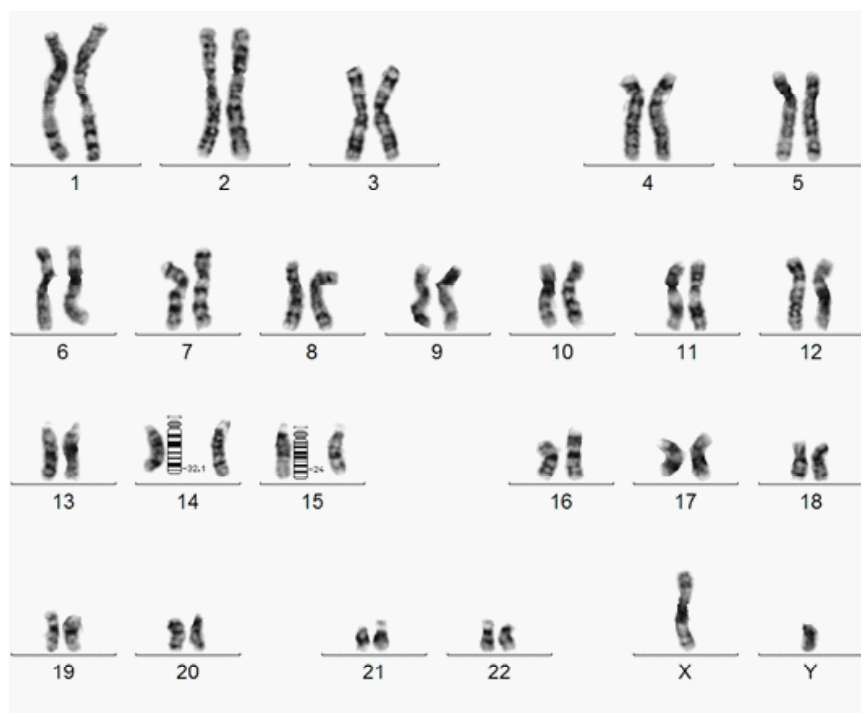


Figure 5: karyotype of the male with 46XY,t(14;15) . Results showing structure and rearrangement of chromosomes. Results showed abnormal male karyotype 46XY, t (14;15) (q32.1,q24) translocation .(X100) by G- banding

Case 5 The last group of couples has average age of 33 years and had 3 spontaneous miscarriages. The chromosomal structure for both couples were as follow: for female, 46, XX, del

(7) (q32) (deletion q arms chromosome 7). For male, 46, XY (normal male karyotype). These results are summarized in Figure 6

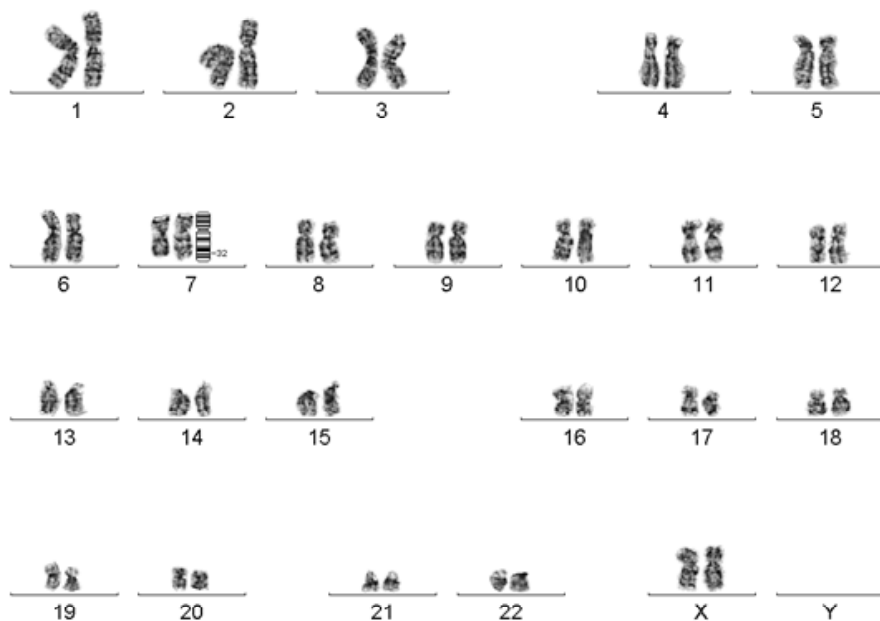


Figure 6 : karyotype of the female with 46 XX , 7 del . Results showed abnormal female karyotype have 46 XX , 7 del (deletion in chromosome 7) . (X100) by G- banding

Dissection:

Cytogenetic studies have an important role in the evaluation of couples with repeated miscarriages . The genetic factors were found to represent more than 50% of early gestation spontaneous abortion and associated with fetal chromosomal abnormalities (10) In present study, we examined the first two couples with recurrent abortion and found a chromosomal abnormality in the female karyotype representing a Robertsonian translocation in chromosome 21. In the same couples we found that the husband is a carrier of variants of chromosome 9 and chromosome 3. These variants were in the heterochromatine region of the long arm of both chromosomes. According to a widely held opinion, the chromatin that causes chromosome hetero-morphism is formed out of the repetitive DNA regions that do not code for genes. Considering the studies of cell biologists, however, heterochromatin plays an essential role in spindle attachment and chromosome movement, meiotic paring, and sister chromatid cohesion (11). Polymorphic heterochromatic regions were found to alter the synapsis of homologous chromosomes during meiosis. These regions are the last to enter synapsis, changing the timing of the whole division and leading first to probable meiotic defects, and eventually to infertility (Codina-Pascual et al., 2006). A number of authors reported that chromosome polymorphisms were related to infertility and recurrent abortions (4). We encountered in our study a male case with increased heterochromatin (qh+) in chromosome 3. Bhasin (2005) reported that chromosomal heteromorphisms may be associated with some clinical conditions because they may carry some structural load; otherwise populations bear-

ing these heteromorphisms are apparently normal (12). Similarly, our finding showed a member having heteromorphic abnormality in chromosome 3 in family experiencing a recurrent pregnancy load. To our knowledge, no previous reports demonstrated the critical role of heteromorphic aberrations in chromosome 3 and its association with repeated abortion that makes our current results as new finding.

Our current results, revealed a male chromosomal abnormality in chromosome 14. That may implicate in recurrent spontaneous abortion in this family. These finding are in keep with studies by Vajira et al (2009) where the investigator found that both maternal 14ps+ and paternal 14ps+ can lead to recurrent pregnancy loss

Anther case showed a male chromosomal abnormality in chromosome 15. Numerous studies have suggested indirect effects such as higher incidence of spontaneous abortions associated with striking chromosomal variants such as large satellites on chromosome 15(14). Interestingly, presence of ps+ on chromosome 15 in recurrent pregnancy loss cases was higher in the males (57.1%) as compared to the females (42.9%) and pregnancy loss observed in those groups of patients was at first and second trimester pregnancy.

In our present study we have a family with translocation in chromosomes 14 and 15. Interestingly there were a significant number of patients with chromosomal abnormalities which considered to be normal polymorphic chromosomal variations rather than true chromosomal abnormalities per say. Such normal polymorphic variants however, are believed to contribute to the instability of chromosomes during meiosis with a tendency towards an increased risk of aneuploidy resulting in recurrent spontaneous pregnancy loss or

sub-fertility (15). These findings are in support of our current finding where translocation between chromosomes 14 and 15 can lead to imbalance in fetal chromosomal structure then cause recurrent miscarriage.

Differs from the above results, the last group of couples studied revealed a wife with abnormality in chromosome 7 [del (7) (q32)]. Chromosome 7 has been a subject of interest in medical genetics because of its frequent association with

chromosome aberrations, rearrangements, and deletions, and because of the localization of several important genes, gene families, and disease loci on this chromosome. A strong correlation has been observed between the presence of a 7q abnormality and the missed abortion (16). From these results it can be stated that individuals with abnormalities in chromosome 7 are indirectly at a high risk for recurrent miscarriage due to fetus threatening by genetic disorders.

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