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Investigation of New Chromosomal Abnormalities Associated with Recurrent Abortion

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Abstract--- *Introduction and objective: recurrent abortion refers to the occurrence of three or more abortions in a clinically known pregnancy before the 20th week. It will be possible to prevent the birth of a disabled child and abortion, if chromosome structural abnormalities are identified. The present study was conducted with the aim of genetic (karyotype) investigation of women with recurrent abortion at Kamali Hospital in Karaj.*

Methodology: *This cross-sectional study was conducted on 69 couples (138 people) with recurrent abortion, referred to Kamali Hospital in Karaj. 2 ml of heparinized blood was taken for high resolution karyotype. The karyotype stages included blood culture for 72 hours, blood cell harvest, protein binding and digestion of chromosomes, preparing slide, and analysis. Chromosomal abnormalities along with the shape of the chromosomes were reported. Chromosomal analysis of abortion products was also performed when accessing the abortion product. Mutation analysis was performed using Chromas software. Data were analyzed by SPSS software.*

Results: *chromosomal rearrangements were found in 7 cases after cytogenetic analysis, 6 of which were female and one was male. Out of these7 cases, six had structural abnormalities and one had Turner Syndrome Mosaicism. Thus, out of 136 patients, 7 (5.14%) had chromosomal abnormalities, 6 (4.35%) of which had structural abnormalities and one (0.72%) had Turner Syndrome Mosaicism.*

Conclusion: *The results of the present study and previous studies suggest that the genetic investigation of the couples is an integral part of investigation of the spontaneous recurrent abortions.*

Keywords: recurrent abortion, genetic investigation, Chromosome abnormality, Karaj.

I. INTRODUCTION

Recurrent abortion refers to the occurrence of three or more abortions in a clinically known pregnancy before week 20. Clinical pregnancy is confirmed by ultrasound or histopathology evaluation and does not include chemical pregnancy. The rate of recurrent abortion (less than 20 weeks) is 10-15% (1). Spontaneous pregnancy loss is the most common complication of pregnancy. Almost 70% of human pregnancies fail to achieve survival and almost 50% of all pregnancies end before clinical diagnosis of a missed period or abnormal cardiac activity in abortion (2, 3).

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Recurrent pregnancy loss (RPL) or recurrent abortion is less common and occurs in about one in 100 pregnant women (4). RPL was previously defined as having three or more clinically known spontaneous pregnancy loss before week 20. According to this definition, out of 300 women, one experiences RPL (2). The etiology of recurrent abortion includes anatomical, immunological, genetic, endocrine, infectious, thrombophilic, and environmental factors (5). Unfortunately, the cause of recurrent abortion is identified in 50% of patients and remains unclear in the rest of the cases (6).

Recent recommendations on supporting clinical intervention after only two consecutive abortions show more prevalence in 100 women, when there are other pregnancy loss characteristics. These additional characteristics include a history of detectable fetal cardiac activity, normal chromosomal content of fetus, high age of mother, low fertility of couples, uterine anatomical abnormalities, endocrine glands abnormalities, infections, immunologic factors, environmental factors, metabolic or hormonal abnormalities, sperm quality, and parental age (7). Standard evaluation of RPL at present time currently includes tests for chromosomal translocation in parents as well as maternal tests for endocrine glands (thyroid), autoimmune (anti-phospholipid lupus and anticoagulant antibodies), anatomic abnormalities (endometrial or uterine abnormalities) and single-gene abnormalities in some cases (such as hereditary thrombophilia) (8). Despite a number of causes suggested, parental chromosomal abnormalities and complications caused by anti-phospholipid antibody syndrome have remained as only undeniable causes of RPL.
RPL is unexplained in approximately 45 to 50% of the patients (9-11). The prognosis is not bad in most cases of RPL. Researchers have shown that the total likelihood of a live birth following RPL is 70 to 75% even at higher maternal age (12-13). Parental chromosomal examination is part of a recurrent abortion evaluation and its aim is to identify Robertsonian translocation or balanced chromosomal abnormalities or to identify states of mosaicism that likely to be transmitted to the fetus (14). Almost half of the bilateral translocation disorders are balanced, one-fourth are Robertsonian and one-tenth are mosaicism of sex chromosomes in women, and the rest are inversion and balanced abnormalities. The karyotype of abortion products is also crucial. Normal karyotype usually indicates environmental factors involved in abortion, while abnormal karyotype is a sufficient reason for abortion. Chromosome structural abnormalities can be hereditary or sporadic. Parents with chromosomal abnormalities are examined using their fetus CVS or amniocentesis, and if chromosomal abnormalities are identified in fetus, the legal abortion license is given. Moreover, IVF along with PGD is another way to prevent the birth of a disabled child or recurrent abortion due to chromosomal abnormalities (15-17). It will be possible to prevent the birth of a disabled child and abortion if chromosome structural abnormalities are identified (18). Other applied examinations in recurrent abortion are molecular investigations of thrombophilia panel. The creation of clot and abnormal uterine placental circulatory system will result into abortion, lack of intrauterine growth, and preeclampsia. Finally, the families that are negative in thrombophilia panel and chromosomal examinations (no abnormality is seen) are candidates for the whole exome examination. Due to the high rate of kinship marriages as well as the different gene storage in Iranian society, it is possible to identify new genetic disorders (19). Hence, the aim of this article is a genetic (karyotype) examination of women with recurrent abortion at Kamali Hospital in Karaj (20).

Methodology

This cross-sectional study was conducted on couples with recurrent abortion referred to Kamali Hospital in Karaj. The sample size was determined by census method and the prevalence of recurrent abortion was investigated at genetic center during one year period from November 2018-2019. Convenient sampling method was used in this study. Inclusion criteria included

people with two or more abortions, no genetic diseases and willingness to participate in the study. Finally, 69 couples (138 persons) were investigated. Data were collected through demographic information questionnaire, genetic analysis of the samples obtained from aborted tissue, and genetic analysis (karyotype) of blood samples taken from parents. After obtaining the consent of subjects and ensuring them that tests are free, 2 ml of heparinized blood was taken for high-resolution karyotype. The karyotype stages included blood culture for 72 hours, blood cell harvest, protein binding and digestion of chromosome, preparation of slides, and analysis. Chromosomal abnormalities along with the shape of the chromosomes were reported. Moreover, in the case of access to abortion product, chromosomal analysis of abortion products are also performed. Mutation analysis was performed using Chromas software. Data were analyzed by SPSS software using descriptive statistics (mean and standard deviation) and inferential statistics of Student t test and p value was considered less than 5%.

Results

The mean age of the patients was 29.21 years with a standard deviation of 4.57. The minimum age of the patients was 18 years and the oldest age of the patients was 41 years (Chart 1).

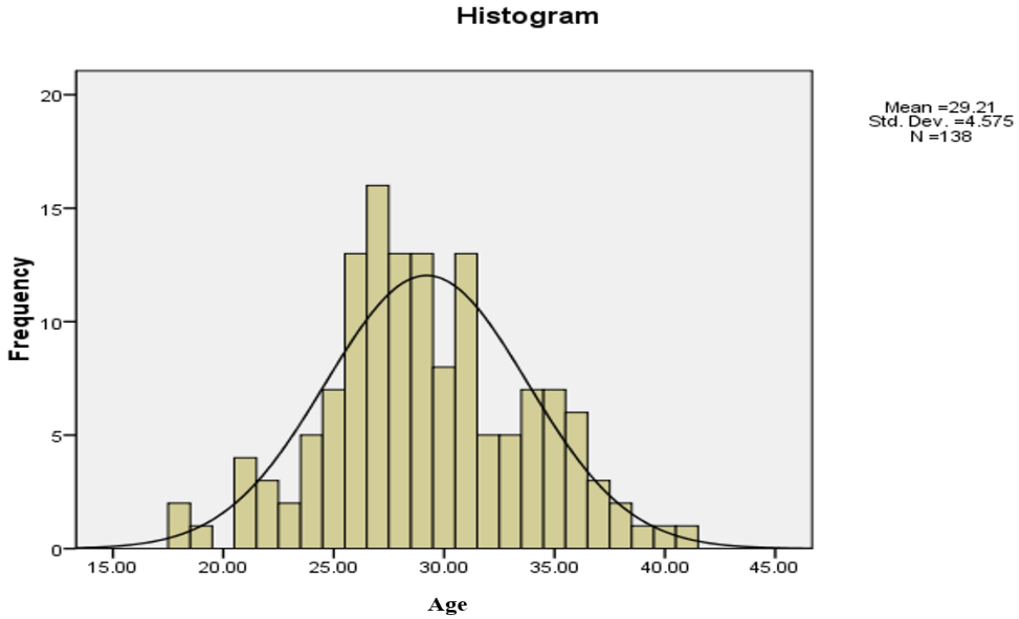

Chart 1. Age frequency of patients

The mean age of males and females is shown in (Table 1).

Table 1. Mean age of patients based on gender

gender	**N (%)**	**Mean (SD)**
male	(50%)69	(4.00) 31.78
female	(50%)69	(3.57) 26.64

After cytogenetic analysis, chromosomal rearrangements were found in 7 cases, 6 of which were female and one was male. Out of them, six had structural abnormalities and one had Turner syndrome mosaicism. Hence, out of 136 patients, chromosomal abnormalities were seen in 7 cases (5.14%) (Chart 2), in which, 6 cases (4.35%) had structural abnormalities and one case (0.72%) had Turner syndrome mosaicism.

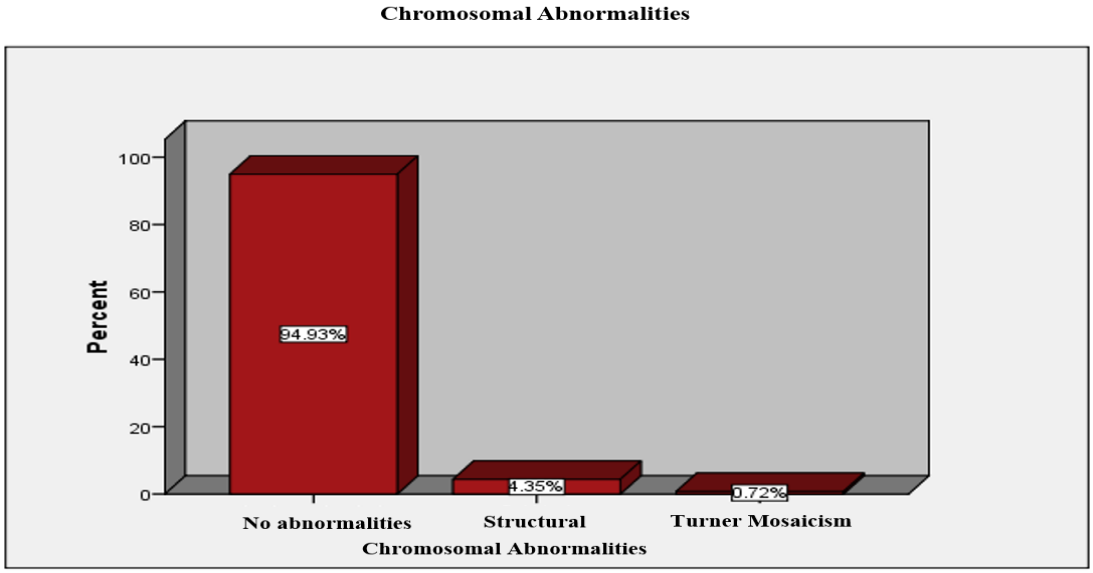

Chart 2. Frequency of chromosomal abnormalities in patients Karyotype and cytogenetic examination of 5 patients as sample are shown as follows:

The patient is 27 years of old man with translocation of chromosomes 2 and 7, as shown in (Figure 1).

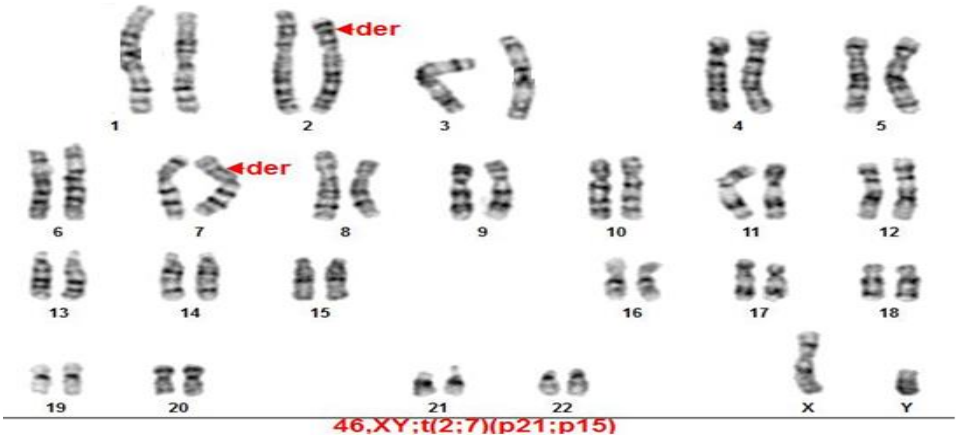

Figure 1. Translocation of chromosomes 2 and 7

The patient is 28 years of old female woman with Turner syndrome mosaicism, shown in (Figure 2).

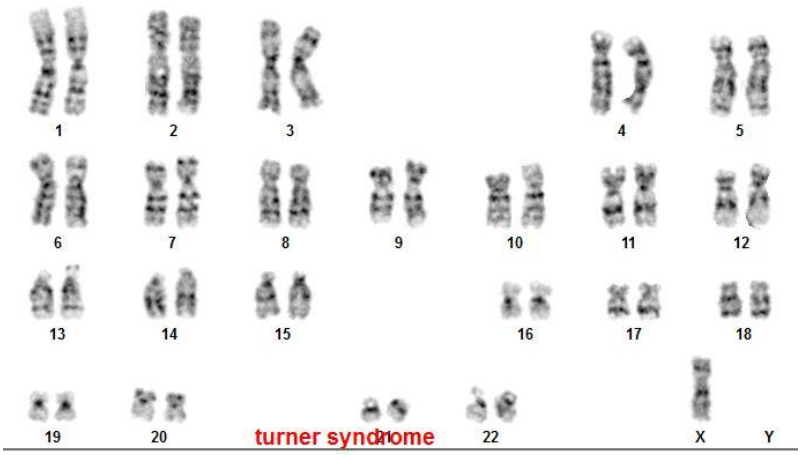

Figure 2. Turner syndrome mosaicism

The patient is 28 years of old woman with inversion of chromosome 9, as shown in (Figure 3).

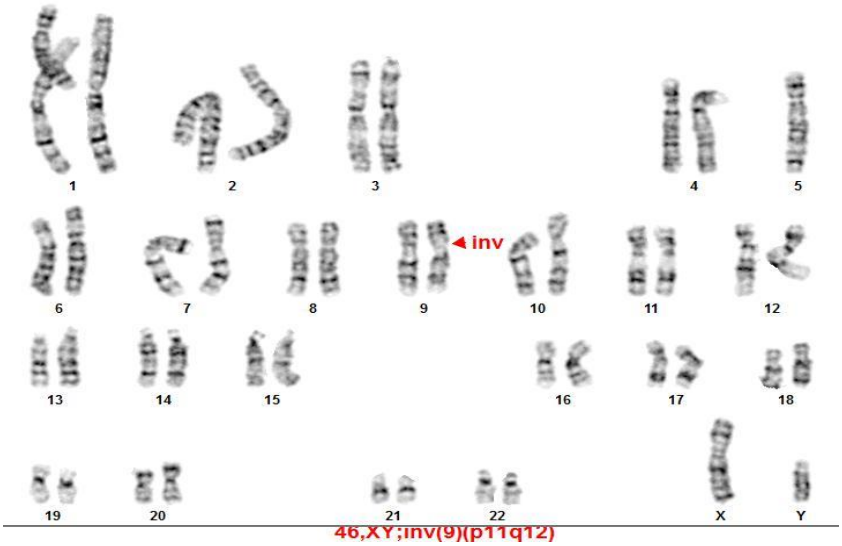

Figure 3. Inversion of chromosome 9

The patient is 25 years of old woman with translocation of chromosomes 13 and 18, as shown in (Figure 4).

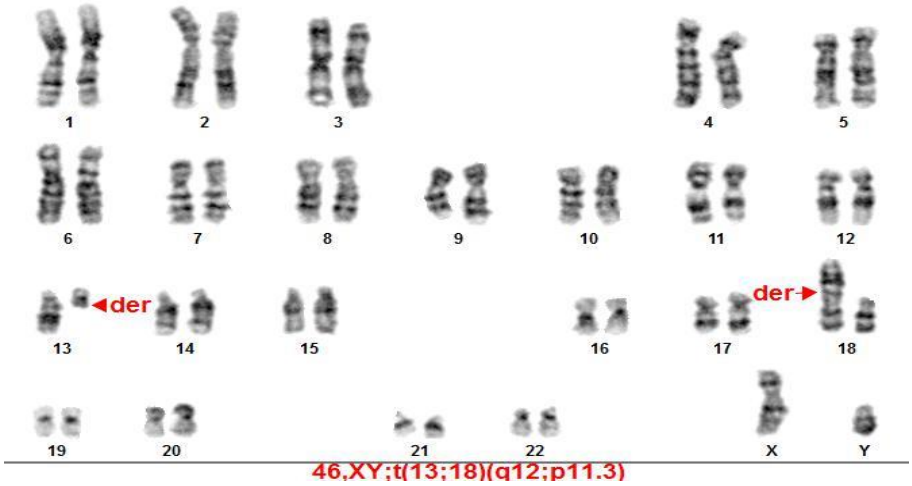

Figure 4. Translocation of chromosomes 13 and 18

The patient is 29 years of old woman with inversion of chromosome 1 is shown in (Figure 5).

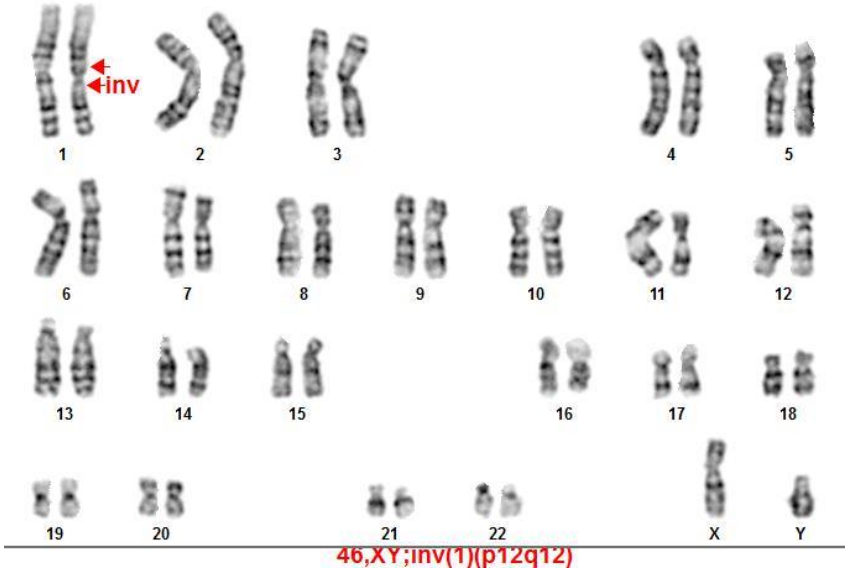

Figure 5. inversion of chromosome

Discussion

This cross-sectional study was conducted on couples with recurrent abortion in Karaj. A total of 69 couples (138 patients) were investigated. Out of 136 patients, 7 (5.14%) had chromosomal abnormalities, of which 6 (4.35%) had structural abnormalities and one (0.72%) had Turner mosaicism. Moreover, out of 7 abnormalities identified, one case (14.28%) was seen in men and 6 cases (85.72%) were seen in women. In 2016, Fan et al examined the chromosomal structural abnormalities in couples with spontaneous abortion in Jilin Province of China. The prevalence of structural chromosomal abnormalities in these couples was 2.98% (21-23), while it was 5.14% in the present study. In addition, in 2018, Pal et al examined chromosomal defects in couples with recurrent abortion in India. This retrospective study was conducted on 172 couples (344 people) with a history of three or more spontaneous abortions. Out of 172 couples, 17 couples (9.88%) had different types of structural or numerical chromosomal abnormalities (24). Its prevalence was 5.14% in the present study.

Priya et al investigated balanced chromosomal translocation in couples with recurrent abortions in India. A retrospective cytogenetic study was conducted on 152 people (76 couples) who had a history of RPL (25-27). Chromosomal abnormalities were observed in 3.2% of all RPL cases (20), confirming the results of the present study. In another study conducted in 2019, Nonaka et al analyzed the chromosomal abnormalities in patients with recurrent abortion, focusing on the prognosis of patients with chromosome inversion in Japan (28). Chromosomal karyotype was performed for 2006 couples with RPL (two or more premature pregnancy loss) with their informed consent. The prevalence of chromosome inversion in the general population was 2.6% (2006.52) and the results of this study revealed that chromosome inversion had no negative effect on subsequent pregnancy (29), which the prevalence of inversion was 1.47% and the prevalence of inversion of chromosome 9 was 0.73% in the present study. Moreover, in another study conducted by Awartani et al in 2018 to examine the cytogenetic abnormalities and outcomes of pregnancy in couples with recurrent abortion in a care center in Saudi Arabia, out of 1074 couples, 77 (7.2%) had some type of chromosomal abnormality and these abnormalities were more in females (48.33%) compared to males (37.3%) (30). Their results confirm the results of the present study, as out of 7 abnormalities identified, one case (14.28%) was seen in males and 6 cases (85.72%) were seen in females.

Conclusion

The results of the present study revealed that chromosomal abnormalities were observed in 5.14% of couples with recurrent spontaneous abortion and the prevalence of these abnormalities was higher in females. Additionally, the most common abnormalities identified in this study included translocation, inversion and mosaicism, respectively. It is recommended that in a multicenter study, besides conducting a study in chromosomal abnormalities, genes suspected to be involved in recurrent spontaneous abortions with larger sample sizes be studied and followed up the patients in terms of success in subsequent pregnancies.

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