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Evaluation of Pregnancies in 25 Families with Balanced/ Unbalanced Chromosomal Translocations

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ABSTRACT The researchers evaluated pregnancies in families with balanced/unbalanced translocations. This clinical cohort consisted of 25 pregnancies with balanced/unbalanced chromosomal translocations in family member(s) (maternal, paternal, fetal, abortion material, and/or previous fetus(es)) who underwent prenatal diagnosis. Translocations were observed in 18 cases (14 balanced and 4 unbalanced translocations). The researchers found 2 and 12 cases among the chromosomal translocations were paternal and maternal in origin, respectively. The researchers demonstrated that parent karyotypes were normal in 4 cases, while only maternal karyotypes were normal in 3 cases with unknown paternal karyotypes. Five of the prenatally diagnosed chromosomal abnormalities were Robertsonian and 13 were reciprocal translocations, Among the Robertsonian translocations, 2 were unbalanced. Early fetal loss or recurrent miscarriages were observed in previous history of 10(40%) and 6(24%) respectively. Prenatal diagnosis is critical in pregnancies with balanced/unbalanced chromosomal translocations in a member(s) of the family or those with poor gestational histories.

INTRODUCTION

Balanced and unbalanced chromosomal translocations are among the main concerns of physicians within the framework of prenatal diagnosis programs (Pourjafari et al. 2012; Page and Silver 2016). Balanced translocations are structural rearrangements of chromosomes without the gain or loss of genetic material and comprise most chromosomal translocations (Etem et al. 2010). Balanced translocation was reported to occur in 0.08 - 0.3 percent of the general population (Morin et al. 2017; Kochhar and Ghosh 2013; Joó et al. 2012). In contrast, unbalanced translocations occur with gain or loss of genetic material and are less common than balanced translocations (Joó et al. 2012). It was previously reported that the incidence of translocations in families with recurrent miscarriages is 2.69 percent (Li et al. 2017).

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Reciprocal translocation is an exchange of chromosomal segments between 2 non-homologous chromosomes (without a change in the number of total chromosomes), while Robertsonian translocation is an exchange between the long arms of two acrocentric chromosomes (chromosomes 13, 14, 15, 21, and 22), which leads to a decrease in the total chromosomal number from 46 to 45. Reciprocal translocations are observed more frequently with an incidence rate of 1/500–625 compared to Robertsonian translocations with an incidence rate of 1/900 (Joó et al. 2012).

Carriers of balanced chromosomal translocations may be normal or have minimal phenotypic variations without clinical signs and symptoms (Baptista et al. 2008). However, these carriers may suffer from infertility problems and repeated miscarriages or may have offspring that suffer from abnormal phenotypes because of the presence of unbalanced translocations (Mokanszki et al. 2012).

Chorion villus sampling, amniocentesis and cord blood sampling are the prenatal invasive tests used for the diagnosis of translocations in the fetus. Chorion villus sampling is the method of choice for the patients with a prior history of chromosomal abnormality as CVS is performed

at earlier gestational weeks and has high rates of culture success (Ekmekçi et al. 2016).

Objectives

In this study, the researchers evaluated the gestational outcomes of the recent pregnancies of 25 women who underwent prenatal diagnosis during pregnancy between 2001 and 2016, with balanced/unbalanced chromosomal translocations in their family member(s) (maternal, paternal, fetal, abortion material, and/or previous fetus(es)).

MATERIAL AND METHODS

This clinical cohort consisted of 25 women from families with balanced/unbalanced chromosomal translocations in family member(s) (maternal, paternal, fetal, abortion material, and/or previous fetus(es)) who underwent prenatal diagnosis during their recent pregnancies.

All patients (including patients referred from other institutions) were included in a special antenatal care program for prenatal diagnosis. Data were obtained from the Hacetttepe University database and perinatology registry. The hospital is a tertiary center for prenatal diagnosis. Personal information, obstetrical history, clinical data, and prenatal diagnosis results were used to evaluate patients.

The necessary consent forms were obtained at all stages of the follow-up procedures and prior to invasive interventions. Prenatally diagnosed unbalanced translocations were terminated with the approval of the families in accordance with legal regulations.

Chorionic villus sampling or amniocentesis was used for prenatal diagnosis of chromosomal abnormalities. Cytogenetic analysis was performed by the G-banding technique using cultures of peripheral lymphocytes obtained from the parents and affected siblings or cultures of cells from chorionic villi samples or cultures of amniocytes at metaphase. If necessary, high-resolution banding was applied during this technique (Howe et al. 2014).

The acquired data was used for descriptive analysis. All the statistical calculations were performed with Microsoft Excel version 2013.

This retrospective study was approved by the Hacettepe University Ethics Committee (GO 18/33).

RESULTS

Table 1 shows the balanced/unbalanced chromosomal translocations present in the family member(s) (maternal, paternal, fetal, abortion material, and/or previous fetus(es)) of women who underwent prenatal diagnosis in their recent pregnancies. Table 1 also shows the previous obstetric history, karyotype of recent pregnancies, and gestational outcomes.

In this study, the researchers showed that 2 and 12 cases among the chromosomal translocations were paternal and maternal in origin, respectively. Additionally, the researchers demonstrated that both paternal and maternal karyotypes were normal in 4 cases, while only maternal karyotypes were normal in 3 cases with unknown paternal karyotypes. In this study, some data was incomplete because some patients were referred from other institutions as well as refusal of karyotyping by the parents.

The researchers found 1 anencephalic fetus, 1 fetus with hypomyelinization, and 1 Robertsonian type Down's syndrome in previous pregnancies of 3 cases. The researchers identified early fetal losses in 10 (40%) cases, 6 (24%) of which were recurrent miscarriages. Table 1 shows the karyotyping results of these cases. Seven prenatal diagnosis results (n = 25) were found to be normal, while various types of balanced and unbalanced translocations were observed in 18 cases (72%) (14 balanced and 4 unbalanced translocations). Five prenatally diagnosed chromosomal abnormalities were Robertsonian translocations, while 13 were reciprocal translocations. Among the Robertsonian translocations, 2 were unbalanced.

Gestational outcomes of the cases are summarized in Table 1. One pregnancy was terminated because of an unbalanced translocation in the fetus. Five and two pregnancies resulted in abortion and intrauterine exitus, respectively. Eight of the remaining 17 patients delivered their offspring at the hospital without any obstetrical complications. Two delivered fetuses had structural abnormalities (one with cleft lip-palate and one with multiple anomalies). Nine of the 25 patients underwent subsequent antenatal follow-up at different institutions and their gestational outcomes were excluded from the researchers' evaluation because of a lack of sufficient data.

Table 1: Prenatal diagnosis and pregnancy outcome of patients

Case	*Origin*	*Prior history*	*Karyotype of fetus*	*Gestational outcome*
I	Maternal		46,XX,t(4;13)(q21;q13) mat (Figure 1)	
II			46,XY,der (10)t(3;10)(p26.3;q25.2)	Termination
III	Maternal		46,XX,t(8;15)(q33.2;q25)	Intrauterin exitus
IV	Maternal	First child diagnosed with Down syndrome	46,XY, rob(14;21)(q10;q10)+21 (Figure 2)	
V	Maternal and paternal karyotype normal	Previous pregnancy with reciprocal translocation	46,XX,t(1;6)(p32;p23) (Figure 3)	
VI	Maternal and paternal karyotype normal	Previous abortus with reciprocal ranslocation (46,XX, t(9;13)(q32;q32)	Normal karyotype	
VII	Paternal	Abortus without karyotype analysis	46,XX, t(6;20)(p21.1;q13.1)	
VIII	Maternal and paternal karyotype normal	Recurrent Pregnancy Loss	46,XX,t(1;6)(q25;p21)mosaicism	Intrauterin exitus
IX	Maternal	Recurrent pregnancy loss, previous pregnancy with translocation 46,XY, t(1;17)(p34.12;p13)	Normal karyotype	Delivery
X	Maternal	Previous pregnancy with translocation 46,XX, t(3;10)(p26.3;p25.2)	Normal karyotype	Delivery
XI	Maternal karyotype normal	Recurrent pregnancy loss	46,XX,t(3;8)	Abortus
XII	Maternal	Fetus with anencephaly	46,XX,rob(13;14)(q10;q10)+14 (Figure 4)	Abortus
XIII			45,XX,rob(21;14)(q10;q10)	
XIV	Maternal karyotype normal		46,XX,t(13;18)(q22;q23)	Abortus
XV	Maternal	Recurrent pregnancy lossprevious abortus with reciprocal translocation 46,XX, t(5;10)(p12;q12)	46,XX,t(5;10)(p12;q12)	Delivery cleft lip/ palate
			46,XX,t(4;9)(q13;q34) (Figure 5)	Abortus
XVI	Maternal karyotype normal			
XVII	Maternal	Previous abortus with reciprocal translocation 46,XX, t(14;20)(q10;q10)	Normal karyotype	Delivery
XVIII	Paternal (45XY, rob (21;22)(q10;q10)		Normal karyotype	Delivery
XIX	Maternal		45,XX,rob(13;14)(q10;q10)	
XX	Maternal	Recurrent pregnancy loss	46,XX,t(10;20)(p12;p11.2)	
XXI			45,XX,rob(13;14)(q10;q10)	
XXII	Maternal and paternal karyotype normal	Previous child with46,XX,inv(3) (p11;p26) t(5,9)(q33,q31)	Normal karyotype	Delivery
XXIII		Previous child with hypomyelinization syndrome with 46,XX,t(5;7) previous abortus	Normal karyotype	Delivery
XXIV	Maternal		46,XX,der(18) t(4;18)(p14;p11.2)	Delivery multiple anomalies
XXV	Maternal	Recurrent pregnancy loss	46,XX,t(5;6)(q35;q23)	Abortus

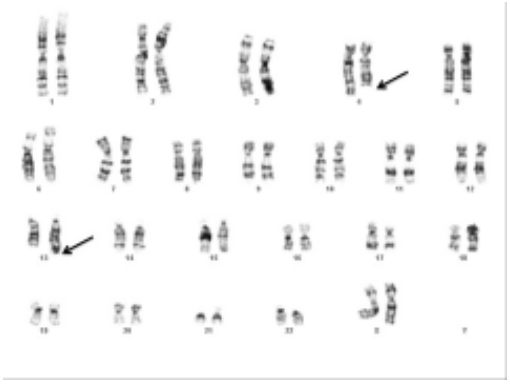

Fig. 1. Metaphase figure of patient I, 46,XX,t(4;13) (q21;q13)

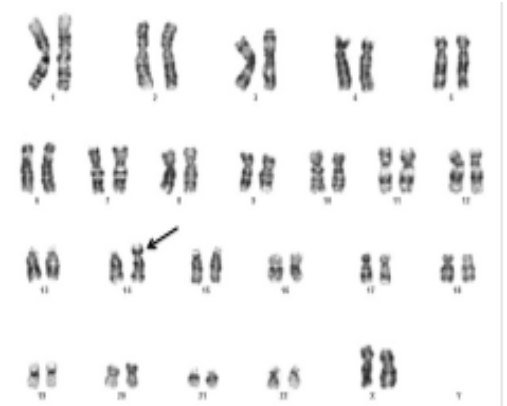

Fig. 2. Metaphase figure of fetus IV, 46,XY, rob(14;21) (q10;q10)+21

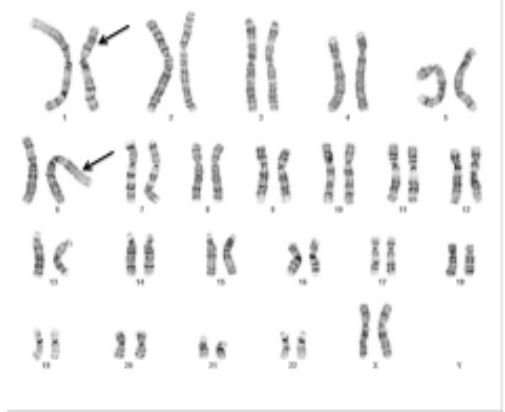

Fig. 3. Metaphase figure of fetus V, 46,XX,t(1;6) (p32;p23)

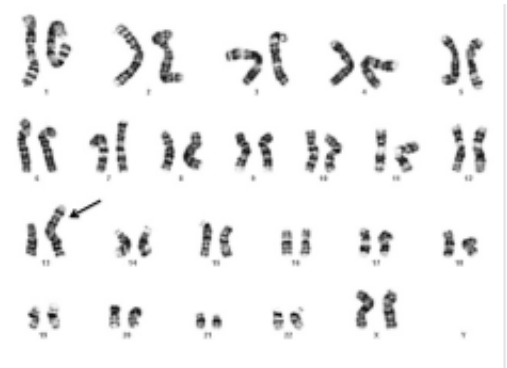

Fig. 4. Metaphase figure of fetus XII, 46,XX,rob (13;14)(q10;q10)+14

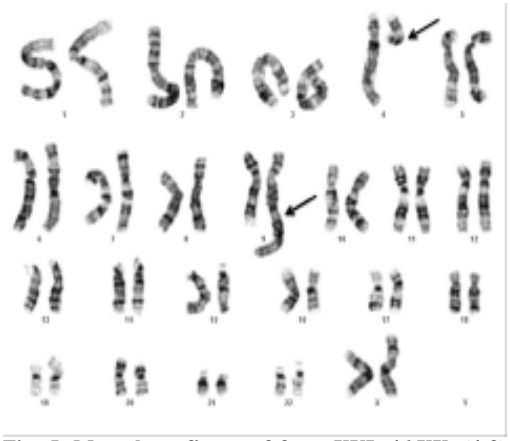

Fig. 5. Metaphase figure of fetus XVI, 46,XX,t(4;9) (q13;q34

DISCUSSION

In the present study, the researchers determined the gestational outcomes of families with known balanced translocations. The researchers demonstrated and confirmed that balanced translocations are more frequent compared to unbalanced translocations, as reported previously (Joó et al. 2012).

A balanced translocation may lead to subfertility and adverse pregnancy outcomes (Mokanszki et al. 2012). Balanced chromosomal translocations have been detected in 0.6 and 9.2 percent of infertile couples and couples with recurrent miscarriages, respectively (Vozdova et al. 2012). Individuals carrying balanced reciprocal translocations are known to have a high risk of being infertile and high risk of conceiving chro-

mosomally abnormal embryos that result in recurrent spontaneous abortions or offspring with congenital anomalies (Mokanszki et al. 2012). The incidence of miscarriages due to balanced translocations was reported to be 1.5 percent (Joó et al. 2012).

Patients carrying balanced reciprocal translocations are prone to meiotic nondisjunction. Therefore, misalignment in metaphase and mispairing of translocated chromosomes during the first meiotic division lead to various forms of chromosomal segregation, creating an unbalanced karyotype that may result in monosomy or trisomy of translocated chromosomes (Pourjafari et al. 2012). Although there is a high risk of conceiving a fetus with aneuploidy, successful gestational outcomes are higher than anticipated (Page and Silver 2016; Joó et al. 2012).

Generally, meiotic segregation between chromosomes with translocation occurs through 2 modes: (i) alternate segregation that produces fetuses with normal karyotypes or balanced translocations similar to their parents or (ii) adjacent 1 segregation that leads to fetuses with unbalanced translocation. Adjacent 2 segregation, 3:1 segregation, and 4:0 segregation are also observed, but are uncommon (Scriven et al. 1998). The co-occurrence of translocations and inversions is commonly referred to as complex rearrangements, which have rarely been reported in the literature (Gribble et al. 2005; Pellestor et al. 2011). Despite this rarity, one of the researchers' cases had an inversion and reciprocal translocation.

The recurrence risk of translocations depends on an imbalance of genetic material, type of translocation, and precise breakpoints of chromosomes involved in translocation (Ozawa et al. 2008). Moreover, conventional cytogenetic analysis cannot detect abnormalities shorter than 5-10 Mb. New technologies such as microarray platforms have advantages such as higher resolution and detection rate compared to conventional chromosomal studies. However, any genomic imbalance is unlikely present in phenotypically normal carriers of apparently balanced translocations (Baptista et al. 2008; Dhillon et al. 2014).

Balanced translocations may be inherited or occur *de novo* with incidence rates of seventy percent and thirty percent, respectively (Joó et al. 2012; Vasilevska et al. 2013). *De novo* translocations are known to occur with a frequency of 1/2000 in the general population (Weckselblatt et al. 2015). Presumed *de novo* translocations may be explained by 2 different hypotheses. First, recurrent balanced translocations may arise from non-allelic homologous recombination between paralogous low-copy repeats or palindromic AT-rich repeats on the chromosomes. Nonrecurrent *de novo* balanced translocations mostly occur because of error-prone non-homologous end joining mechanisms or micro-homology-mediated repair after the formation of random double-strand breaks (Kurahashi et al. 2010; Thomas et al. 2010; Ou et al. 2011; Robberecht et al. 2013). *De novo* unbalanced translocation formation occurs because of non-allelic homologous recombination between retrotransposons, predominantly long interspersed elements (Robberecht et al. 2013; Weckselblatt and Rudd 2015). Second, gonadal mosaicism may explain fetal cases with translocations in parents with normal karyotypes. However, gonadal mosaicism of translocations has rarely been reported, and further studies are needed to clarify these points (Kovaleva and Cotter 2016).

Although it is widely accepted that maternal age is associated with the risk of nondisjunction, male gametogenesis and paternal age are also associated with the formation of balanced translocations. Various studies demonstrated that familial cases generally have a maternal origin, while *de novo* translocations occur by paternal transmission (Pellestor et al. 2011; Thomas et al. 2010). The association between paternal age and non-recurrent translocations suggest that translocation occurs during pre-meiotic mitosis or post-meiotic processes such as a double-strand breaks repaired by non-homologous end-joining (Thomas et al. 2010). However, in this study, paternal age was not considered because of the database structure.

Previous studies showed that paternal transmission of a reciprocal translocation results in spontaneous abortion or live birth with incidence rates of seventy-five percent and 4.9 percent, respectively (Kohn et al. 2015). In the researchers' study, among the 2 individuals carrying fetuses with paternal translocations, one had an abortion during a previous pregnancy and unknown outcome for the recent pregnancy, while the other had a healthy term delivery.

Among the chromosomes involved in the translocations, the most common Robertsonian

translocation occurred between chromosomes 13 and 14 (Chang et al. 2013). In the researchers' study, 3 of 5 Robertsonian translocations occurred between chromosomes 13 and 14, which is consistent with the results of previous studies.

However, despite the known relationship between parental carriers of structural chromosomal rearrangements and the history of recurrent loss of pregnancy, the probability of natural spontaneous pregnancies at a later time remains feasible.

Assisted reproductive technologies can be used to produce healthy offspring in couples with recurrent miscarriages because of balanced translocations (Keymolen et al. 2009). However, these techniques are associated with risks of congenital malformations (Balci et al. 2008). In contrast, natural conception can be considered for carriers of balanced chromosomal translocations after detailed and well-informed genetic counseling (Zhang et al. 2015; Page and Silver 2016). Furthermore, prenatal diagnosis is an option for detecting probable genetic problems in the presence of prior obstetric history related to translocations.

Prenatal invasive techniques may be safely used for the detection of chrosomal abnormalities, as risk for miscarriages for CVS and amniocentesis were found to be 0.81 and 2.18 percent, respectively (Akolekar et al. 2015). On the other hand, miscarriage risks for reciprocal and Robertsonian translocations were reported to be as high as fifty percent (Neri et al. 1983).

Retrospective design and relatively low number of the cases is the limitations of this study. On the other hand, detailed literature review and existence of various types of translocations in the researchers' cohort is the strength of their study.

CONCLUSION

Prenatal diagnosis is critical in pregnancies with balanced/unbalanced chromosomal translocations in member(s) of the family (maternal, paternal, fetal, abortion material and/or previous fetus(es)) or in those with poor gestational histories.

RECOMMENDATIONS

According to the researchers' experiences and literature findings, they may conclude that chorion villus sampling may be safely used for the diagnosis of chromosomal translocations at the patients with a prior history of a fetus with chromosomal translocation.

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