

Chromosomal Analysis of Couples with Bad Obstetric History

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Abstract

Chromosome Abnormalities (CAs) are one of the most important reason of reproductive diseases. The aim of this study was to exhibited the frequency and nature of CAs which is associated with the Bad Obstetric History (BOH) in the south of Turkey. This study was carried out in a total of 895 individuals including 360 couples and 175 single women having BOH and with various incomes were investigated for CAs using blood culture and chromosomal banding technique. A total of 895 individuals with BOH were analyzed, cytogenetically. The chromosomal abnormality was found in 4.4% of the sample studied. The 3.7% of these CAs was structural aberrations, and also numerical CAs was 0.7%. Although in one couple it was the wife and husband who had an abnormal karyotype. Specifically, inversions were the most common karyotypes (1.6%) among the all cases. For example, inversion chromosome 9 was seen among structural anomalies (1.2%). In 6 cases (0.7%), translocations were demonstrated. The others structural CAs (1.5%) were determined with i(9q), fra(Xq28), fra(20%), small(Y), Yqh+ and several CAs variations. Aproximately, 0.7% of individuals with BOH have the numerical CAs and aneuploidies.

It was found out that abnormal karyotypes were present in 4.4% of patients with BOH, and associated to female and bad obstetric history. Also, our findings confirm that the structural CAs, such as translocations and inversions were associated with a higher risk of BOH. Therefore, in couples with BOH, chromosomal evaluation can have a diagnostic value.

Keywords: Bad obstetric history; Karyotype; Chromosomal abnormalities

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Introduction

Pregnancy termination, recurrent abortion, live births with congenital malformations and still born are one of the common complications during pregnancy and in patients with a BOH. Among reproductive failures causes, CAs are encountered quite frequently, and are common in couples with reproductive disorders including recurrent abortions [1]. CAs are responsible for at least half of spontaneous abortions or miscarriages and are an important cause of congenital malformations [2-4]. Karyotyping of the couples should be done when there is a history of three consecutive early pregnancy losses or if there has been a history of an abnormal fetus or infant in addition to abortion [5]. A report suggested the importance of cytogenetic analysis in phenotypically normal parents with a pervious bad obstetric history [6]. It is estimated that 50-60% of all first trimester pregnancy losses harbor a CA, which leads to abnormal

development of the pregnancy. The purpose of the present study was to evaluate the cytogenetic profile associated with reproductive failure.

Materials and Methods

A prospective study from 1992 to 2009 was carried out in a total of 895 individuals including 360 couples and 175 single women having BOH (history of unexplained stillbirth/neonatal death, three or more consecutive abortions etc). The study included 360 couples and 175 single women referred to the outpatient clinic of the Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University. This study was approved by the Ethics Committee of Medical Faculty, Çukurova University. The initial diagnosis of BOH as made by Department of Obstetrics and Gynecology, Faculty of Medicine, Çukurova University, based on the available clinical details. The age of the analyzed

population ranged between 19 and 50 years and the average age was 34.6 years. The cytogenetic analyses were performed in the Cytogenetics Laboratory, at the Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University. Metaphase chromosome preparations from peripheral blood were made according to the standard cytogenetic protocols. Fifty metaphases were analyzed in all the patients, but in cases of abnormalities and mosaicism the study was extended up to 100 metaphases. All CAs were reported according to the current international standard nomenclature (ISCN, 2009).

Results

As showed in **Table 1**, a total of 895 individuals with BOH were analyzed, cytogenetically. Karyotype results were divided into two categories: Structural and numerical CAs. One couple (two individuals) and 37 single women or men were studied cytogenetically for detection of abnormal karyotypes in patients with a BOH. The karyotype results were normal in 856 (95.6%) of 895 individuals. However, CAs was detected in 4.4% (39 individuals) of all individuals (21 males, 18 females).

The 3.7% of these CAs was structural aberrations (inversion, translocation, isochromosome, and the others structural CAs), and also numerical CAs were 0.7%. Although in one couple it was the wife and husband who had an abnormal karyotype [46,XX/45,XX,-18(15%) and 46,XY,i(9q)]. Specifically, inversions were the most common karyotypes (1.6%, 14 cases) among the all cases. For example, inversion chromosome 9 [inv(9)] was most common karyotype seen among structural anomalies (1.2% of all individuals). The other inversions were determined with breakage around regions 7p11, 7q22, 7p22, 11p11 and 11p15. In 6 cases (0.7%), translocations were demonstrated; t(3,13)(q23;q32); t(4;9)(q14;q34); t(7q); robt(13;14); t(12;16)(q24;q24) and t(1;9)(p34.2;q34.3). The others structural CAs (1.5%) were determined with i(9q), fra(Xq28); fra(20%); small(Y); Yqh+ and several chromosomal aberrations variations. Approximately, 0.7% of individuals with BOH have the numerical CAs; 46,XX/47,XXX(20%); 46,XX/45,XX,-18(15%) and aneuploidies.

Discussion

Constitutional aberrant karyotypes can account for the terms recurrent miscarriage/habitual abortion/recurrent spontaneous

Table 1 Frequencies and distributions of the karyotypes in patients with bad obstetric history.

Cytogenetic category	Karyotypes	No. of cases	Frequency in all cases (%)
Normal	46,XX or 46,XY	856	95.6
Abnormal	Structural and numerical chromosome abnormalities	39	4.4
Structural chromosome abnormalities	Total	895	-
	Abnormal	-	-
Translocations	46,XX,t(3,13)(q23;q32)	1	-
	46,XX,t(4;9)(q14;q34)	1	-
	46,XY,t(7q)	1	-
	45,XX,robt(13;14)	1	-
	46,XX,t(12;16)(q24;q24)	1	-
	46,XY,t(1;9)(p34.2;q34.3)	1	0.7
	Total	6	0.7
Inversions	46, XX,inv(7)(p11;q22)	1	-
	46,XY/46, XY,inv(7p22;q22)	1	-
	46,XX,inv(9)(p11;q13)	6	-
	46,XY,inv(9)(p12;q13)	2	-
	46,XX,inv(9)(p11;q12)	3	-
	46,XY,inv(11)(p11;p15)	1	1.6
The others structural chromosome abnormalities	46,XY,i(9q)	1	-
	46,XX, fra(Xq28)	1	-
	46,XY, fra(20%)	1	-
	46,XY, small(Y)	4	-
	46,XY, Yqh+	3	-
	46,XX or 46,XY, chromosomal aberrations	3	-
Total	33	3.7	
Numerical chromosome abnormalities	46,XX/47,XXX (20%)	1	-
	46,XX/45,XX,-18(15%)	1	-
	46,XX or 46,XY,aneuploidies	4	-
Total	6	0.7	
General total	39	-	

abortion/recurrent or repetitive pregnancy loss, reproductive failure and infertility. CAs are responsible for at least half of spontaneous abortions or miscarriages and are an important cause of congenital malformations [2-4]. Many other studies reported different frequencies varying between 0 and 17% [7-12]. In the present study, an incidence of 4.4% for chromosomal abnormality among patients with a bad obstetric history was found out. In our earlier study, major CAs in couples with pregnancy losses and recurrent miscarriages were seen in 4.9% [13]. This also shows that there is have a correlation between BOH and structural variations (inversions and translocations).

Structural CAs were found in 3.7% of couples, where inversions were the most commonly observed structural CA (1.6%), and out of 14, the 13 cases were pericentric inversions, the only one case was paracentric inversion. The pericentric inversion of chromosome 9 was most common karyotype seen among structural anomalies, and was found in 1.2% of couples in the present study. The inv(9) is commonly seen in normal humans and the frequency estimated to be 1 to 3% in general population [13-16]. However, in a study, it was indicated the high frequency of inv(9)(p11;q11) in one of the couples with recurrent miscarriages [17]. The risk is highly dependent on the type of inversion, and the size of the inverted segment. Previous studies on reproductive disorders reported inversions in different chromosomes [18-20]. In the present study and pericentric and paracentric inversions involving different chromosomes except the chromosome 9 were found in 0.4% of couples such as inv(7)(p11;q22); inv(7)(p22;q22) and inv(11)(p11;p15), and the variants were mostly involved with chromosome 7. Especially, inv(9)s are most important aberrational category found in couples with BOH. This inversion seems to be of importance in causing CAs, as stated by some investigators, and which is usually considered as a important, its clinical consequences remain unclear [13-20]. Pericentric inversions involving a large chromosomal segment occur with an increased incidence in the recurrent miscarriage populations [20-22]. We think this is important, because in a report it's been speculated that the outcomes of different inversions are more harmful than that of the inversion chromosome 9.

In the present study, XX/XX,-18 mosaicism and i(9q) have been found in a couple who was ascertained because of repeated spontaneous abortions. The husband has the isochromosome for the long arm of chromosome 9, and wife has mosaicism of chromosome 18. Cytogenetic analysis demonstrated maternal uniparental isodisomy for the whole chromosome 9. Trisomy 9p is one of the most frequent autosomal anomalies compatible with long survival rate, after trisomies 21, 13 and 18. The spectrum of clinical severity in trisomy 9 roughly correlates with the extent of trisomic chromosome material. Trisomy 9p is a clinically well delineated syndrome and of all stigmata craniofacial dysmorphism is most specific. Clinically it is characterized by psychomotor retardation, malformations that can affect various organs and sometimes epilepsy. This isochromosome and monosomy 18 mosaicism seem to be of importance in causing BOH.

The cytogenetic studies in couples with repeated pregnancy losses has showed that the structural CA such as translocations both reciprocal and Robertsonian and inversions were associated with a higher risk of pregnancy wastage [23]. In the present study, translocations were also associated with a risk of pregnancy (0.7%). Previous studies on couples with defective reproductive success reported prevalence ranging from 2.4 to 13.1% in which one of the partners was the carrier for a balanced chromosomal rearrangement in contrast to an incidence of less than 0.55% in the general population [23-28]. According to these results, our translocations ratios are compatible with ratios in the literature. In literature, there have been reports of reciprocal translocation carriers with varying combination of the involved chromosomes, resulting in RM and reproductive failure. The frequency of balanced chromosomal translocations in the general population is 0.3% [29]. The incidence of chromosome unbalanced is at least 50%, balanced rearrangements appear in 3-6% of couples with recurrent miscarriages [30,31]. Carriers of balanced complex translocation have a high risk of having spontaneous abortions or children with an unbalanced karyotype. As carriers of balanced and Robertsonian translocations, parents might be phenotypically normal, however in their meiosis, unequal crossing over of chromosomes can result in unbalanced karyotype in producing gametes.

In the present study, numerical CAs were less frequent than structural CAs (0.7% and 3.7% of cases respectively), aneuploidies were the most common, and found in four cases. Numerical aberrations include aneuploidies of various chromosomes. Numerical aberration ratios in couples with recurrent spontaneous abortion were reported as being 29%, 5.3% of all aberrations, in some other studies, which are not in accordance with ratio we found [32,33]. It's been reported that the numerical CAs were less frequent among couples with RMs, but it is clear that various studies reported various results. But always in all studies, unidentified additional chromosomes, namely marker chromosomes and sex chromosome aneuploidies constitutes important portion of numerical aberrations, which is partly true for our study as well. Mosaics with 46,XX/47,XXX karyotype is the observed sex CA in a female [34-35]. If sex chromosome mosaicism is a predictor of early menopause, the observation that aneuploidy is associated with early menopause could explain increased losses in these women [36].

Conclusion

In the present study, we conclude that CAs are the underlying bases of reproductive failure, the translocations and inversions and the clinical conditions were associated to female and BOH. Chromosomal analysis is strongly recommended in evaluating couples with more than three abortions or the unexplained stillbirths/neonatal deaths and concerned physicians should seriously consider CAs as one cause of BOH. It is a great necessity doing cytogenetic analysis in couples with history of BOH. Therefore, cytogenetic examination of both males and females may be helpful in predicting recurrence as well as form.

References

- 1 Fryns JP, Van Buggenhout G (1998) Structural chromosome rearrangements in couples with recurrent fetal wastage. *Eur J Obstet Gynecol Reprod Biol* 81: 171-176.
- 2 Rimoni DL, Connor JM, Pyeritz RE, Korf BR (2002) Principles and Medical Genetics (6th edn.) Edinburgh, Churchill Livingstone.
- 3 Bhasin MK (2005) Human population cytogenetics: A review. *Int J Hum Genet* 5: 83-152.
- 4 Korteweg FJ, Bouman K, Erwich JJHM (2008) Cytogenetic analysis after evaluation of 750 fetal deaths. Proposal for diagnostic work-up. *Obstet Gynecol* 111: 856.
- 5 Arjun G (1996) Recurrent early pregnancy loss. *IJC P'S MedicineMS Pacre* No. 4.
- 6 Panicker H, Tarnekar AM, Anbalagan J, Ghosh SK, Fulzele RR, et al. (2004) A newborn proband with der(15) and maternal karyotype 46,XX,der(15)t(9;15) with a bad obstetric histor. *J Anat Soc India* 53: 55-57.
- 7 Lyberatu-Moraitu E, Grigori-kostaraki P, Retzpopulou Z, Kosmaidou-Aravidou Z (1983) Cytogenetics of recurrent abortion. *Clin Genet* 23: 294-297.
- 8 Mameli M, Cardia S, Millia A, Aste A, Santucci S, et al. (2006) Cytogenetic study in 50 couples with recurrent abortion. *Gynecol Obstet Invest* 17: 84-88.
- 9 Malekasgar AM, Motlagh ME, Tabar MH, Ghafari MA (2006) Chromosomal Analysis Of Couples With Bad Obstetric History. *Iranian Journal of Pathology* 1: 91-98
- 10 Purandare H, Fernandes NV, Deshmukh SV, Chavan S (2011) Heterochromatic Variations and Pregnancy Losses in Humans. *Int J Hum Genet* 11: 167-175.
- 11 Tunç E, Demirhan O, Demir C, Tastemir D (2007) Cytogenetic study of recurrent miscarriages and their parents. *Genetika* 43: 545-552.
- 12 Sheth F, Pani J, Desai M, Sheth J (2011) Single Cell Abnormality in Couples with Bad Obstetric History and Repeated Fetal Loss: Occurrence and Clinical Outcome. *Int J Hum Genet* 11: 259-263.
- 13 Ko TM, Hsieh FJ, Chang LS, Pan MF, Lee TY (1992) Pericentric inversions of chromosome 9 in Taiwanese fetuses. *J Forms Med Assoc* 91: 473-474.
- 14 Teo SH, Tarn M, Knight L, Nag I (1995) Pericentric inversion 9-incidence and clinical significance. *Ann Acad Med Singapore* 24: 302-304.
- 15 Thomas IM (1999) Cytogenetic basis of recurrent abortions. *Perinatology* 1: 181-187.
- 16 Demirhan O, Pazarbasi A, Suleymanova-Karahan D, Tanriverdi N, Kilinc Y (2008) Correlation of clinical phenotype with a pericentric inversion of chromosome 9 and genetic counseling. *Saudi Med J* 29: 946-951.
- 17 Tho SP, Byrd JR, McDonough PG (1982) Chromosome polymorphism in 110 couples with reproductive failure and subsequent pregnancy outcome. *Fertil Steril* 38: 688-694.
- 18 Peschka B, Leygraaf J, van der Ven K (1999) Type and frequency of chromosome aberrations in 781 couples undergoing intracytoplasmic sperm injection. *Hum Reprod* 14: 2257-263.
- 19 Al Hussain M, Al-Nuaim L, Abu Talib Z, Zaki OK (2000) Cytogenetic study in cases with recurrent abortion in Saudi Arabia. *Annals of Saudi Medicine* 20: 233-236.
- 20 Tavokina LV, Baronova EV, Sopko NI (2007) The most frequent chromosomal abnormalities in karyotypes of patients with reproductive disorders. *Cytology and Genetics* 41: 237-242.
- 21 Amiel A, Sardos-Albertini F, Fejgin MD (2001) Interchromosomal effect leading to an increase aneuploidy in sperm nuclei in a man heterozygous for pericentric inversion and C-heterochromatin. *J Med Genet* 46: 245-250.
- 22 Petit P, Fryns JP (1983) Two pericentric inversions inv(7)(p15;q32) and inv(9)(p11;q13) in a male with absence of vas deferens. *Hum Genet* 64: 303.
- 23 De Braekeleer M, Dao TN (1990) Cytogenetic studies in couples experiencing repeated pregnancy losses. *Hum Reprod* 5: 519-528.
- 24 Makino T, Tabuchi T, Nakada K, Iwasaki K, Tamura S, et al. (1990) Chromosomal analysis in Japanese couples with repeated spontaneous abortions. *Int J Fertil* 35: 266-70.
- 25 Maione S, Lamberti L, Alovise C, Armellino F (1995) Retrospective study of couples with a history of recurrent spontaneous abortion. *Acta Eur Fertil* 26: 95-100.
- 26 Coulam CB (1991) Epidemiology of recurrent spontaneous abortion. *Am J Reprod Immunol* 26: 23-27.
- 27 Rajangam S, Tilak P, Aruna N, Devi R (2007) Karyotyping and counseling in bad obstetric history and infertility. *Iranian J Reprod Med* 5: 7-12.
- 28 Nagaishi M, Yamamoto T, Linuma K (2004) Chromosome abnormalities identified in 347 spontaneous abortions collected in Japan. *J Obstet Gynaecol Res* 30: 237-241.
- 29 Jacobs PA, Frankiewicz A, Law P (1972) Incidence in mutation rates of structural rearrangements of the autosomes in man. *Ann Hum Genet* 35: 301-319.
- 30 Del Porto G, D'Alessandro E, Grommatico P, Coghi IM, DeSanctis S, et al. (1993) Chromosome heteromorphisms and early recurrent abortions. *Hum Reprod* 8: 755-758.
- 31 James DK, Ster PJ, Weiner CP, Gonik B (1999) High Risk Pregnancy. *Harcourt Brace* pp: 95-103.
- 32 Dubey S, Chowdhury MR, Prahlad B, Kumar V, Mathur R, et al. (2005) Cytogenetic causes for recurrent spontaneous abortions-an experience of 742 couples (1484 cases). *Indian J Hum Genet* 11: 94-98.
- 33 Iyer P, Wani L, Joshi S, Lakshmi J, Dalvi R, et al. (2007) Cytogenetic investigations in couples with repeated miscarriages and malformed children report of a novel insertion. *Reprod Biomed Online* 14: 314-321.
- 34 Goud TM, Harassi SMA, Salmani KKA, Busaidy SMA, Rajab A (2009) Cytogenetic studies in couples with recurrent miscarriage in the Sultanate of Oman. *Reprod Biomed Online* 18: 424-429.
- 35 Saxena SG, Desai K, Shewale L, Ranjan P, Saranath D (2012) Chromosomal aberrations in 2000 couples of Indian ethnicity with reproductive failure. *Reprod Biomed Online* 25: 209-218.
- 36 Kline J, Kinney A, Levin B, Warburton D (2000) Trisomic pregnancy and earlier age at menopause. *Am J Hum Genet* 67: 395-404.