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Estimating the Risk for Chromosomal Abnormalities and Heteromorphic Variants in Azoospermic and Severe Oligozoospermic Men

Zakiye Nadeali[1], Peyman Salehi[2], Marzieh Derakhshan-Horeh[3], Erfan Sadeghi[4,5], Amin Izaditabar[1], Mansoor Salehi[1,6], Mahdi Zamani[7], Majid Hosseinzadeh[1,7*]

Abstract

Objectives: A reasonable number of male infertility cases are related to genetic factors. Considering the high prevalence of chromosomal abnormalities related to male infertility, this study investigated the association of the chromosomal aberrations and chromosome variants with hormonal levels, a positive family history, parental consanguinity and a specific lifestyle. We also aimed to find a predictive factor to estimate the risk of the presence of an abnormal karyotype in the azoospermic and especially sever oligozoospermic men.

Materials and Methods: A total of 230 infertile men and 50 healthy controls enrolled in the study for cytogenetic evaluation. Data on patients' characteristics were gathered, accurately.

Results: Among aforementioned factors, only luteinizing hormone (LH) >12 IU/l raised the chance of detecting a chromosomal abnormality ($P<0.05$). The results also showed a higher level of follicle stimulating hormone (FSH) and parental consanguinity and a positive family history of infertility in infertile men compared with the control group ($P<0.05$). The incidence of chromosome abnormalities and chromosomal variants were 15.2% and 10.9%, respectively. The investigated variables revealed no association with the prevalence of chromosome heteromorphic variants.

Conclusiond: This study suggests a positive family history of infertility, parental consanguineous marriages and high levels of FSH as strong determinants or risk factors for male infertility. Nonetheless, the presence of these patient characteristics did not prove to have a direct correlation with chromosomal abnormalities in male infertility. Among the various possible risk factors studied, an elevated gonadotropin level provides a better risk assessment for the incidence of chromosomal abnormality in infertile men.

Keywords: Male infertility, Chromosomal abnormalities, Heteromorphic variants, Parental consanguinity, Family history

Introduction

Approximately 15% to 20% of couples are infertile and suffer from inability to conceive after at least 1 year of frequent unprotected intercourse. In almost 50% of the couples with infertility, the causes are male-related (1-3). Male infertility is a multifactorial disorder in which the contribution of genetic abnormalities has been estimated to be 50% (4,5).

Different factors including biological, clinical, environmental and other factors are known for their contribution to the severity of infertility, their role in worsening the effects of pre-existing genetic or medical factors and hence their effect on gamete and embryo development and reduced sperm quality leading to infertility (6-9). To date, sperm parameters are the most frequently investigated factor associated with the prevalence of chromosomal abnormalities in male infertility. But there have been few studies on the possible correlation between a special patient characteristics and lifestyle and chromosomal abnormalities as well as heteromorphic variants or worsening the effects of pre-existing genetic or medical factors (10-12).

This is the first study to examine the association between chromosomal abnormalities and heteromorphic variants and parental consanguineous marriages in male infertility. Due to the aforementioned high risk of chromosomal aberrations, it would be of high importance to perform chromosomal screening prior to IVF/ICSI in

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[1]Medical Genetics Laboratory, Alzahra University Hospital, Isfahan, Iran. [2]Shahid Beheshti Infertility Center, Isfahan, Iran. [3]Department of Anatomy, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. [4]Students Research Committee, Kermanshah University of Medical Sciences, Kermanshah, Iran. [5]Department of Biostatistics and Epidemiology, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran. [6]Department of Genetics and Molecular Biology, Medical School, Isfahan University of Medical Sciences, Isfahan, Iran. [7]Department of Medical Genetics, School of Medicine, Tehran University of Medical Science, Tehran, Iran
***Corresponding Author:** Majid Hosseinzadeh, MD; Tel/Fax: +983136201281, Email: hosseinzadeh@azh.mui.ac.ir

men with azoospermia and severe oligozoospermia, as they are assumed to have the highest risk of abnormalities (13,14). However, karyotyping is costly and hence it would be beneficial to allow more direct evidence of the risk and identify patients who would benefit from screening by the use of parameters other than sperm concentration to provide patients with appropriate genetic counseling regarding the potential genetic concerns of ICSI.

In this study we aimed to evaluate the prevalence and nature of chromosomal aberrations and chromosomal heteromorphic variants in azoospermic and severe oligozoospermic men in Isfahan, Iran. Furthermore, several clinical parameters and more detailed patient characteristics including serum hormonal levels, positive family history, parental consanguinity, smoking, alcohol habits and so on were investigated. This research may help to predict the possible effect of parameters studied on the risk of sperm aneuploidy in the group of infertile males in the absence of analysis of sperm karyotypes.

Materials and Methods

The study samples included 230 Iranian infertile males (213 azoospermic and 17 sever oligospermic men) who attended the infertility center of Shahid Beheshti hospital of Isfahan, Iran from 2011 to 2015. Fifty fertile normozoospermic men with proven fertility and normal semen parameters were also included as controls. Informed consent was obtained from each participant before sampling. Cases were classified into 2 categories using sperm count: Azoospermia was characterized as the total absence of sperm cells and severe oligozoospermia was defined as less than 5 million/mL sperm cells in seminal fluid. All patients underwent an andrological work-up, including a comprehensive medical history, testicular ultrasonography, physical examination, hormonal estimation and routine semen analysis according to the World Health Organization guidelines (15).

Among the infertile men, those with obstruction of the seminal tract, endocrine failure and defective spermatogenesis secondary to infection shown on history or clinical examination were excluded.

All men completed a comprehensive questionnaire containing information on family history regarding infertility (male relatives with infertility), parental consanguinity (first cousin or second cousin), and habits relating to smoking and alcohol consumption. Family history of infertility was asked using a special questionnaire; first-degree blood relatives included parents, siblings and children. Meanwhile, second-degree blood relatives were grandparents, uncles, aunts, niece, nephews and half-siblings.

Serum concentrations of luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin were measured by radioimmunoassay (RIA). In the present study, the reference ranges for FSH, LH, testosterone and prolactin level were 2–10 mIU/mL, 2–12 mIU/mL, 2.84–8 ng/mL and 1.8-20.3 ng/ml, respectively.

Chromosome Examination

Karyotyping was performed on cultures of peripheral blood lymphocytes according to standard cytogenetic procedures (16). In brief, the samples were cultured for 72 hours, using RPMI-1640 medium containing 10% fetal bovine serum and 2% phytohemagglutinin (PHA). At the end of 72 hours, the cultures were harvested and metaphases were stained with Giemsa using the G-banding technique. Selective banding study by the use of C-banding technique was performed for heterochromatin polymorphism detection. The karyotypes were analyzed according to the International System for Human Cytogenetic Nomenclature (17).

Statistical Analysis

The statistical analysis of data was performed using SPSS version 20.0 (SPSS, Chicago, IL, USA). To evaluate the associations between the disease status and risk factors, a multiple logistic regression using the Enter method was performed, taking disease status as the binary response variable (Case = 1, Control = 0). Then, for further investigation, if chromosomal abnormalities and chromosomal variants are associated with corresponding risk factors, 2 other logistic models were applied with the following coding for response variables: (Abnormal = 1, Normal = 0) and (Variant = 1, Normal = 0). All the variables were dichotomous (Yes/No), so the odds ratio (OR) represents the odds of carrying a chromosomal abnormality compared with the reference category which is "NO". $P<0.05$ was considered statistically significant.

Results

A total of 230 infertile men as well as 50 healthy controls were studied for the cytogenetic evaluation. Characteristics of the case and control groups are summarized in Table 1. The mean age of patients was 33.7 years (range 21 to 53), the infertile men's mean body mass index (BMI) was 25.4 ± 4.6 (15-42) and the median duration of infertility of the couples was of 4.5 years (range 0 to 20) at the time of sapling in our center. A chromosomal abnormality was found in 15.2% (35) of all infertile men studied (CI 11.1–20.4). Characteristics of the chromosomal abnormalities detected in patients are summarized in Table 1. Two out of 35 cases with chromosomal abnormality were oligozoospermic (5.71%) and 33 (94.28%) were azoospermic. Reciprocal

Table1. The Main Cytogenetic Findings in Case and Control Group

Group	Total	Karyotype		
		Chromosomal Abnormality	Chromosomal Variant	Normal Karyotype
Azoospermia	213	33	22	158
Oligoospermia	17	2	3	12
Control	50	-	3	47

chromosomal translocation was detected in 2 men in the group of infertile patients. Klinefelter syndrome (KS) was the most frequent chromosomal abnormality among infertile men (10.43%). One out of 24 patients with KS had oligozoospermia.

Our findings also revealed some kinds of chromosome variants in 25 (10.9%) men in the group of infertile patients (CI 7.4–15.6). These variants consisted of pericentric inversion of chromosome 9, pericentric inversion of chromosome Y, 46, XY, 9qh+, 1qh+, 16qh+, Yqh+ and Yqh- (Table 2). Three chromosome variants were found in control group including 9qh+, 16qh+ and Inv (9). In the oligozoospermia cases, 2 chromosomal abnormalities and 3 chromosomal variants were detected.

Data on hormone levels were available for 130 out of 230 infertile men (56.52%) in our study population.

Comparing the patients with the control group, the regression analysis confirmed the expected positive association between FSH concentrations and male infertility (OR: 1.218, $P=0.001$) but no association was found in levels of LH, testosterone and prolactin. There was also a significant association between a positive family history of infertility and recurrence of the disease in the offspring (OR: 7.858, $P=0.052$). Moreover, compared with men whose parents were not consanguineous, men with parental consanguinity had a higher prevalence of infertility (OR: 5.312, $P=0.034$) (Table 3). Regarding other variables including a positive andrologic history (e.g. genital infection, varicocele, cryptorchidism, vasectomy and chemotherapy), smoking habits and alcohol consumption, there was no significant differences between case and control group.

Among the hormone levels studied, only LH>12 IU/l raised the chance of detecting a chromosomal abnormality (OR: 16.258, $P<0.001$). Parental consanguinity, positive family history or alcohol and cigarette consumption showed no statistically significant association with the risk of carrying a chromosomal abnormality (Table 4). In addition, no association was found between a positive andrologic history and the prevalence of chromosomal aberrations.

Statistical analysis showed no significant association between any of the studied variables and the existence of chromosomal heteromorphic variants (Table 5).

Table 2. Different Types of Chromosomal Abnormalities and Chromosomal Variants Encountered in 35 and 25 Infertile Men, Respectively

Sex/Chromosome Aneuploidies	No. of Patients	%
47,XXY	24	68.57
47,XYY	2	5.71
46,XX male	2	5.71
46,X+mar	1	2.85
46,XY, Del Y (q11.2)	1	2.85
46,XX, add Xp	1	2.85
46,XY, Y der	1	2.85
46,XY, t (3;13) (q25;q12)	1	2.85
46, XY, t (14;21)	1	2.85
46,XY, ins1 (q12)	1	2.85
Chromosomal Variants		
46,XY, Yqh+	10	40
46,XY, Yqh+, 9qh+	1	4
46,XY, Yqh-, 9qh+	1	4
46,XY, 21ps+, Yqh+	1	4
46,XY, 16qh+	1	4
46,XY, 1qh+	2	8
46,XY, inv (Y)	3	12
46,XY, inv (9)	6	24

Discussion

Although karyotyping infertile men is recommended by guidelines, using parameters other than sperm concentration such as hormonal levels, positive family history, parental consanguinity, and a specific life style appears to be beneficial in order to identify men with the highest risk of chromosomal abnormalities, especially in the management of oligospermia. So far, few studies on chromosomal aberrations found in infertile men have focused on patients with such characteristics. In addition, no studies have attempted to examine the association between chromosomal abnormalities and parental consanguineous marriages in male infertility.

The frequency of chromosomal abnormalities found in our cohort from Isfahan province of Iran was 15.2% (37.1%

Table 3. Clinical Data, Characteristics and Statistical Analysis of the Case and Control Groups

Factor	Case (n = 230)	Control (n = 50)	OR	95% CI		*P* Value
				Lower	Upper	
FSH	12.81 (3-46)	5.72 (2.1-10.8)	1.218	1.088	1.362	0.001*
LH	7.86 (2-24.9)	5.53 (1-9.1)	0.926	0.796	1.078	0.321
Prolactin	10.42 (3-28.5)	10.03 (2-19.7)	1.066	0.991	1.147	0.088
Testosterone	9.21 (2-26)	6.58 (3-10.5)	1.003	0.985	1.021	0.734
Positive family history	44 (19.1%)	1 (2%)	7.858	0.982	62.870	0.052*
Parental consanguinity	33 (14.3%)	2 (4%)	5.312	1.133	24.901	0.034*
Cigarette consumption	33 (14.3%)	7 (14%)	0.722	0.244	2.131	0.555
Alcohol consumption	12 (5.2%)	1 (2%)	5.329	0.559	50.772	0.146

The reference ranges for FSH, LH, testosterone and prolactin level were 2–10 mIU/mL, 2–12 mIU/mL, 2.84–8 ng/mL and 1.8-20.3 ng/ml, respectively.
Descriptive data are indicated by mean (range) for continuous variables, and number (%) for discrete variables.
* Significant at 0.05.

Table 4. Patient Characteristics and Prevalence of Chromosomal Abnormalities in the Case Group

Factor	Abnormal Karyotype	Normal Karyotype	OR	95% CI		*P* Value
				Lower	Upper	
FSH	17 (70.8)	45 (47.4)	0.618	0.141	2.708	0.5240
LH	16 (66.7)	16 (16.8)	16.258	3.751	70.465	<0.001
Prolactin	1 (4.2)	10 (10.5)	0.298	0.028	3.207	0.3180
Testosterone	7 (29.2)	21 (22.1)	1.859	0.565	6.123	0.3080
Positive family history	9 (25.7)	31 (18.2)	1.911	0.541	6.748	0.3150
Parental consanguinity	4 (11.4)	38 (22.4)	1.250	0.305	5.123	0.7560
Cigarette consumption	5 (14.3)	28 (16.5)	0.356	0.076	1.671	0.1900
Positive andrologic history	5 (14.3)	34 (20)	0.286	0.064	1.282	0.1020

The reference ranges for FSH, LH, testosterone and prolactin level were 2–10 mIU/mL, 2–12 mIU/mL, 2.84–8 ng/mL and 1.8-20.3 ng/ml, respectively.
Descriptive data are indicated by number (%).
* Significant at 0.05.

Table 5. Patient Characteristics and Prevalence of Chromosomal Variants in the Case Group

Factor	Chromosomal Variant	Normal Karyotype	OR	95% CI		*P* Value
				Lower	Upper	
FSH	2(18.2)	45(47.4)	0.176	0.026	1.200	0.076
LH	1(9.1)	16(16.8)	1.482	0.112	19.598	0.765
Prolactin	1(9.1)	10(10.5)	0.724	0.076	6.907	0.779
Testosterone	5(45.5)	21(22.1)	3.238	0.824	12.731	0.093
Positive family history	4(16)	31(18.2)	1.865	0.430	8.084	0.405
Parental consanguinity	5(20)	38(22.4)	0.746	0.130	4.265	0.741
Positive andrologic history	5(20)	34(20)	0.554	0.101	3.024	0.495

The reference ranges for FSH, LH, testosterone and prolactin level were 2–10 mIU/mL, 2–12 mIU/mL, 2.84–8 ng/mL and 1.8-20.3 ng/ml, respectively.
Descriptive data are indicated by number (%).
* Significant at 0.05.

autosomal and 62.8% sex chromosome aberrations) which is within the range of the 2.1 to 28.4% mentioned in published studies (18). Especially in Iran, comparable frequencies in the observed abnormal karyotype were reported by others (15.30, 13.96 and 15.5%) (19-21).

The differences between the prevalence of chromosomal variants in infertile men (10.9%) compared to the control group (6%) was not significant ($P=0.298$). It has been postulated that quantitative and positional alterations of the constitutive heterochromatin may affect non-disjunction of chromosomes during meiosis or inhibit gene transcription through a silencing effect on the genes with normal expression in close proximity (22,23). To date, the contribution of chromosomal variants to the state of male fertility is still a controversial issue (22-26). Recently, it has been suggested that heterochromatin regions may have more important role than previously thought. Therefore chromosome variants should not be ignored by cytogeneticists and clinicians (22).

We found that LH >12 IU/l increased the chance of detecting a chromosomal abnormality. The same result was found for FSH >10, despite the lack of statistically significant association. These findings may be in part consistent with studies which reported a significant association between LH, FSH concentrations and chromosomal abnormalities and the possibility of testicular dysgenesis linked with a karyotype anomaly (XXY etc.) (4,10,27). Distribution of an abnormal hormone level in infertile cases with chromosomal abnormality and in cases with normal karyotype is shown in Figure 1. Although FSH is considered to be a prognostic factor in testicular function, however, considering its prognostic implication for chromosomal abnormality in infertile men is remained to be confirmed (28).

According to our findings, the rates of consanguinity among parents of infertile men were relatively higher than control group, so infertile men were fivefold as frequent as fertile men born to consanguineous parents with second or third degree of relativity. These results are in line with a study by Demirtas et al who reported a significantly increased ratio of parental consanguinity

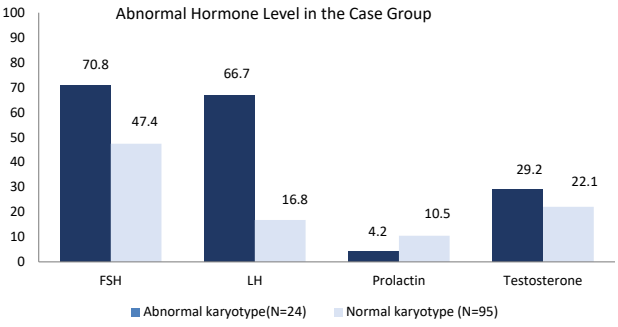

Figure 1. Distribution of an Abnormal Hormone Level in Cases Group With Chromosomal Abnormality and Normal Karyotype. The reference ranges for FSH, LH, testosterone and prolactin level were 2–10 mIU/mL, 2–12 mIU/mL, 2.84–8 ng/mL and 1.8-20.3 ng/ml, respectively.

in Non-obstructive azoospermia (NOA) patients (29). However, no significant association was seen between parental consanguinity and risk of carrying chromosomal abnormality. In Iranian society, in which consanguineous marriages are quite common, no studies focusing on consanguinity and infertility are available. Also, the offspring of consanguineous marriages are at increased risk of recessive disorders because the consanguinity results in raising the rate of homozygous genotype expression (30,31). Furthermore, the lack of association between the rate of chromosomal aberrations in infertile men and the presence of consanguinity could be explained by the rare genetic recessive disorders, including those related to male factor infertility (32).

Our findings also indicated a significantly higher proportion of positive family history of infertility in the first-degree and second-degree blood relatives of infertile men compared to controls. However, no significant differences were found between the presence of chromosomal abnormalities as well as chromosomal variants and the distribution of positive family history of infertility. In consistent with the results of a study by Dul et al, no association was observed between a positive family history of infertility and risk of carrying chromosomal aberrations in our study.

We detected no correlation between a positive andrologic history and the frequency of chromosomal aberrations. On the contrary, Dul et al found that a positive andrologic history declined the risk of an abnormal karyotype (10).

In this study, the frequency of chromosomal abnormalities in infertile men was 15.2%. However, the rest of the infertile men with abnormal spermogram showed no chromosomal abnormality although their spermograms were abnormal. It is maybe due to the fact that karyotype analysis detects large-scale genetic changes and submicroscopic changes in DNA sequence like Y chromosome microdeletions are not detected using this technique. Therefore, following the detection of normal karyotype, male infertility clinics should always offer complementary genetic examinations for the male infertility diagnosis such as detection of Y chromosome microdeletions, and genetic analysis of sperm by the fluorescent *in situ* hybridization (FISH) method.

Conclusions

This study suggests a positive family history of infertility, parental consanguineous marriages and high levels of FSH as strong determinants or risk factors for male infertility. Nonetheless, the presence of these patient characteristics did not prove to have a direct correlation with chromosomal abnormalities in male infertility. Among the various possible risk factors studied, an elevated gonadotropin level provides a better risk assessment for occurring chromosomal abnormality in infertile men. However, more evidences based on larger prospective cohort studies in different geographical areas are needed to confirm our findings.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

The ethics committee approval of the study was obtained from Isfahan University of Medical Sciences.

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References

1. Plaseska-Karanfilska D, Noveski P, Plaseski T, Maleva I, Madjunkova S, Moneva Z. Genetic causes of male infertility. Balkan J Med Genet. 2012;15 (Suppl):31-34. doi:10.2478/v10034-012-0015-x
2. Mafra FA, Christofolini DM, Bianco B, et al. Chromosomal and molecular abnormalities in a group of Brazilian infertile men with severe oligozoospermia or non-obstructive azoospermia attending an infertility service. Int Braz J Urol. 2011;37 (2):244-250; discussion 250-241.
3. Yerebasmaz N, Demir B, Kahyaoglu I, Ocal A, Kaplanoglu I, Mollamahmutoglu L. Does male factor infertility affect intracytoplasmic sperm injection pregnancy results? Crescent J Med Biol Sci. 2017;4 (2):85-89.
4. Yoshida A, Miura K, Shirai M. Cytogenetic survey of 1,007 infertile males. Urol Int. 1997;58 (3):166-176.
5. Lipshultz LI, Lamb DJ. Risk of transmission of genetic diseases by assisted reproduction. Nat Clin Pract Urol. 2007;4 (9):460-461. doi:10.1038/ncpuro0879
6. Maciel-Guerra AT, de Mello MP, Coeli FB, et al. XX Maleness and XX true hermaphroditism in SRY-negative monozygotic twins: additional evidence for a common origin. J Clin Endocrinol Metab. 2008;93 (2):339-343. doi:10.1210/jc.2007-1115
7. Sharpe RM. Lifestyle and environmental contribution to male infertility. Br Med Bull. 2000;56 (3):630-642. doi:10.1258/0007142001903436
8. Chatziparasidou A, Christoforidis N, Samolada G, Nijs M. Sperm aneuploidy in infertile male patients: a systematic review of the literature. Andrologia. 2015;47 (8):847-860. doi:10.1111/and.12362
9. Ouladsahebmadarek E, Giasi GS, Khaki A, et al. The effect of compound herbal remedy used in male infertility on spermatogenesis and pregnancy rate. Int J Womens Health Reprod Sci. 2016;4 (4):185-188. doi:10.15296/ijwhr.2016.41
10. Dul EC, Groen H, van Ravenswaaij-Arts CM, Dijkhuizen T, van Echten-Arends J, Land JA. The prevalence of chromosomal abnormalities in subgroups of infertile men. Hum Reprod. 2012;27 (1):36-43. doi:10.1093/humrep/der374
11. Dul EC, van Ravenswaaij-Arts CM, Groen H, van Echten-Arends J, Land JA. Who should be screened for chromosomal abnormalities before ICSI treatment? Hum Reprod. 2010;25 (11):2673-2677. doi:10.1093/humrep/deq258
12. Suganya J, Kujur SB, Selvaraj K, Suruli MS, Haripriya G, Samuel CR. Chromosomal Abnormalities in Infertile Men

from Southern India. J Clin Diagn Res. 2015;9 (7):Gc05-10. doi:10.7860/jcdr/2015/14429.6247
13. McLachlan RI, O'Bryan MK. State of the Art for Genetic Testing of Infertile Men. J Clin Endocrinol Metab. 2010;95 (3):1013-1024. doi:10.1210/jc.2009-1925
14. Harton GL, Tempest HG. Chromosomal disorders and male infertility. Asian J Androl. 2012;14 (1):32-39. doi:10.1038/aja.2011.66
15. Rowe PJ, Comhaire FH. WHO manual for the standardized investigation and diagnosis of the infertile male. Cambridge University Press; 2000.
16. Barch MJ, Knutsen T, Spurbeck JL. The AGT cytogenetics laboratory manual. 3rd ed. Philadelphia: Lippincott-Raven Publishers; 1997.
17. Shaffer LG, Slovak ML, Campbell LJ. An international system for human cytogenetic nomenclature: Recommendations of the international standing committee on human cytogenetic nomenclature. Cytogenetic and Genome Research; 2009.
18. Balkan M, Tekes S, Gedik A. Cytogenetic and Y chromosome microdeletion screening studies in infertile males with Oligozoospermia and Azoospermia in Southeast Turkey. J Assist Reprod Genet. 2008;25 (11-12):559-565. doi:10.1007/s10815-008-9272-8
19. Mahjoubi F, Soleimani S, Mantegy S. Chromosomal abnormalities in infertile men referred to iran blood transfusion organization research center. J Reprod Infertil. 2010;11 (3):175-178.
20. Akbari MT, Behjati F, Pourmand GR, Asbagh FA, Kachoui MA. Cytogenetic abnormalities in 222 infertile men with azoospermia and oligospermia in Iran: Report and review. Indian J Hum Genet. 2012;18 (2):198-203. doi:10.4103/0971-6866.100764
21. Salahshourifar I, Gilani MAS, Masoudi NS, Gourabi H. Chromosomal abnormalities in Iranian infertile males who are candidates for assisted reproductive techniques. Iran J Fertil Steril. 2007;1 (2):75-79.
22. Madon PF, Athalye AS, Parikh FR. Polymorphic variants on chromosomes probably play a significant role in infertility. Reprod Biomed Online. 2005;11 (6):726-732. doi:10.1016/S1472-6483 (10)61691-4
23. Minocherhomji S, Athalye AS, Madon PF, Kulkarni D, Uttamchandani SA, Parikh FR. A case-control study identifying chromosomal polymorphic variations as forms of epigenetic alterations associated with the infertility phenotype. Fertil Steril. 2009;92 (1):88-95. doi:10.1016/j.fertnstert.2008.05.071
24. Purandare H, Fernandes NV, Deshmukh SV, Chavan S. Heterochromatic Variations and Pregnancy Losses in Humans. Int J Hum Genet. 2011;11 (3):167-175. doi:10.1080/09723757.2011.11886139
25. Sahin FI, Yilmaz Z, Yuregir OO, Bulakbasi T, Ozer O, Zeyneloglu HB. Chromosome heteromorphisms: an impact on infertility. J Assist Reprod Genet. 2008;25 (5):191-195. doi:10.1007/s10815-008-9216-3
26. Nagvenkar P, Desai K, Hinduja I, Zaveri K. Chromosomal studies in infertile men with oligozoospermia & non-obstructive azoospermia. Indian J Med Res. 2005;122 (1):34-42.
27. Sultan C, Craste de Paulet B, Audran F, Iqbal Y, Ville C. [Hormonal evaluation in male infertility]. Ann Biol Clin (Paris). 1985;43 (1):63-66.
28. Kosar PA, Ozcelik N, Kosar A. Cytogenetic abnormalities detected in patients with non-obstructive azoospermia and severe oligozoospermia. J Assist Reprod Genet. 2010;27 (1):17-21. doi:10.1007/s10815-009-9366-y
29. Demirtas A, Akinsal EC, Ekmekcioglu O. Parental consanguinity in infertile males. Open J Urol. 2013;3 (2):53-57. doi:10.4236/oju.2013.32010
30. Bittles AH, Grant JC, Sullivan SG, Hussain R. Does inbreeding lead to decreased human fertility? Ann Hum Biol. 2002;29 (2):111-130. doi:10.1080/03014460110075657
31. Bittles AH, Mason WM, Greene J, Rao NA. Reproductive behavior and health in consanguineous marriages. Science. 1991;252 (5007):789-794. doi:10.1126/science.2028254
32. Inhorn MC, Kobeissi L, Nassar Z, Lakkis D, Fakih MH. Consanguinity and family clustering of male factor infertility in Lebanon. Fertil Steril. 2009;91 (4):1104-1109. doi:10.1016/j.fertnstert.2008.01.008