SJIF Impact Factor: 7.001| ISI I.F.Value:1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 5 | Issue: 10 | October 2020 - Peer Reviewed Journal

THE ROLE OF AZF GENE DELETIONS IN THE DEVELOPMENT OF MALE INFERTILITY

Nazhmetdinova Dilfuza Farkhodovna
Ph.D., Republican Specialized Scientific-Practical Medical Center of Obstetrics and Gynecology, Uzbekistan.

Yusupov Usman Yuldashevich
Doctor of Medical Sciences, Professor. Republican Specialized Scientific-Practical Medical Center of Obstetrics and Gynecology, Uzbekistan.

Faizirakhmanova Maria Mikhailovna
Candidate of Medical Sciences, Republican Specialized Scientific-Practical Medical Center of Obstetrics and Gynecology, Uzbekistan.

DISCUSSION

Infertility in marriage is one of the most important and complex medical, socio-demographic and economic problems. The frequency of infertile marriages in many countries of the world ranges from 8 to 29%, and in half of the cases, the cause is a male factor. According to WHO estimates, this figure reaches 15% (60-80 million pairs). At the same time, primary infertility is observed in 30% of spouses [8, 35, 42].

Studies of 3956 infertile couples in seven laboratories around the world have shown that male infertility is observed in 40% of cases [30, 39]. According to a report on studies conducted in 33 centers in 25 countries of the world, 10.7% of men in infertile marriages have azoospermia or oligozoospermia [5, 28, 19].

Modern diagnostic and medical care for infertility is based on fundamental achievements in the field of reproduction, which include: deciphering the mechanisms of hormonal regulation of the reproductive process, ultrasound diagnostics, endoscopic surgery, assisted reproductive technologies. However, in 8-10% of cases, it is not possible to establish the cause of infertility, which is associated with a large number of various factors that affect the reproductive process [6, 41]. According to some authors, in 30% of cases it is not possible to find out the cause of infertility, the so-called idiopathic infertility. Most likely, idiopathic male infertility is based on insufficiently studied genetic mechanisms for the regulation of spermatogenesis [9]; a certain proportion of cases may be related to the pathology of meiosis, impaired differentiation and maturation of spermatids into a mature reproductive cell, etc. [36, 43].

The results of the initial medical examination and spermiological analysis allow a preliminary assessment of the cause of the reproductive dysfunction in a man. Usually male infertility is classified based on the results of the semen analysis. In 2010, WHO reissued the standard protocol for the study of infertile couples. According to these recommendations, normal sperm counts should be as follows: sperm count 15 × 106 / ml, of which more than 40% are motile, more than 58% are live, about 4% with normal morphology, and should not contain more than 1 × 106 / ml leukocytes [45].

The processes of spermatogenesis can be negatively influenced by various reasons: diseases of the genital organs, unhealthy diet, hormonal imbalance, chemical and physical factors, allergization, the use of certain drugs, bad habits, and genetic defects [36, 38]. Studies have shown that genetic factors are clearly involved in the decline in male reproductive potential [10]. The frequency of cytogenetic abnormalities is estimated at 2.1 - 28.4% of cases in infertile men and only 0.7-1% among the male population as a whole [21]. According to other studies, genetic defects (mutations and chromosomal abnormalities) are observed in 30% of cases of male infertility [17, 28].

SJIF Impact Factor: 7.001| ISI I.F.Value:1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 5 | Issue: 10 | October 2020 - Peer Reviewed Journal

Mutations in the male genome lead to a change in the normal function of the genetic apparatus, as a result of this, disorders can occur at different levels: during the formation of genitals, spermatogenesis, maturation of sperm in the appendages, their transport in the reproductive tract and ejaculation, penetration through cervical mucus, capacitation, acrosomal reaction, fertilization of the egg, etc. [10].

Chromosomal abnormalities that cause infertility are divided into two types: changes in the karyotype in somatic and germ cells and meiotic disorders.

The incidence of karyotype disorders in infertile men is about 7% [17]. Chromosomal abnormalities are more often detected in patients with azoospermia - in 13.7% of cases (the majority is Klinefelter's syndrome) [23]. Sex chromosome abnormalities prevail in men with azoospermia, autosomal abnormalities - in patients with oligozoospermia [22].

Meiotic disorders are observed in 6% of men, and this frequency rises to 17.5% in individuals with oligozoospermia (≤1 × 106 / ml). To date, many genes are already known (A-MYB, AZH, BCLW, HPY, LVS, etc.) located on different chromosomes that are responsible for the process of spermatogenesis. And the violation of this process is due to a large number of mutations in the coordinator genes [2].

Chromosomal abnormalities in infertile males can be numerical or structural in relation to sex chromosomes (eg, 47, XXY) or autosomes (eg, in Robertsonian translocation) [23]. Among the factors of infertility, Y-chromosome microdeletions rank second after Klinefelter's syndrome. It should be noted that the cause of genetically determined male infertility associated with impaired spermatogenesis, in 10-15% of cases, is a consequence of structural abnormalities in the Y-chromosome.

Previously, it was believed that the function of the Y chromosome in mammals is limited to the control of sex differentiation, but in 1976 evidence was presented for the importance of the human Y chromosome for spermatogenesis. The Y chromosome, one of the smallest chromosomes in the human genome, is about 60Mb in size, 30 of which are in the euchromatin domains, and the rest is in the heterochromatin block in the distal part of the long arm, which can vary greatly in size in different individuals. In general, the chromosome is divided into three regions: the euchromatin short arm (Yp11), the euchromatin proximal long arm (Yq11), and the heterochromatin distal region (Yq12). Euchromatic regions are not variable in size. The named areas are arranged in a mosaic pattern within the chromosome.

Thus, the human Y chromosome consists of about 60 million nucleotides, that is, it is much less than in other chromosomes, and 95% of the genes concentrated in this sex chromosome are responsible for the development of male characteristics and fertility [35, 37].

The first hypothesis on the correlation between Y-chromosome deletions and male infertility was put forward by Tiepolo L. and Zuffardi O. in 1976. Analyzing the terminal deletion of the Y chromosome in 6 sterile men with a normal phenotype and azoospermia, Tiepolo and Zuffardi hypothesized the existence of a male fertility gene complex in the distal region of the euchromatin part of the long arm of the Y chromosome (Yq11). This locus was named the azoospermia factor (AZF) [14].

Further cytogenetic and molecular genetic studies made it possible to construct a detailed map of the Y chromosome, including 43 deletion intervals. Currently, cytogenetic and molecular genetic methods can be used to diagnose macro- and microdeletions of the Y-chromosome, capturing the AZF locus, which can be detected in 1015% of patients with azoospermia and in 5-10% with severe oligozoospermia. It is known that the Y chromosome contains 220 gene regions; 104 of them are coding genes, 111 are pseudogenes and 5 genes with not yet clarified functions. 16 coding genes are located in the AZF region and are responsible for the manifestation of male fertility.

To date, more than 12 types of microdeletions have been identified in the AZFY chromosome region [12, 20, 29, 34]. Most of the microdeletions that cause azoospermia or oligozoospermia are located in the long arm, these microdeletions are too small to be detected by karyotyping. They can be identified using polymerase chain reaction (PCR).

Further work in this area revealed that there are three non-overlapping regions of the Y chromosome that play an important role in the process of spermatogenesis. These regions are AZFa, AZFb and AZFc and are located along the Yq shoulder from proximal to distal [30]. The fourth region (AZFd) was discovered later and assigned to region C [46]. Subsequently, for each subregion, candidate genes responsible for spermatogenesis disorders were identified: for AZFa - USP9Y (DFFRY) and DBY, for AZFb - RBMY, for the AZFc region - DAZ. The nucleotide sequence and size of each subregion were determined: AZFa about 800 thousand bp, AZFb - 3.2 million bp. and AZFc- 3.5 million base pairs. Unlike the candidate genes of

SJIF Impact Factor: 7.001| ISI I.F.Value:1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 5 | Issue: 10 | October 2020 - Peer Reviewed Journal

the AZFb and AZFc subregions, the genes of the AZFa subregion are represented on the chromosome by a single copy; therefore, even point mutations can cause impaired spermatogenesis and lead to infertility in men [33].

Chromosomal abnormalities and microdeletions of Y chromosomes in the Yq11 region are recognized as the genetic underlying in male infertility. As mentioned earlier, the genes that control spermatogenesis located in the Yq11 region are called the genes of the azoospermia factor (AZF) [11]. The azoospermia factor (AZF) and its subregions AZFa, AZFb, and AZFc are the main targets for molecular diagnostics [7, 19]. To date, the relationship between microdeletions of the AZF locus and the manifestation of azoospermia and oligozoospermia has been accurately established [20]. The frequency of microdeletions a, b, c of the AZF locus is as follows: microdeletion in the AZF c subregion is detected in 75-80% of cases; in sub-regions AZFb + c - 2022%; in the L2Ba subregion - 3-5% of cases [1].

Most of the literature indicates that AZFc deletions may be associated with azoospermia (54%) and severe oligozoospermia (46%); The histological assessment of testicular tissue ranges from Sertoli cell syndrome (SCS) to hypospermatogenesis. It is also considered possible that testicular damage caused by the deletion of AZFc can progress in patients with oligozoospermia, and azoospermia can develop with age [21].

Complete deletions of certain AZF regions are associated with various disorders of spermatogenesis, for example: deletions of loci of the AZFa region - with Sertoli cell syndrome, deletions of loci of the AZFb / AZF region with the absence of meiosis 1 and, therefore, with the absence of spermatogenesis cells or their underdevelopment. Deletions of the AZFc region loci lead to hypospermatogenesis, leading to severe oligozoospermia and azoospermia. It was also noted that microdeletions of the entire AZFa or AZFb regions predict a negative result during testicular biopsy and TESE, while with a complete deletion of the AZFc region, successful sperm retrieval is predicted [7].

Nevertheless, deletions of the AZFc region are common in patients with obstructive azoospermia or severe oligozoospermia, reaching about 70% of all cases [11]. The AZFc region contains 11 families of transcriptional units, expressed only in the testis. Five of them encode proteins, four pseudogenes, and two open reading frames [22].

The deleted in azoospermia gene DAZ is expressed in spermatogonia and encodes an RNA-binding protein important for spermatogenesis. Four copies of this gene (DAZ1, DAZ2, DAZ3, DAZ4) are located at the AZFc locus [22, 23, 24]. Gene Y (CDY) encodes a protein containing histone acetyltransferase located in the nucleus of mature spermatids, where histone hyperacetylation occurs. The human Y chromosome has two identical copies of this gene in the AZFc region (CDY1A and CDY1B) and a pair of closely related genes in P5 (CDY2A and CDY2B) [25,17]. Gene Y 2 (BPY2) is specifically expressed in the testis and its protein product is involved in the development of male germ cells, or the development of male infertility.

Three almost identical copies of this gene are found on the Y chromosome [26]. Along with this, partial microdeletions at the AZFc locus were revealed, which to one degree or another affect the process of spermatogenesis. These deletions include changes in the gr / gr, b2 / b3, b1 / b3 and b3 / b4 genes, but the most significant is the deletion of the gr / gr region, which includes 2 copies of the DAZ gene and 1 copy of the CDY1 gene. These genes are the most important candidate genes associated with the process of spermatogenesis in the AZFc region. Recently, gr / gr deletions have been increasingly found in men with a diagnosis of infertility, suffering from impaired spermatogenesis to varying degrees [20, 27].

High structural variability of the Y chromosome, including deletions, duplications, and inversions [21], as well as its polymorphism, especially a wide range of Yq12, correlates with impaired reproductive function [22]. It should be noted that microdeletions and chromosomal abnormalities in the AZF region have become a clinically important indicator for assisted reproductive technologies (ART), such as intracytoplasmic sperm injection (ICSI), and are being successfully introduced into clinical practice [23].

Also, according to the literature, among the regions of the AZF gene, the frequency of deletions of loci of the AZFc region is 60%, combined deletions involving various AZF regions - 35%, and AZFa deletions about 5% [28].

Deletions of the AZF region are phenotypically different. They can be complete, that is, they completely remove one or more AZF regions, and partial, if the deletions do not completely cover any of its three regions.

Deletions of the AZF locus are associated with varying degrees of impairment of spermatogenesis - from a moderate decrease in its activity (hypospermatogenesis) or block of spermatogenesis to the almost complete absence of

SJIF Impact Factor: 7.001| ISI I.F.Value:1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 5 | Issue: 10 | October 2020 - Peer Reviewed Journal

germ cells in the seminiferous tubules - Sertoli cell syndrome (SCS). In almost all cases, complete deletions are de novo mutations and lead to severe azoospermia or oligozoospermia [29, 21].

It is considered possible that testicular damage caused by the AZFc deletion may progress and patients with oligozoospermia may develop azoospermia with age. However, in men with AZFc deletions, in about 71% of cases, it is possible to obtain mature spermatozoa suitable for artificial insemination, while in patients with deletions of AZFa and AZFb subregions it is impossible to obtain mature germ cells [30].

Deletions at the AZF locus can be complete, i.e. completely deleting one AZF region or more, and partial, if the deletions do not completely cover any of its three regions. In almost all cases, complete deletions are de novo mutations and lead to severe azoospermia or oligozoospermia [13].

No strict dependence of the degree and stage of impaired spermatogenesis on the localization and size of the AZF locus deletions was found, but a number of general genophenotypic correlations were identified [13, 22].

Deletions of AZFa and AZFb regions cause azoospermia in 2/3 of cases and more rarely phenotypically manifest themselves as oligozoospermia. On histological examination of testicular tissue, the AZFa deletion always manifests itself as SCS. Based on this, scientists believe that the genes of the AZFa region regulate the first phases of spermatogenesis or the activity of stem cells.

Variable impairments of spermatogenesis with deletions of the AZFb region indicate multiple functional activity of the RBMY gene or its combinatorial activity with other genes.

Consequently, patients with deletions of AZFa and AZFb subregions, which are associated with the inability to obtain mature germ cells (it is impossible to obtain spermatozoa during a diagnostic biopsy), should be recommended other ways of solving reproductive problems - donor programs or adoption [14].

Analysis of the literature showed that AZFc deletions can be associated with azoospermia (54%) and severe oligozoospermia (46%); The histological assessment of testicular tissue ranges from SCS to hypospermatogenesis. Moreover, tubules with different defects can be found in the same individual. It is also considered possible that testicular damage due to the deletion of AZFc may progress, and patients with oligozoospermia may develop azoospermia with age. However, in men with AZFc deletions in about 71% of cases, it is possible to obtain mature spermatozoa suitable for artificial insemination [14, 15, 18].

The variable phenotype observed upon deletion of AZFb and AZFc regions can be explained by the following hypotheses [16, 31].

Deletions can affect the entire AZFb or AZFc region, or they can be minimal, capturing only one gene, gene cluster, or several STS markers. It is assumed that the severity of phenotypic manifestations directly depends on the size of the deletion. However, some cases refute this hypothesis [23, 40].

Each AZF gene has a homologue on the X chromosome (DBX, USP9X, RBMX) or on autosomes (DAZL1). The participation of homologues in the process of spermatogenesis is not observed; however, it can be assumed that their expression changes with deletions on the Y chromosome. The genetic background (other genes of the family) can also modify the phenotypic effect of existing deletions [3, 32, 44].

Currently, for men with a severe form of oligozoospermia, the only effective method of overcoming infertility is the Intracytoplasmic Sperm Injection (ICSI) method - the injection of sperm into the cytoplasm of the egg, and for patients with azoospermia - ICSI in combination with the extraction of testicular sperm using TESA or TESE testicles and from the resulting tissue, spermatozoa are isolated, with which the egg is fertilized later) [3, 4].

In some cases, the use of modern assisted reproductive technologies allows men with Y-chromosome deletions to have their own children. However, it should be noted that they have a risk of transmission of this deletion of the Y chromosome (in 100% of cases), as well as an increased risk of having children with mosaicism 45, X0 / 46, XY [26].

It should be noted that it is extremely important for infertile men to find out the presence of genetic defects before using assisted reproduction technologies to avoid the transmission of abnormalities to offspring and, in cases of impossibility of carrying out these manipulations to overcome the problem of male infertility, to recommend other ways of solving reproductive problems - donor programs or adoption.

REFERENCES

1. *Bykov V.L. Spermatogenesis in men at the end of the 20th century (literature review) // Problems of reproduction. - 2000. - No. 1. - S. 6-13*
2. *Vartanyan E.V., Petrin A.N., Kurnosova T.R. Genetic factors of male infertility // Problems of reproduction. - 2010. - No. 2.- P.74-78*

SJIF Impact Factor: 7.001| ISI I.F.Value:1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 5 | Issue: 10 | October 2020 - Peer Reviewed Journal

3. *Gogolevsky P.A. et al. AZF- microdeletions and male infertility // Andrology and genital surgery. -2001. -№4. -FROM. 73-77.*
4. *Gogolevsky P.A., Gogolevskaya I.K. Y-chromosome and male infertility (literature review) // Problems of reproduction. - 1999. - №5. –T5. –S.26-34.*
5. *Gogolevsky P.A., Kalugina A.S., Bondarevidr D.A. AZF- microdeletions and male infertility // Andrology and genital surgery. - 2001. - No. 4. - S. 73-77*
6. *Goncharova N.N., Martyshkina E.Yu., Kaznacheeva T.V., Arslanyan K.N., Adamyan L.V., Kurilo L.F., Sorokina T.M., Chernykh V.B. Medical and genetic aspects of infertility // Obstetrics. Gynecology. Reproduction. - 2012. - T.6, No. 2. - S. 35-40*
7. *Degemerzanova N.K., Solomadin M.V. AZF microdeletions of the Y chromosome. Molecular genetic studies in male infertility, available in Kazakhstan // KMZh (Kazakhstan Medical Journal). - 2012. - No. 6 (30). - S. 86-89.*
8. *Denisenko S.V., Dariy A.S. Reproduction genetics: Kiev. - 2008.*
9. *Kurilo L.F., Gordeeva S.I. Types of chromosomal abnormalities in patients with impaired formation and / or function of the organs of the reproductive system // Andrology and Genital Surgery. - 2009. - No. 3. - S. 24-28*
10. *Nikitin OD Male factor of infertile marriage: the state of the problem // Women's health.- №10.- 2009.-p.173-177.*
11. *Rakisheva Z.B., Degemerzanova N.K., Erdenova A.Kh., Solomadin M.V. Molecular genetic diagnostics in male infertility // Journal of Laboratory Diagnostics. - 2016. -No. 1 (16) .- P.30-33.*
12. *Chernykh V. B. AZF deletions are a common genetic cause of male infertility: state of the art research. // Problems of reproduction.-№1.- 2009.-p.10-15.*
13. *Chernykh V. B. Analysis of microdeletions at the AZF locus in men with infertility: joint research experience // Med. gene. - 2003. -№8. - T.2. – S.367-379.*
14. *Chernykh V.B., Kurilo L.F., Polyakov V.A. Y chromosome, AZF deletions and idiopathic infertility in men // Problems of reproduction. - 2001. - T.7, No. 5. - S. 47-58*
15. *Vartanyan E.V., Petrin A.N., Kurnosova T.R. Genetic factors of male infertility // Problems of reproduction. - 2012. -№2.*
16. *Ali S., Hasnain S.E.Genomics of the human Y-chromo- some. // Association with male infertility//Gene. - 2003. - Vol.4. - N321. - P. 25-37.*
17. *Bhasin S.Ma & de Kretse DM. Y-chromosome microdeletions and male infertility// Annals of Medicine .- 1997.-P.261-269.*
18. *Cai Z.M. Y chromosome microdeletion and male infertility: past, present and future // Zhonghua Nan Ke Xue. - 2010. Vol.16, N5. - P. 387-394*
1. *Camhaire FH, de Kretser D. Towards more objectivity in diagnosis and management of male infertility// Diagnosis and treatment of infertility. – 1982 . – P/1-33.*
2. *Choi J., SongS.H., Bak C.W., et al. Impaired Spermatogenesis and gr/gr Deletions Related to Y Chromosome Haplo- groups in Korean Men // PLoS One. - 2012. - N7. - e43550*
3. *FerlinA, Arredi B, Foresta CGenetic causes of male infertility // Reprod Toxicol. - 2006. - N22. - P. 133-141*
4. *Foresta C. Y chromosome microdeletions and alterations of spermatogenesis// University of Padova. Italy., 2002*
5. *Foresta C., Moro E., Ferlin A. Y chromosome microdeletions and alterations of spermatogenesis // Endocr. Rev. 2001. - Vol. 22, N2. - P. 226-239*
6. *Huang W..J, Lin Y.W., Hsiao K.N., Eilber K.S., Salido E.C., et al. Restricted expression of the human DAZ protein in premeiotic germ cells // Hum Reprod. - 2008. - N23. - P.1280-1289*
7. *Human reproductive ecology. Interactions of Environment, Fertility, and Behavior// Annals of The New York Academy of Science*
8. *Kent-First M.G. et al. The incidence and possible relevance of Y-linked microdeletions and their infertile fathers//Mol.Hum.Reprod. – 1996. – P.943-949.*
9. *Kumari A., Yadav S.K., Ali S. Organizational and functional status of the Y-linked genes and loci in the infertile patients having normal spermiogra // PLoS One. - 2012. - N7. - e41488*
10. *Kun Ma, Con Mallidis. The role of Y chromosome deletion in male in fertility//Eu.jornal of endocrinology. – 2000.*
11. *Kuroda-Kawaguchi T., Skaletsky H., Brown L.G., Minx P.J., Cordum H.S., et al. The AZFc region of the Y chromosome features massive palindromes and uniform recurrent deletions in infertile men // Nat Genet. - 2001. - N29. - P. 279-286*
12. *Lahn B.T., Tang Z.L., Zhou J., Barndt R.J., Parvinen M., et al. Previously uncharacterized histone acetyltransferases implicated in mammalian spermatogenesis // Proc Natl Acad Sci USA. - 2002. - N99. - P. 8707-8712*
13. *Liu R. Z. AZF deletions and male infertility // Zhonghua Nan Ke Xue. - 2012. - Vol. 18, N11. - P. 963-8*
14. *Pina-Neto J.M., Carrara R.C., Bisinella R., Mazzucatto L.F., Martins M.D., Sartoratto E., Yamasaki R. Somatic cytogenetic and azoospermia factor gene microdeletion studies in infertile men //Braz J Med Biol Res. - 2006. - N39. - P. 555-561*
15. *Poongothai J., Gopenath T.S., Manonayaki S. Genetics of human male infertility //Singapore Med J. - 2009. - Vol. 50, - N4. - P. 336-347*
16. *Reijo R.A., Dorfman D.M., Slee R., Renshaw A.A.,*

SJIF Impact Factor: 7.001| ISI I.F.Value:1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 5 | Issue: 10 | October 2020 - Peer Reviewed Journal

Loughlin K.R., et al. DAZ family proteins exist throughout male germ cell development and transit from nucleus to cytoplasm at meiosis in humans and mice // Biol Reprod. - 2000. - N63. P. 1490-1496

17. *Repping S., Skaletsky H., Lange J., Silber S., Van Der Veen F., et al. Recombination between palindromes P5 and P1 on the human Y chromosome causes massive deletions and spermatogenic failure // Am J Hum Genet. - 2002. - №71. - P. 906-922*
18. *Shi Y.C., CuiY.X., WeiL. etal. AZF microdeletions on the Y chromosome in infertile Chinese men: a five-year retrospective analysis // Zhonghua Nan Ke Xue. - 2010. - N16. - P. 314-319.*
19. *Simoni M., Bakker E., Krausz C. EAA/EMQN best practice guidelines for molecular diagnosis of Y-chromosomal microdeletions // Int J Androl. - 2004. - N27. - C. 240-249*
20. *Skakkebaek N.E., Giwercman A., de Kretser D. Patogenesis and management of male infertility //Lancet. - 1994. - Vol. 3436. N8911. - P. 1473-1479*
21. *Spira A. Epidemiology of human reproduction// Hum. Reprod.- 1986.- P.111-115.*
22. *Tiepolo L., Zuffardi O. Localisation of factors controlling spermatogenesis in the non fluorescent portion of the human Y-chromosome long arm // Hum. Genet. - 1976. - Vol. 34. - P. 119-124*
23. *Van Golde R.J. Decreased fertilization rate and embryo quality after ICSI in oligozoospermic men with microdeletios in the azoospermia factor region of the Y chromosome// Hum.Reprod. – 2001. -№2 .-P.289-292.*
24. *Vogt PH, Edelmann A, Kirsch S, Henegariu O, Hirschmann P, et al. (1996) Human Y chromosome azoospermia factors (AZF) mapped to different subregions in Yq11// HumMolGenet. - 1996. - N5. - P. 933-943*
25. *Vollrath D.The Human Y chromosome:a 43-interval map based on naturally occurring deletions// Science. – 1992. - P.52-59.*
26. *Wang R.X., Fu C., Yang Y.P., Han R.R., Dong Y., Dai R.L., Liu R.Z. Male infertility in China: laboratory finding for AZF microdeletions and chromosomal abnormalities in infertile men from Northeastern China // J Assist Reprod Genet. - 2010. N27. - P. 391-396*
27. *WHO laboratory manual for the examination of human semen and sperm-cervical mucus interaction. Third edition//World Health Organization .-2017. – P.44.*
28. *Wong E.Y., Tse J.Y., Yao K.M., Lui V.C., Tam P.C., et al. Identification and characterization of human VCY2-interacting protein: VCY2IP-1, a microtubule-associated protein-like protein // Biol Reprod. - 2004. - N70. - P. 775-784*