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REVIEW ARTICLE

Effects of Y chromosome Microdeletions on Male Fertility

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Abstract: **Background:** In the process of human reproduction, spermatogenesis is one of the most important stages, which is controled by special genes on Y chromosome. Previous studies show that some infertile men have microdeletions on Y chromosome, which cause the reduction of sperm count. Three prominent spermatogenesis loci have been identified on the Y chromosome and entitled "azoospermia factors" (AZFa, b, and c). Hereby, this review article aimed to investigate the content of the Y chromosome microdeletions and their importance in male fertility. **Methods:** Data and information were collected on English-language articles from PubMed and MEDLINE databases. For Persian articles, Persian-language databases, including SID Scientific Database, IranMedex Medical Articles Database, IranDoc (Iran Scientific Information and Documents Research Institute), Magiran Publication Information, and MedLib were investigated. More than 50 articles on Y chromosome microdeletions and infertility published during 2000-2020 were studied. **Results:** Previous studies implicated that Y chromosome microdeletions in AZFa, AZFb, and AZFc regions are accompanied by defect in spermatogenesis, leading to oligo / azoospermia. Patients with AZFa and AZFb microdeletions present secretory azoospermia and do not have sperm in their seminiferous tubules. Complete AZFc deletion involves region b2/b4, which contains a total of 12 genes. Incomplete deletion of AZFc includes b1/b3, b2/b3 and gr/gr. The most common of which are gr/gr. In men with gr/gr deletion, sperm count and motility were lower than control group. **Conclusion:** Y chromosomal microdeletions emerged as the most frequent structural chromosome anomaly associated with the quantitative reduction of sperm. The development of assisted reproductive techniques (ART) like intracytoplasmic sperm injection (ICSI) and testicular sperm extraction (TESE) helps to bypass the natural barriers of fertilization.

Keywords: Microdeletion; Y chromosome; Male Fertility; Azoospermia

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1. Introduction

Infertility is an important worldwide problem. According to the World Health Organization (WHO), if a couple does not have children within a year of unprotected sexual activity, they become infertile. About 15% of young couples do not have children in the first year and seek medical attention. One in eight couples in Europe needs help with their first pregnancy (1). Most global statistics show that almost half of the cases of infertility are related to abnormalities in sperm quality and quantity (2). In spermatozoa of infertile men, there is an increase in aneuploidy, structural chromosomal abnormalities, and DNA damage. In 30-40% of infertile men, there is no clear cause, and infertility may be caused by various environmental pollutants, oxygen-free radicals, and genetic and epigenetic abnormalities. The most important reasons for male infertility are as follows: 1- Congenital or acquired abnormalities of the genitourinary system, 2- malignancies, 3- Urogenital infections, 4- Scrotal fever (varicocele), 5- Endocrine disorders, 6- Genetic abnormalities, and 7- Immunological causes.

In a study of 10469 infertile people with a variety of causes, 11.2% of them had azoospermia (3), which means they

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lacked sperm in their semen (4). The causes of azoospermia can be classified as obstructive and non-obstructive. Obstructive azoospermia is defined as the absence of spermatozoa in the ejaculate despite normal spermatogenesis because of problems in the transfer of the sperm from the testicle to the ejaculatory duct of the urethra (5). Non-obstructive azoospermia is a heterogeneous disorder in which the testis cannot produce an adequate amount of sperm in the semen. Factors affecting non-obstructive azoospermia include genetic and environmental factors. The most important genetic factors include inherited hypothalamic-pituitary disorders, chromosomal abnormalities, microdeletions of the Y chromosome, polymorphisms, and gene mutations (6-8).

The long and short arms of Y chromosome have many genes. The region determining the male sex is located on the short arm, while the genes effective in spermatogenesis are located on the long arm. The identification and analysis of Y chromosome microdeletions (YCM) are very important for assessing and studying male infertility (9-11). YCM in the Yq11 region are effective in male infertility. This region is known as the azoospermia (AZF) region. The factors controlling spermatogenesis are located on the AZFa, AZFb, and AZFc on the long arm of the Y chromosome (12) (Figure 1). The genes in the AZF region code proteins that bind to RNA; these proteins are involved in gene expression, RNA metabolism, cytoplasm transfer, and RNA splicing (8, 9, 13). Deletions that occur in these areas can cause severe spermatogenic defects such as oligospermia and azoospermia. The reason for these deletions is the recombination between long bands of highly repetitive DNA sequences during meiosis (14). Each AZF region undergoes special stages in different stages of spermatogenesis (15, 16). Deletion of AZFa is associated with a complete lack of reproductive cells and Sertoli cell syndrome. Deletion of AZFb stops the growth of meiotic cells during the clearance phase and leads to the cessation of meiosis. AZFc deletions are associated with decreased sperm production or cessation of sperm maturation associated with low sperm count. Therefore, the deletions of any AZF region leads to specific phenotypes (17). Specific deletion of a gene, has only been reported in the AZFa region and belongs to the USP9Y gene. These studies suggest that USP9Y is likely to be a "good regulator" for sperm production (18). The highest frequency of YCM are seen in men with azoospermia (8-12%) and oligozoospermia (3-7%) (14). The most common AZF deletion is related to AZFc with (65-70%) followed by YCM from AZFb, AZFb+c, and AZFa+b+c (25-30%), and deletion of the AZFa region is rare (5%) (14). Deletion of "gr/gr" results in the deletion of half of the gene content. In the AZFc region, which increases the oligozoospermia by 2.5-8 times, deletion of gr/gr is a significant risk factor for impaired sperm production (19). It is worth noting that its phenotypic expression vary in different ethnic groups, so that in some groups, it has no effect on spermatogenesis (20). A significant proportion of sperm from men with complete removal of AZFc is nullisomic for chromosomes (21), which represents a potential risk for any child to develop X0 45, Turner syndrome, and other phenotypic abnormalities associated with sex chromosome mosaicism, including ambiguous genitalia (21). Despite this theoretical risk, infants born to fathers with Yq deletions are phenotypically normal (22).This may be due to reduced implantation rates and the possibility of spontaneous abortion of embryos with a 45 X0 karyotype. When ICSI is used in the presence of YCM, long-term follow-up of each baby boy is required according to their fertility status and sperm freezing at a young age can be considered for them. Therefore, assessing AZF deletions is important because it is possible that it would be transferred to the child (boy), especially when assisted reproductive technology (ART) is used (23).

Infertility and its individual and social problems are one of the most important issues for couples, and this is significant in that the cause of male infertility is detectable in only 40% of cases and in 60% of cases is not pathologically detectable (24).Therefore, infertility treatment is more difficult in men than in women. According to studies conducted in other countries and regions, it has been determined that the factors affecting male infertility are different in each region, and it is of special importance to study the effects of each (25). Currently, because of the widespread use of ART for infertile people, the study of AZF deletions becomes more important because the chances of transmitting deletions to the child increase. Therefore, small YCM are recommended in infertile patients with spermatogenesis defects, especially before the application of intracytoplasmic sperm injection (ICSI). Because the finding of genetic factors leading to infertility not only facilitates the transmission of genetic defects from parents to the offspring but also because it can lead to more extensive offsprings, genetic studies can provide the necessary information to the individual in the application of complementary methods for fertility. Therefore, studies to investigate the effective causes of male infertility are very valuable. In this study, the role of YCM in male fertility was investigated.

2. Methods

For this study, as a narrative review, information on English-language articles from PubMed and MEDLINE databases were collected. For Persian articles, Persian-language databases, including SID Scientific Database, IranMedex Medical Articles Database, IranDoc (Iran Scientific Information and Documents Research Institute), Magiran Publication Information, and MedLib were investigated. More than 50 articles on Y chromosome microdeletions and infertility published during 2000-2020 were studied. The keywords

searched in this study were: microdeletion, Y chromosome, DNA, sperm, and infertility. To select the documents, the titles of them were reviewed thematically using the search engine. Then, the titles of the articles were evaluated in terms of relevance to the subject and purpose and were studied after selecting the appropriate items. Findings and results which are related to the correlation between infertility in men and YCM obtained from 50 articles studied were analyzed as the main data of this study. The common results obtained from previous studies and their inferences are mentioned as part of the conclusion in this review article. In general, the steps are included: searching for resources, selecting content, determining keywords, categorizing content, summarizing, and concluding.

3. Results

3.1. The Prevalence of YCM

Previous studies revealed that the prevalence of YCM varies from 5 to 15% in men with azoospermia and between 2 and 5% in men with Oligospermia. Of course, the prevalence varies in different populations. Prevalence range is influenced by multiple agents, for example: The type of diagnostic method used can increase the number of false positive cases and sometimes a partial YCM is considered as complete YCM (26).

3.2. Types of YCM

The attendance of an obligatory spermatogenesis factor called azoospermia factor (AZF) was identified preliminary in 1976 from a de novo Yq deletions in azoospermia patients (27). Deletions of the Y chromosome areas that possess the AZF are discussed as the most common genetic imperfection in male infertility (28).

Three frequently deleted non-overlapping sub-regions in proximal, middle, and distal Yq11 were described and determined "AZFa," "AZFb," and "AZFc," respectively.

The AZFa and AZFb regions are necessary in beginning of spermatogenesis and the AZFc region is obligatory to complete this process. The important AZFb interval is essential for spermatocyte maturation. The AZFb locus is placed in the central region of Yq11. The AZFc is placed at the distal part of deletion interval 6 (subintervals 6C–6E) on the Y chromosome and is the most generally deleted zone of the AZF locus in infertile men. A special partial deletion of AZFc named gr/gr deletion is remarkably correlated with male infertility among Caucasians in Europe and the Western Pacific region (29).

3.3. The consequences of YCM

3.3.1. Azoospermia

The European association of urology (EAU) guideline reports a prevalence of microdeletion in men with azoospermia and infertility is 8 to 12%. In most cases, azoospermia and infertility occur in men with complete elimination of AZFa/b/ (30). Sperm extraction is almost always unsuccessful in these men, they are infertile and unable to reproduce with their sperm. The only choice for these patients is to use sperm or embryo donation to have a child. Of course, in several cases, there have been rare reports of sperm extraction from the testis in AZFb or AZFb-c, but no clinical or chemical pregnancy resulting from microinjection has been reported (31).

Complete deletion of AZFc may be associated with azoospermia. In these men, microscopic surgery is found in up to 50% of sperm cases and then used for microinjection (32).

3.3.2. Oligospermia

Preliminary Y chromosome microdeletion studies were divided into two categories:

1- Severe oligospermia (zero to five million per ml)

2-Oligospermia (more than five million per ml) (33)

Recent EAU and American society for reproductive medicine (ASRM) guidelines have reported a prevalence of early microdeletion in severe oligospermia of 3-7% and 5%, respectively.

Both of these guidelines recommend screening men with sperm counts less than five million per ml (7). Therefore, in cases of severe oligospermia, in addition to karyotype testing, AZF testing is required. Although YCM is present in men with oligospermia with more than five million sperm count, genetic testing is not recommended due to its high cost and low prevalence. A meta-analysis of 12,492 patients with oligospermia found that all cases of YCM occurred in men with AZFc (26). Thus, only AZFc deletion can give degrees of oligospermia and sometimes azoospermia, but AZFa and AZFb are associated with azoospermia only. In this study, the prevalence of AZFc in men with oligospermia was 0-1 mil/ml (5%) higher than 1-5 mil/ml (0.8%), and it was also higher than 5 mil/ml (0.5%).

Therefore, according to the above results, it can be concluded that most men with AZFc (5.8%) are in the group of severe oligospermia (less than 5 mill/ml) and it does not seem logical that for men with oligospermia more than 1 mill/ml request AZFc. This is in contrast to the EAU guideline, which recommends screening for AZF in men with severe oligospermia less than 5 mill/ml.

In men with oligospermia due to AZFc deletion, there is a possibility of natural fertility by the couple and it does not seem to have an effect on the formed fetus (14). Also in men with partial AZFb/AZFc, spermogram parameters may be normal or sperm count may decrease but they might be able to have normal fertility (34). At present, the data in the literature do not show an increase in the incidence of congenital anomalies or chromosomal abnormalities in offspring from Y chromosome microdeletion (34).

3.4. Inheritance of AZF to the male newborn

The Y chromosome contains a male-specific region (MSY: male specific region of Ychromosome) that is inherited from father to son during meiosis. Men with AZFa and AZFb are often infertile because they have azoospermia, and most cases of sperm extraction from the testicle fail, so there is no possibility of transmitting the disease to the son. Only if partial deletion occurs in this area in oligospermic men there is a possibility of transmitting the disease to the son (35).

Therefore, in men with incomplete AZFc deletion, it is recommended to undergo genetic counseling, and according to the recommendation of a geneticist and the consent of the couple, they can be candidates of ICSI with PGD. If they are azoosperm, sperm can be retrieved from micro TESE, if they have severe oligospermia in the semen itself, only the female embryos can be transferred and therefore the transmission of this microdeletion to male offspring will not occur. This process diminish the miscarriage and transmission of chromosomal microdeletion to the offspring, as well as prevent possible defects in the formed fetus.

3.5. Reduction of progressive spermatogenesis and the need for sperm freezing

Progressive reduction of sperm count has been shown in patients with AZFc deletion (28, 36). Sperm cryopreservation in men with AZFc deletion in early adolescence is a rational and practical choice for these individuals (34). The sperm can survive for up to 15 years after freezing, so if sperms are reduced or absent in patients with AZFcdeletion genetic disorder, frozen sperm can be used for ICSI.

3.6. YCM and ART outcome

Deletions of the AZFa, AZFb and AZFc regions are associated with abnormal spermatogenesis and although certain deletions have a detrimental effect on sperm retrieval, the majority of men with AZFc deletions have no problems during sperm retrieval for use in ART. However, men with these deletion(s) may optionally be subjected to further evaluations to determine the extent of the effects of such deletions (37).

The method of ICSI combined with sperm retrieval techniques such as testicular sperm extraction (TESE), can increase the fertility rate in men with Y chromosome microdeletions.

Mulhall et al. (1997) compared eight azoospermic men with AZFc deletions with 28 controls with normal Y chromosomes. All patients were treated with TESE and subsequent ICSI. While fertilization rates seemed to be lower in the AZFc deletion group compared to controls (36 versus 45%), there was no statistically significant difference. Pregnancy rates did not differ between the two groups (38). Van Golde et al. (2001) compared the success rate of 19 ICSI treatments in eight couples with AZFc microdeletions to a control group of 239 ICSI treatments in 107 couples. Ejaculated spermatozoa were used in both study groups. Although they found significantly lower fertilization rates (55 versus 71%, P, 0.01) and embryo scores in couples with AZFc microdeletions, overall pregnancy rates did not differ (39).

Choi et al. (2004) reported their experience with 17 men with different types of Y chromosome microdeletions. Consistent with previous reports, they were unable to obtain spermatozoa with TESE in men with complete deletion of AZFa or AZFb or AZFbc regions.

Spermatozoa were obtained from men with AZFc deficiencies and one with partial AZFb deficiency. Patients with Y chromosome microdeletions were studied in two groups depending on whether TESE or ejaculated spermatozoa was used. These were compared to matched controls. Although there was a tendency towards decreased fertilization and pregnancy rates, the differences were not statistically significant (40).

Overall, studies of ART outcome in patients with AZFc deletions suggest a tendency toward decreased fertilization rates but not a significant change in overall pregnancy and delivery rates compared to matched controls (38).

4. Discussion

Spermatogenesis is regulated by some of the genes on Y chromosome and autosome chromosomes. Among chromosomal abnormalities, sex chromosomal abnormalities were more reported in the azoospermia group, while autosomal abnormalities were more common in the oligospermia group (41). The Y chromosome is a target for increased genetic damage. It is reported that the risk of genetic damage to the Y chromosome increases due to the rapid division of reproductive cells during embryonic and pubertal life (42). YCM is an important factor in male infertility (43). About 15% of men with azoospermia and 10-15% of men with oligospermia have YCM. Moreover, since all genes on this chromosome are haploid, it seems that defects in one gene can lead to further defects even if that defect is completed by the presence of several copies on Y chromosome (42). Ethnic and regional differences are important factors in the diversity and prevalence of YCM. Phenotypic differences created by deletions of AZF regions can be due to different environmental influences. The results of studies over the past decade have shown that most Y chromosome deletions in the AZFc region occur in 60% of men with infertility (43, 44). In one study, more than 80% of deletions were observed in the AZFc region and the rest in the AZFb region, and no deletions were observed in the AZFa region (45). A recent study showed that AZFc deletion leads to severe azoospermia or oligospermia (46). In another study, complete AZFb and AZFb+c deletions

led to azoospermia (47, 48). Most microparticles occur in the AZFc region and are associated with reduced sperm production to azoospermia (8, 27). The results show that in men with complete deletions in any of the AZFa, abc, and bc regions, sperm cannot be retrieved from the testis tissue, while 75% of testicular sperm extraction (TESE) cases have been successful when only the c region was deleted (14).
Also, in a study on infertile men with azoospermia, the highest YCM were reported in the AZFb region with a frequency of 66.67% and in the AZFc region with a frequency of 41.67% (12). In contrast, no significant deletions in AZF were reported on the Y chromosome of infertile men (9, 27). On the other hand, in another study on 97 infertile men, no chromosome Y microdeletions were seen (49). Some studies have reported AZFc microdeletions in 5% of men, and the total number of microdeletions were reported to be very low (37, 50).
This difference in the frequency of deletions and deleted points in different studies may be due to genetic differences in different populations. In addition, the number of patients studied, how to select patients according to the severity of sperm disorder, etiology of spermatogenesis, and climatic differences are effective factors. Moreover, the different primers used in different studies can be effective in assessing chromosomal microdeletions and the various reported frequencies (51). According to the results of recent studies, many cases of azoospermia and non-obstructive oligospermia have a genetic origin. Therefore, it is recommended that male offspring of men with AZF deletions undergo andrological examinations due to the progressive negative effect of YCM on sperm production during puberty and preserve their sperm at younger ages before being further damaged (40). However, these microdeletions cannot be predicted and identified by clinical findings, age analysis, and cytological methods. PCR methods based on the identification of Y chromosome microdeletions are required for better diagnosis and patient management (39). According to previous studies and since the rate of YCM increases with spermatogenesis defects, these microdeletions can be the main
.

5. Conclusion

The detection of microdeletions in the AZF region is significant from a diagnostic viewpoint. Deletions of the AZFa, AZFb and AZFc regions are associated with abnormal spermatogenesis and although certain deletions have a detrimental effect on sperm retrieval, the majority of men with AZFc deletions have no problems during sperm retrieval for use in ART. In people with AZFa and b deletion, surgery is not recommend, and for people with AZFc, it is recommended to freeze sperm. Spermatozoa can be preserved by storing and freezing to prevent invasive procedures such as TESE/ICSI in the future.

6. Appendix

6.1. Acknowledgment

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6.2. Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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None.

6.4. Author's contributions

All the authors have the same contribution.

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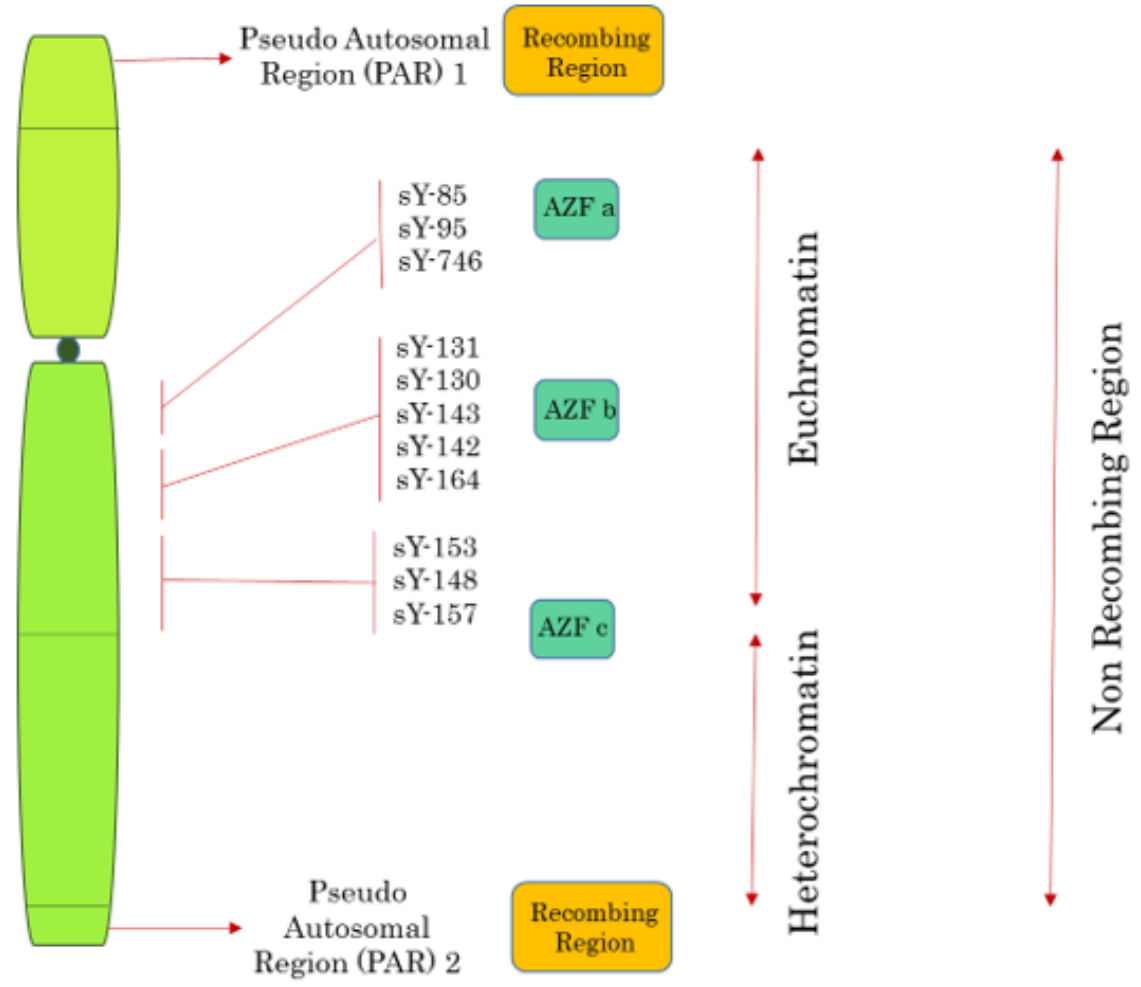

Figure 1: The human Y-chromosome.