African Journal of Advanced Pure and Applied Sciences (AJAPAS)
Online ISSN: 2957-644X
Volume 4, Issue 1, January - March 2025
Page No: 36-40
Website: https://aaasjournals.com/index.php/ajapas/index
ISI 2024: 0.877 SJIFactor 2024: 6.752 معامل التأثير العربي: 1.62

Impact of Chromosomal Aberrations on Infertility: Diagnosis, Management, and Assisted Reproductive Technologies

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تأثير الانحرافات الكروموسومية على العقم: التشخيص والإدارة وتقنيات الإنجاب المساعدة

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Received: November 14, 2024	Accepted: January 05, 2025	Published: January 12, 2025

Abstract:
Chromosomal polymorphisms may be linked to infertility since they are more common among infertile couples However, their exact impact on reproduction, particularly when assisted reproductive technologies (ART) are used, remains unclear. This review article aims to explore infertility related to chromosomal aberrations and discuss the techniques that are used for diagnosis. Most faulty oocytes exhibit numerical abnormalities (monosomy, trisomy), while most abnormal spermatozoa show structural defects (translocations, inversions, deletions, and duplications). These differences in defect types lead to aneuploidy, miscarriages, and infertility. Azoospermia, oligospermia, and gonadal dysgenesis are indicators of spermatogenic failure and characteristic features of male chromosomal infertility. Additionally, factors affecting ovarian development, oocyte maturation, fertilization competence, pre-implantation embryo development, implantation, and fetal support are key contributors to female infertility. Performing a karyotype before beginning any in vitro fertilization (IVF) procedure is advisable, as it helps reduce the risk of procedural failure. The review also emphasizes the importance of understanding specific chromosomal abnormalities in infertile individuals, which can lead to more personalized treatment approaches. Tailoring treatments may potentially improve the success rates of assisted reproductive technologies and reduce the risk of miscarriages and genetic disorders in offspring. This highlights the critical role of genetic counseling and advanced diagnostic techniques in managing infertility and achieving better reproductive outcomes.
Keywords: Sterility, Abnormalities, Aberrations, Assisted Reproductive Technologies, Miscarriage, Pre-Implantation Genetic Testing, Genetic Counseling.

الملخص
قد ترتبط تعددات الأشكال الكروموسومية بالعقم لأنها أكثر شيوعًا بين الأزواج المصابين بالعقم ومع ذلك، فإن تأثيرها الدقيق على التكاثر، وخاصة عند استخدام تقنيات الإنجاب المساعد (ART)، لا يزال غير واضح. تهدف مقالة المراجعة هذه إلى استكشاف العقم المرتبط بالانحرافات الكروموسومية ومناقشة التقنيات المستخدمة للتشخيص. تظهر معظم البويضات المعيبة تشوهات عددية (أحادية الصبغي، ثلاثية الصبغي)، في حين تظهر معظم الحيوانات المنوية غير الطبيعية عيوبًا هيكلية (انتقالات، وانعكاسات، وحذف، وتضاعف). تؤدي هذه الاختلافات في أنواع العيوب إلى اختلال الصيغة الصبغية والإجهاض والعقم. تعد انعدام الحيوانات المنوية وقلة الحيوانات المنوية وخلل تكون الغدد التناسلية مؤشرات على فشل تكوين الحيوانات المنوية والسمات المميزة للعقم الكروموسومي الذكري. بالإضافة إلى ذلك، فإن العوامل التي تؤثر على نمو المبيض، ونضج البويضة، وكفاءة الإخصاب، ونمو الجنين قبل الزرع، والزرع، ودعم الجنين هي عوامل رئيسية تساهم في العقم عند النساء. يُنصح بإجراء النمط النووي قبل البدء في أي إجراء للتلقيح الصناعي (IVF)، لأنه يساعد في تقليل مخاطر فشل الإجراء. كما تؤكد المراجعة على أهمية فهم التشوهات الكروموسومية المحددة لدى الأفراد المصابين بالعقم، مما قد يؤدي إلى طرق

علاج أكثر تخصيصًا. قد يؤدي تصميم العلاجات إلى تحسين معدلات نجاح تقنيات الإنجاب المساعدة وتقليل مخاطر الإجهاض والاضطرابات الوراثية في النسل. يسلط هذا الضوء على الدور الحاسم للاستشارة الوراثية وتقنيات التشخيص المتقدمة في إدارة العقم وتحقيق نتائج إنجابية أفضل.
الكلمات المفتاحية: العقم، التشوهات، الانحرافات، تقنيات الإنجاب المساعد، الإجهاض، الاختبار الجيني قبل الزرع، الاستشارة الوراثية.

Introduction

Normal chromosomes (euploid) in eggs and sperm are required for conception, implantation, and term delivery of developmentally healthy children. A morphological or numerical change in one or more chromosomes affecting the autosomes, sex chromosomes, or both is known as a chromosomal aberration. Oocytes and sperm undergo rather different processes during gametogenesis, which is the process of making gametes. The majority of oocytes are chromosomally aneuploid, suggesting that oocytes are the source of chromosomal abnormalities in miscarried and premature infants. However, the majority of structural abnormalities originate from sperm. There are more chromosomal abnormalities because aging females have a longer meiotic time [1]. Furthermore, the most common chromosomal losses are monosomy 45, X (known as Turner syndrome), and chromosome growth trisomy XXY (known as Klinefelter syndrome). In contrast, only a small number of chromosomes (13, 18, 21, X, and Y) can survive to term in a trisomy state, such as 47, XX21, or 47, XY21 Down syndrome. Human developmental disorders and pregnancy loss are most commonly caused by chromosomal aneuploidy [2].

Material and methods

This study adopted the qualitative method by inductive approaches, dependent upon the secondary sources and published resources related to impact of chromosomal aberrations on infertility. Science Direct, PubMed, SCOPUS, and Google Scholar were used as sources of information that were searched up to 2024.

Results and discussion

This study includes 30 studies and the primary findings are summarized below:

Meiotic and mitotic errors

Human gametes have defective chromosomes in a shockingly high percentage (21% of oocytes and 9% of spermatozoa). Chromosome segregation and recombination mistakes in gametes occur during meiosis, whereas mitotic errors occur in postzygotes [3]. The meiotic processes first associated with non-disjunction in infertile males were synapsis and recombination [4]. After fertilization, however, some defects may develop in somatic cells, resulting in mosaicism, in which some cells display the abnormalities while other cells do not [5]. Over 50% of blastocysts, however, have blast genes with various chromosomal compositions. To some extent, early divisions at mitosis can indicate the probability that an embryo will progress to the blastocyst stage, which correlates with aneuploidy [6]. Thus, human gametes and autosome aneuploidy are caused by flaws in the acentrosomal meiotic spindle's structure.

Female infertility

At least 35% of all cases of infertility are due to female variables alone, which include a variety of factors impacting ovarian development, oocyte maturation, fertilization competence, and the capability of an egg that is fertilized prior to implantation growth, implantation of eggs, and fetal growth. A rapid loss of primordial oocytes during the development of female fetuses is linked to visible deletions, duplications of genes, and balanced and unbalanced X-autosome rearrangements; this causes streak gonads at birth. Germ cell loss may be primarily caused by structural X chromosome defects rather than gene-specific problems [7]. X-linked genes in humans are connected to a particular phenotype, and many X-linked genes are thought to have male-lethal pathogenic mutations, mosaicism, infertility, and repeated miscarriage [8]. A study was performed on a large group of premature ovarian failure (POF) patients, and it identified 27 chromosomal abnormalities associated with POF. Moreover, it is assessed that there is a higher frequency of X chromosome aneuploidy in POF patients than in the general population group, in particular an increased rate of X chromosome loss observed by Flourecence In Siute Hyberdization (FISH) on interphase nuclei [9]. Patients with polycystic ovary syndrome (PCOS) have been linked to cellular structural disturbances and chromosomal X mutations [10]. As a result of many studies, sterile females are associated with chromosomal abnormalities.

Male infertility

There have been reports of various chromosomal abnormalities, single-gene, and polygenic connections with deficiencies in the male factor. These flaws show up as infertility-causing sperm quantity or quality abnormalities. Nonetheless, the genetic cause of male infertility is still unknown in over 40% of cases. Comprehending the underlying genetic elements is essential for proficient patient care and counseling [11]. Accounts for

approximately genetic causes are responsible for approximately 15% of infertility in men [12]. A fetus with several malformations, the birth of an infant with birth defects, or spontaneous abortion are all possible outcomes for inversion carriers who create aberrant gametes, which can result in partial duplication or deletion of the embryonic chromosomes 46, XX, inv (10) (p13q22), and inv (10) (q21.2q22.1) [13]. Male chromosomal infertility is notable for having spermatogenic failure, which is indicated by azoospermia, oligospermia, and gonadal dysgenesis [14]. Males who have structural or numerical karyotype anomalies are also more likely to produce aneuploid sperm, especially with the chromosomal causes of Y chromosomal microdeletions, morphological and numerical karyotype anomalies, and male infertility with Klinefelter syndrome and with the 46, XX disorders of sex development (DSD) syndrome [15]. Gene deletions in the AZF areas lead to Y chromosomal sterility. Sertoli cell-only syndrome is a common presenting symptom for men with deletions in the AZFa region, which are frequently the most severe [16]. Balanced translocations, Robinson translocation (ROB), and reciprocal translocation (RCT) are physically normal adults who appear to have reproductive problems, recurrent abortions, and the delivery of infants with chromosomal abnormalities. Male (ROB) t (13; 14) (q10; q10) carriers may experience infertility issues and abnormal semen analysis [17]. The importance of duplication in male infertility and severe testicular abnormalities associated with 19p13.3 [18]. Therefore, chromosomal structure in males plays a role in the emergence of recurrent abortions and sterility.

Implantation genetic diagnosis (PGD) methods

Since its initial application in 1990 to sex embryos by Handyside et al. in the United Kingdom, pre-implantation genetic testing, or PGT, has been carried out all over the world. Blastocyst biopsy (trophectoderm; TE biopsy) became commonplace in 2012; however, cleavage stage embryo biopsy and fluorescent in situ hybridization (FISH) remained the norm until around 2010. Furthermore, next-generation sequencing (NGS), which is utilized all over the world, was developed from array comparative genomic hybridization (aCGH), which was employed for analysis [19]. PGT is a multi-step process that necessitates tight coordination between gyneologists, specialists in assisted reproduction, embryologists, and specialists in germ cell micromanipulation and embryo biopsy, and geneticists, specialists in single-cell genetic analysis [20]. A number of crucial procedures are involved in preimplantation genetic diagnosis (PGD), which is usually incorporated into the in vitro fertilization (IVF) procedure. An overview of the procedures is provided below:

1. Biopsy techniques for preimplantation genetic testing (PGT)

Three distinct cell types may be subjected to PGT during pre-implantation development: (i) polar bodies (PBs) (Figure 1), (ii) blastomere(s) from cleavage-stage embryos (Figure 2), and (iii) blastocyst from zygote (Figure 3) [21]. Less than 50% of spontaneously conceived human embryos are capable of developing to term, even in the event of a successful pregnancy. Chromosomal aneuploidy is one of the most important causes contributing to this high rate of embryo loss, while there are other variables as well [22].

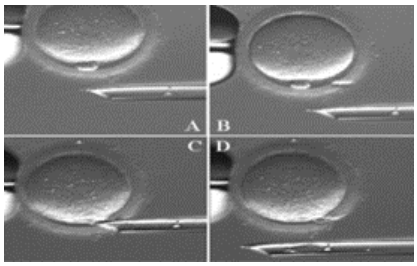

Figure (1) Polar Body Biobsy: First polar boday (PB) biopsy (A) PB was kept at 6 O' clock. (B) Zona pellucida dissection with three laser impacts. (C) PB extrusion. (D) PB in micropipette, [23]

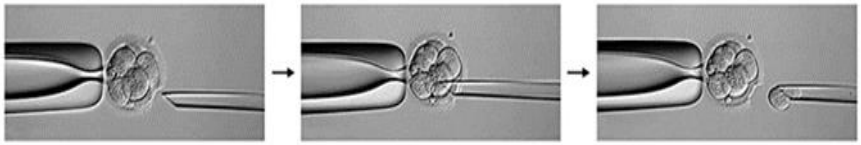

Figure (2) Blastomere biopsy (day 3), [24]

Figure (3) Blastocyst biopsy (days 5-6), [24]

2. Pre-implantation genetic testing (PGT) technologies and applications

(PGT) was first known as preimplantation genetic screening (PGS) and pre-implantation genetic diagnostic (PGD). It is advised that patients with reproductive problems brought on by advanced maternal age, chromosomal abnormality carrier status, or pathogenic variant(s) carry out preimplantation genetic testing (PGT) in order to maximize the likelihood of a healthy live birth and prevent the delivery of possibly harmed offspring. PGT is now divided into three categories: (i) PGT for aneuploidies, (PGT-A), (ii) PGT for monogenic/single-gene abnormalities (PGT-M), and (iii) PGT for chromosomal structural rearrangements (PGT-SR) [25]. PGT-A techniques, such as FISH, have their roots in the development of the first tools for the genetic study of embryonic cells in the 1990s. It uses chromosome-specific probes to find the copy number of a given chromosome or specific chromosomal areas within the nucleus. It is mostly used to test for common chromosomal aneuploidies including chromosomes 13, 18, 21, X, and Y. Different fluorochromes can be used to label individual probes, making it possible to see different chromosomal targets within the same nucleus at the same time [26]. FISH-based PGT-A cannot identify mosaicism; however, TE biopsies using next-generation technologies, like NGS or CGH, have demonstrated a high mosaicism identification rate [27].

PGT-M techniques are to avoid transferring embryos affected by a specific monogenic disease; a multiplex PCR can be used to identify both the mutation and genetic markers in the case of target amplification. Single nucleotide polymorphism (SNP) arrays, multiplex PCR, and NGS are available methods for whole-genome amplification. The foundation of all these methods is the concept of haplotyping, which selects informative markers (SNPs or STRs) and uses their segregation with the mutation to identify the risk-related haplotype associated with the mutation. Using this method aids in identifying if the embryo has inherited the wild-type gene or the risk allele. In contrast, as it is not possible to phase out the at-risk haplotype, it is not recommended in cases of significant gene deletions/duplications or de novo triplet expansions [28]. As PGT-SR, a number of techniques are used, such as FISH, aCGH, and NGS. A preclinical setting is not necessary for this kind of genetic testing, which is primarily carried out on embryonic biopsies taken at the cleavage or blastocyst stage [29].

3. Genetic counseling and repreductive manegment

The PGT requests are assessed by a multidisciplinary team, and when further guidance is required, experts are consulted. The local ethics boards may also review the PGT requests. Comprehensive genetic and reproductive counseling is necessary prior to initiating a clinical cycle. Psychological assistance can be given at any stage of the process. The various facets of the PGT treatment are explained to the couples, including the likelihood of a misdiagnosis and typical success rates. Informed permission for the embryo selection process via PGT is requested to be signed by the future parent(s). Information about the procedure, the possibility of a false-negative diagnosis, possible dangers from transferring chromosomally mosaic embryos, recommendations for prenatal testing after PGT, and concerns about what to do with embryos that are not genetically transferable should all be included in the informed consent form [30].

Conclusion

The majority of chromosomal abnormalities, which result from meiotic and mitotic mistakes during gamete development and fetal growth, arise spontaneously and cannot be cured. As a result of meiosis errors, fetuses can be miscarried, abnormal, or infertile. Due to numerical chromosomal polymorphisms (monosomy, trisomy) or structural chromosomal polymorphisms (translocations, deletion, inversion, duplication) of gametes, which result in aneuploid fetuses The standard chromosomal analysis (karyotype) should be taken into consideration as a crucial diagnostic step in the evaluation of infertility. Genetic counseling is an important step to educate those who have a hereditary condition or are at high risk of of passing one to their offspring, especially women over 35 years old. Therefore, Counselors provide information on the progression of genetic conditions, potential treatments, and reproductive options.

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