Medical Science

Male infertility - causes, diagnostics, and treatment options review

Szymon Bienia[1*], **Sara Hassan**[1], **Aisha Hassan**[2], **Kamil Hassan**[3], **Klaudia Konieczna**[4], **Wafa Al-Batool**[5], **Izabela Zarecka**[5], **Jakub Leicht**[2], **Aleksandra Kossakowska**[2], **Paweł Godlewski**[2]

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Authors' Affiliation:
[1]Medical University of Silesia, 18 Medyków Street, 40-752 Katowice, Poland
[2]Cardinal Stefan Wyszyński University in Warsaw, Wóycickiego 1/3, 01-938 Warsaw, Poland
[3]Social Academy of Sciences in Łódź, Henryka Sienkiewicza 9, 90-113 Łódź, Poland
[4]Medical University of Silesia, Dr. Henryka Jordana 19, 41-808 Zabrze, Poland
[5]Wroclaw Medical University, wyb. Ludwika Pasteura 1, 50-367 Wrocław, Poland

[*]**Corresponding Author**
Medical University of Silesia, 18 Medyków Street, 40-752 Katowice, Poland
Email: szymonbienia1@gmail.com
ORCID: 0009-0000-7632-5125

Contact List

Szymon Bienia	szymonbienia1@gmail.com
Sara Hassan	sara.hassan2605@gmail.com
Aisha Hassan	114039@student.uksw.edu.pl
Kamil Hassan	hassimma99@gmail.com
Klaudia Konieczna	klodika01@gmail.com
Wafa Al-Batool	szafahebanowa@gmail.com
Izabela Zarecka	zareckaaizaa@gmail.com
Jakub Leicht	jakubleicht@icloud.com
Aleksandra Kossakowska	kossakowska.aleksandra00@gmail.com
Paweł Godlewski	p.godlewski@student.uksw.edu.pl

ORCID List

Szymon Bienia	0009-0000-7632-5125
Sara Hassan	0009-0009-3297-8250
Aisha Hassan	0009-0001-5078-7724
Kamil Hassan	0009-0008-3207-4836
Klaudia Konieczna	0009-0008-4729-9798
Wafa Al-Batool	0009-0002-8666-5400
Izabela Zarecka	0009-0000-1376-4040
Jakub Leicht	0009-0000-8512-2776
Aleksandra Kossakowska	0009-0003-5338-0182
Paweł Godlewski	0009-0004-9935-4091

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ABSTRACT

Male infertility is a complicated problem that often poses a challenge to couples trying to conceive. Its causes may be very diverse and may result from genetic or environmental factors such as excess stress, obesity, and smoking. Moreover, infertility may be caused by structural changes or abnormalities in the functioning of the endocrine system. Biomarkers, genetic tests, and AI can all be used to improve semen analysis to help doctors make better evaluations and ensure that each patient gets the best care. This research talks about drug, surgery, and assisted reproductive technology treatments for male infertility problems. Medicines fix hormonal abnormalities and microelement deficiency. More invasive procedures such as TESA, PESA, TESE, and MESA can help with obstructive azoospermia. Doctors can cure structural problems with surgical techniques, such as varicocelectomy and vasovasostomy, including effect removal from past vasectomies. Men facing difficulties with conception can explore fertility options like in vitro fertilization (IVF), intrauterine ultrasonic (IUI), and intracytoplasmic sperm injection (ICSI) when other family planning approaches fail. The medical background of the patient, the cause of their infertility, and their intended results define most of the degree of efficacy of the treatment. Further research is required to consider the ethical and social consequences and possible applications of artificial intelligence in reproductive medicine. A thorough, patient-centered approach helps couples trying to conceive and those dealing with male infertility benefit from therapy.

Keywords: Male infertility, hormonal imbalance, reproductive health, sperm retrieval techniques

DISCOVERY SCIENTIFIC SOCIETY

1. INTRODUCTION

Male infertility is a significant health concern globally, impacting approximately 7% of men around the world (Krausz and Riera-Escamilla, 2018). In about 40-50% of infertile couples, male factors are either the sole (only) cause (~20%) or contribute to infertility (Attaman et al., 2012). Researchers have linked the rising incidence of male infertility to factors such as environmental toxins Attaman et al., (2012) and also lifestyle changes, for instance, dietary modifications (Kaltsas et al., 2024). In addition to the physical consequences, male infertility can have profound effects on mental health. Men experiencing fertility problems experience low mood, depression, or low self-esteem, which in turn leads to a significant reduction in the quality of life (Biggs et al., 2024).

Moreover, fertility disorders also have a negative impact on couples, making it difficult for them to have intercourse and emotional connection (Greil et al., 2010). We created this work to evaluate various therapeutic methods for treating male infertility, focusing on assisted reproductive techniques such as intrauterine insemination (IUI), in vitro fertilization (IVF), and microsurgical procedures. After evaluating the advantages and disadvantages of various infertility treatment approaches, this work aims to highlight the most effective treatment methods from the point of view of both medicine and patients.

2. METHODOLOGY

Our review is written based on articles posted on open-access medical databases, such as PubMed. Keywords such as “Male infertility” and “Male infertility treatment” were used to search for suitable articles. We selected relevant articles based on abstracts that were published from January 1995 to August 2024. In our review, we looked for the most effective methods of treating male infertility, both pharmacological techniques and surgical procedures, taking into account the diagnostics leading to the selection of optimal treatment.

3. RESULT AND DISCUSSION

Definition of Male Infertility

Male infertility is characterized by the failure to conceive with a fertile partner after a minimum of one year of consistent, unprotected sexual activity. This condition can result from various factors, including decreased sperm quality, hormonal imbalances, or the complete absence of sperm in semen (Durairajanayagam et al., 2014). The World Health Organization (WHO) considers abnormalities in sperm characteristics, including count, movement, and shape, as indicators of infertility. A semen analysis showing a sperm concentration of less than 15 million sperm per milliliter or motility below 40% is typically classified as subfertile or infertile (Cooper et al., 2010). Male infertility can also result from azoospermia, where no sperm is present in the ejaculate, which can be due to blockages in the reproductive tract or problems with sperm production (Esteves et al., 2012).

Physiological Causes of Male Infertility

Congenital Structural Abnormalities of the Reproductive Organs

Congenital abnormalities in the reproductive organs are significant physiological causes of male infertility. Structural defects like cryptorchidism (undescended testes), hypospadias (a malformation of the urethra), and varicocele (enlarged veins in the scrotum) can disrupt sperm production and transportation. Cryptorchidism, in particular, affects the testes' ability to produce viable sperm due to their abnormal positioning, which can lead to testicular dysfunction if left untreated. Studies suggest that men with untreated cryptorchidism are at an increased risk of infertility because of the impaired maturation of sperm cells (Goel et al., 2015). Varicocele is one of the most often associated with infertility. As a result of this medical condition, the temperature of the scrotum may increase, resulting in oxidative stress in the testicles, which often results in a decrease in sperm quality (Naughton et al., 2001).

Hormonal Disorders

Hormonal imbalances are a leading cause of male infertility, as hormones regulate the production and maturation of sperm cells. Hypogonadotropic hypogonadism, a condition in which the pituitary gland does not secrete adequate levels of gonadotropins (LH and FSH), leads to low testosterone production and impaired spermatogenesis (Millar et al., 2021). This condition is often associated with genetic syndromes, such as Kallmann syndrome, where hormonal regulation is disrupted due to a deficiency in gonadotropin-releasing hormone (GnRH).

Primary hypogonadism, another hormonal cause, occurs when the testes themselves have dysfunctions, resulting in low testosterone and poor sperm production despite normal or elevated gonadotropin levels (Basaria, 2014). Hormonal imbalances may also arise from pituitary conditions, like prolactinomas, which are noncancerous tumors of the pituitary gland that secrete excess prolactin, leading to reduced libido, erectile dysfunction, and suppressed testosterone levels (De-Rosa et al., 2003).

Genetic Factors

Genetic abnormalities are another major cause of male infertility, especially chromosomal disorders that impair spermatogenesis. Klinefelter syndrome (47, XXY), a prevalent chromosomal abnormality in males, leads to small testes, reduced testosterone levels, and low sperm production or even azoospermia (Forti and Krausz, 1998). Males affected by Klinefelter syndrome often exhibit infertility as a primary symptom, and their sperm production capacity is usually limited due to an extra X chromosome.

Another example of a genetic cause of infertility is Y chromosome microdeletions, which affect critical regions involved in spermatogenesis. Research has indicated that microdeletions in the azoospermia factor (AZF) regions may result in reduced sperm count or a total lack of sperm in semen (Simoni et al., 2004). Changes in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, commonly linked to cystic fibrosis, can also lead to congenital bilateral absence of the vas deferens (CBAVD), resulting in azoospermia (Chillón et al., 1995).

Lifestyle and Environmental Factors Affecting Male Fertility

Lifestyle and environmental factors are now considered crucial in influencing male fertility. Phenomena such as chronic stress may lead to hormonal disorders, in particular, reduced testosterone levels and, consequently, impaired sperm production (Odetayo et al., 2024). Obesity has also been linked to altered hormonal profiles, with increased estrogen levels and decreased testosterone contributing to lower sperm quality and count (Katib, 2015). Smoking introduces oxidative stress and DNA damage in sperm, further reducing fertility potential (Walke et al., 2023). Studies indicate that consuming alcohol in excess can have a significant impact on lowering testosterone levels in med, in addition to damaging sperm DNA, thus hindering reproduction (Finelli et al., 2021). Environmental toxins like pesticides and heavy metals also disrupt endocrine function, reducing sperm motility and viability (Krzastek et al., 2020a).

Diagnostics options for male infertility

Studies prove that semen analysis (SA), together with biomarkers, should be the basic screening test in the diagnosis of male infertility. In addition, other tests may be performed at later stages, such as anti-sperm antibody (ASA) and DNA fragmentation testing, which may provide more information about the cause of infertility. DNA fragmentation tests help guide treatment options, including intracytoplasmic sperm injection (ICSI) or testicular sperm extraction for those with high DNA fragmentation. With advances in genetic research, genomics, including epigenetics, metabolomics, and proteomics, are being explored for more precise, cost-effective diagnostics and personalized treatment of male infertility (Krzastek et al., 2020b).

Proteins of Seminal Plasma can also help indicate the cause of infertility

In a study comparing seminal plasma proteins between vasectomized and normozoospermic men, 32 proteins unique to normozoospermic men were identified, mostly of testicular or epididymal origin. These potential obstructive and non-obstructive azoospermia biomarkers include DPEP3, ADAM7, PGK2, HIST1H2BA, HSPA4L, SPACA3, and GAPDHS. These proteins, involved in sperm maturation, motility, chromatin condensation, and sperm-oocyte interaction, highlight crucial aspects of sperm quality and development (Ješeta et al., 2023). Other causes of male infertility may be related to disorders of the endocrine system, and their diagnosis is based on measuring the levels of specific hormones in the blood, depending on the suspected cause.

Hypogonadotropic Hypogonadism (HH), often genetic, results from low gonadotropin levels, leading to reduced testosterone and fertility issues.

Hypergonadotropic Hypogonadism, primarily affecting testicular function, is characterized by elevated gonadotropin levels due to inadequate androgen production.

Androgen Excess, from either external testosterone sources or internal overproduction, suppresses spermatogenesis by disrupting hypothalamic signals.

Estrogen Excess, often resulting from obesity, reduces fertility through its inhibiting effect on the hypothalamic-pituitary-gonadal axis.

Hypothyroidism reduces testosterone and libido, impacting fertility, while Hyperprolactinemia, marked by high prolactin, impairs gonadotropin secretion and fertility.

Each of the abnormalities mentioned above disrupts the hormonal balance, providing an opportunity to increase fertility through the use of appropriate pharmacological therapy (Sengupta et al., 2021).

The evaluation of male infertility traditionally relies on conventional semen analysis, which has limited accuracy. Advancements in Artificial intelligence (AI) and machine learning (ML) enable improvements in this field, such as predicting sperm improvements post-surgery and assessing sperm motility. AI also enhances intracytoplasmic sperm injection (ICSI) by helping select optimal sperm and assessing morphology in real-time. However, challenges include inconsistent data, lack of standard protocols, regulatory hurdles, high costs, and ethical issues concerning patient care and equitable access. Although AI still requires significant development to be considered reliable, there is hope for a more objective and practical selection of therapies in the future (Gül et al., 2024).

Main methods of male infertility treatment

Pharmacological Treatment of Male Infertility

Hormonal Stimulation

Male infertility is a problem often resulting from hormonal abnormalities. One of the causes of these abnormalities is hypogonadism, where testosterone levels are reduced. In this case, doctors use hormone therapy with testosterone and GnRH analogs as first-line treatment. Testosterone replacement therapy (TRT) is typically prescribed to restore normal testosterone levels. However, while TRT helps alleviate symptoms of testosterone deficiency (such as fatigue and low libido), it does not directly improve spermatogenesis, as it can suppress the hypothalamic-pituitary-gonadal axis, which controls sperm production (Patel et al., 2019).

Men who have hypogonadotropic hypogonadism, a condition where there is inadequate secretion of gonadotropins, may benefit from treatment with pulsatile gonadotropin-releasing hormone (GnRH), which can help stimulate normal testicular function. GnRH analogs stimulate the release of LH (luteinizing hormone) and FSH (follicle-stimulating hormone), which directly enhance testicular function and promote spermatogenesis (De-Waal, 2004).

Aromatase Inhibitors and Antiestrogens

Aromatase inhibitors and antiestrogens are another therapeutic approach for male infertility. Aromatase inhibitors, like anastrozole, prevent the transformation of androgens to estrogens. Elevated estrogen levels can impair spermatogenesis, and by lowering estrogen, aromatase inhibitors can improve sperm count and motility in some men (Schlegel, 2012). Clomiphene citrate, an antiestrogen, is an alternative medication used to treat male reproductive dysfunction. It functions by inhibiting estrogen receptors in the hypothalamus, triggering the secretion of LH and FSH, which in turn enhances sperm production. Studies show that clomiphene can improve sperm count and motility in men with mild hypogonadism or unexplained infertility (Huijben et al., 2023).

Micronutrient and Vitamin Supplementation

Micronutrient deficiencies can negatively affect sperm quality. Zinc and selenium are vital for male fertility. Zinc is involved in testosterone synthesis and is a key antioxidant for sperm cells. Supplementing with zinc has increased sperm mobility in deficient men (Allouche-Fitoussi and Breitbart, 2020). Selenium is also essential for the proper movement of sperm and DNA integrity (Alahmar, 2023). Reduced sperm movement and low testosterone have been associated with vitamin D deficiency. Supplementing with vitamin D in deficient men can improve sperm function and overall fertility (Cito et al., 2020). In particular, studies associate vitamins C and E with sperm protection from oxidative stress, which can significantly improve its quality. Supplementation of these vitamins is additionally associated with increased sperm motility (Ahmadi et al., 2016).

Surgical treatment options

Vasovasostomy

One method of treating infertility is restoring the continuity of the vas deferens after a vasectomy, which is called vasovasostomy. Before performing the procedure, Doctors should conduct a thorough patient interview, a physical examination, and lab tests, including blood tests, to assess FSH and testosterone levels (Patel et al., 2016). The laboratory should also do semen analysis. The presence of sperm increases the likelihood of achieving the desired outcomes post-surgery (Herrel and Hsiao, 2013). Contemporary VV

anastomotic techniques include a modified one-layer and a multi-layer method. The one-layer uses full-thickness 9-0 Nylon sutures, while the multi-layer approximates mucosa first, then seromuscular layers (Patel et al., 2016).

Voricolectomy

Voricolectomy is a method mainly used to treat varicocele. New research indicates that physicians can also use it to treat non-obstructive azoospermia (NOA) as well as hypogonadism (Machen and Sandlow, 2019). However, the primary use of varicocelectomy is the treatment of varicocele. Varicoceles are found in 35% of men experiencing primary infertility and 75% of those with secondary infertility, while in general, the male population percentage varies around 15%.

The impact on spermatogenesis remains debated, but most men diagnosed with varicocele are fertile and mostly asymptomatic (Mehta and Goldstein, 2013). Meta-analyses show significant improvements in semen parameters and pregnancy rates post-surgery, with notable benefits in randomized trials. Conflicting evidence persists regarding varicoceles' progressive influence on testicular function and their role in non-obstructive azoospermia (NOA). Recent findings suggest varicocelectomy may help sperm recovery in some NOA cases. Overall, varicocelectomy benefits semen quality and pregnancy rates (Mehta and Goldstein, 2013).

Obstructive azoospermia treatment

Obstructive azoospermia is one of the major causes of male infertility. Caused by blockage in the male reproductive tract, results in no sperm in the ejaculate and accounts for about 40% of azoospermia cases. Blockages may be congenital (e.g., CBAVD, idiopathic epididymal obstruction) or acquired (e.g., vasectomy, infection, trauma, or iatrogenic injury) and affect the epididymis, vas deferens, or ejaculatory ducts (Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society for Male Reproduction and Urology, 2019). The treatment is mainly based on sperm retrieval from the testes (TESA) epididymis (PESA), as well as open techniques, including testicular sperm extraction (TESE) and microsurgical epididymal sperm aspiration (MESA) (Coward and Mills, 2017).

TESA (Testicular Sperm Aspiration)

TESA involves inserting a needle into the testicle to aspirate sperm cells directly from seminiferous tubules. It is also often used to check the presence of sperm in azoospermic patients. This method is minimally invasive and performed under local anesthesia, but compared to other surgical procedures, it provides a smaller amount of sperm.

PESA (Percutaneous Epididymal Sperm Aspiration)

PESA retrieves sperm from the epididymis using a needle to aspirate sperm, typically under local anesthesia. It is a simple, office-based technique providing motile sperm but may yield limited sperm quantity, and failure can require transitioning to another method like TESA.

TESE (Testicular Sperm Extraction)

TESE is a surgical method involving a small incision in the testicle to extract tissue containing sperm. It offers a high sperm retrieval success rate. It provides sperm for cryopreservation but requires more recovery time than needle-based techniques and may cause some testicular scarring.

MESA (Microsurgical Epididymal Sperm Aspiration)

MESA uses a microscope to retrieve high-quality motile sperm directly from the epididymis, ideal for cryopreservation. Although this technique yields high sperm numbers, it generally requires general anesthesia and specialized microsurgical skills, making it costlier and more complex than simpler aspiration methods.

Assisted Reproductive Technologies in Male Infertility

Intrauterine Insemination (IUI)

Intrauterine insemination is a method used on a broad scale, especially in cases of mild male infertility, e.g., in the case of low sperm count or reduced sperm motility. It involves directly inserting sperm into the uterus at the time of ovulation, which significantly

increases the probability of fertilizing a woman (Table 1). Doctors can also use it in cases of unexplained infertility or when cervical factors are suspected to interfere with conception (Duran et al., 2002). The procedure starts with sperm collection, which is then processed and concentrated in the laboratory to isolate the healthiest and most motile sperm.

The sperm is then injected into the uterus using a thin catheter, bypassing the cervix (ESHRE Capri Workshop Group, 2009). To improve success rates, IUI is often combined with ovulation induction using medications like clomiphene citrate or gonadotropins. The chances of achieving success with intrauterine insemination (IUI) differ based on factors like the female partner's age, sperm quality, and the underlying cause of infertility. Generally, pregnancy rates per cycle range from 10% to 20%, with younger women and those with mild male infertility typically experiencing higher success rates (Duran et al., 2002).

Table 1 Male Infertility Treatment Methods Overview

Treatment Method	Pros	Cons
Hormonal Stimulation	Restores hormonal balance and promotes spermatogenesis	May suppress natural sperm production
Aromatase Inhibitors and Antiestrogens	Improves sperm count and motility by reducing estrogen levels	Not effective for all patients, potential side effects
Micronutrient and Vitamin Supplementation	Enhances sperm quality and reduces oxidative stress	Limited impact without addressing the underlying cause of infertility
Vasovasostomy	Restores fertility after vasectomy with high success rates	Requires skilled surgical techniques; recovery time needed
Varicocelectomy	Improves semen parameters and pregnancy rates post-surgery	The effectiveness of testicular function remains debated
Obstructive Azoospermia Treatment	Retrieves sperm directly for use in assisted reproduction	Invasive procedures may result in limited sperm quantity
Intrauterine insemination (IUI)	Minimally invasive and cost-effective for mild infertility cases	Lower success rates compared to IVF or ICSI
In Vitro Fertilization (IVF)	High success rates for severe infertility issues	Expensive and potential risks to embryo development
Intracytoplasmic Sperm Injection (ICSI)	Enables fertilization even with a very low sperm count	Expensive and potential dangers to embryo development

In Vitro Fertilization (IVF)

In vitro fertilization (IVF) is a more advanced treatment for male infertility, often recommended when IUI fails despite multiple tries (Lai et al., 2024). IVF includes retrieving eggs from the female partner, fertilization with sperm in the laboratory, and embryo transfer into the uterus. The IVF process begins with ovarian stimulation to encourage the production of multiple eggs. After egg retrieval, technicians prepare the sperm in the laboratory, and fertilization occurs either by conventional insemination or through a more specialized technique like intracytoplasmic sperm injection (ICSI).

IVF allows for better control of over-fertilization and is often preferred when sperm abnormalities are severe or when sperm count is extremely low. The success of IVF depends on various factors, including the female partner's age, the quality of the eggs and sperm, and the health of the reproductive system (Choe and Shanks, 2023). IVF success rates vary between 30% and 40% per cycle, but outcomes are highly individualized (Wang and Sauer, 2006).

ICSI

The intracytoplasmic sperm injection (ICSI) technique is focusing on high-quality sperm selection. ICSI is a procedure where a single sperm is precisely injected into an egg, bypassing the natural barriers of the female reproductive system. However, ICSI is not without its drawbacks. In a situation where injection of sperm with reduced motility or quality occurs, it may negatively affect the development of the offspring. ICSI is performed by manually selecting sperm for injection into an oocyte, often using classic sperm selection

techniques like swim-up (SU) and DGC-density gradient centrifugation. SU isolates sperm based on their ability to swim upwards, while DGC separates them by density. Both methods are economical and straightforward but may not yield the best sperm quality or be effective for all samples.

Advanced techniques seek to improve sperm quality by targeting membrane characteristics or morphology. For example, magnetic-activated cell sorting (MACS) separates non-apoptotic sperm, and physiological ICSI (PICSI) uses hyaluronic acid to select mature sperm. Innovative methods like microfluidics also mimic natural selection pathways, using flow dynamics to improve selection accuracy, but remain costly and complex. While these techniques show promise, none is a definitive solution for optimizing ICSI outcomes. Each has advantages (such as simplicity or high-quality sperm yield) and disadvantages (like increased reactive oxygen species or high costs), indicating a need for further research to establish a gold-standard selection method in ART (Baldini et al., 2021).

Comparison of Male Infertility Treatment Methods

The treatment of male infertility includes many different approaches. For example, pharmacological and surgical treatment and assisted reproductive technologies (ART) are possible. When choosing a treatment option, it is necessary to know the basis of the infertility problem, the success rate, and the invasiveness of the procedures performed by the physicians.

Pharmacological Treatments

Doctors use pharmacological therapy when the cause of infertility is hormonal abnormalities. For instance, testosterone replacement therapy (TRT) addresses low testosterone but does not directly improve sperm production due to its suppressive effects on the hypothalamic-pituitary-gonadal axis. In contrast, Gonadotropin-releasing hormone (GnRH) analogs stimulate gonadotropins, enhancing testicular function and promoting spermatogenesis in cases of hypogonadotropic hypogonadism. Antiestrogens like clomiphene citrate are another choice; they block estrogen receptors, stimulating sperm production and improving sperm count and motility. Micronutrient supplementation, such as zinc, selenium, and vitamins C and E, also addresses deficiencies that impair sperm quality.

Surgical Treatments

When anatomical or physical blockages cause infertility, doctors often consider surgical treatment. Vasovasostomy is a reversal procedure for vasectomy patients involving the reconnection of the vas deferens. Another method, varicocelectomy, treats varicocele, where enlarged veins disrupt spermatogenesis. Though evidence on varicocele's impact on fertility remains debated, studies show improved semen quality and pregnancy rates post-surgery. For obstructive azoospermia, surgical sperm retrieval techniques like Testicular Sperm Aspiration (TESA) and Microsurgical Epididymal Sperm Aspiration (MESA) are used. These methods retrieve sperm directly from the testis or epididymis. Though some procedures, such as MESA, require general anesthesia and specialized skills, they yield higher-quality sperm.

Assisted Reproductive Technologies (ART)

ART procedures, including Intrauterine Insemination (IUI), In Vitro Fertilization (IVF), and Intracytoplasmic Sperm Injection (ICSI), are often used when pharmacological and surgical therapies fail. IUI involves placing sperm in the uterus during ovulation, increasing the chance of pregnancy when the problem is reduced sperm count or mobility. IVF, as a more complicated procedure, involves egg extraction and fertilization in the laboratory, where embryos are created and then implemented into the uterus. For men with severe infertility or notable abnormalities in semen quality, Intracytoplasmic Sperm Injection (ICSI) is often the most effective treatment.

4. CONCLUSION

Male infertility represents a complex and increasingly prevalent health issue, impacting approximately 7% of men globally and contributing significantly to couple infertility. The causes are multifaceted, encompassing physiological and genetic factors—such as structural abnormalities, hormonal imbalances, and genetic mutations—and lifestyle and environmental influences, including smoking, stress, obesity, alcohol consumption, and exposure to toxins. Taking into account that infertility is a complex issue that may have very different causes, diagnostics should begin with more screening tests, often providing an answer to what is the reason, such as semen

analysis, to more advanced methods, such as genetic testing, g to improve diagnostics precision. Treatment options are very diverse, from non-invasive pharmacological treatments through surgical methods to assisted reproductive technologies (ART).

When doctors choose pharmacological treatment, the goal is usually to correct abnormal levels of sex hormones and micronutrients, such as zinc and selenium, that support sperm health and motility. Surgical options, including varicocelectomy and vasovasostomy, are effective for structural issues like varicocele and vasectomy reversal, while sperm retrieval techniques (TESA, PESA, TESE, and MESA) provide solutions for men with obstructive azoospermia. For cases where pharmacological and surgical approaches fall short, ART methods like in vitro fertilization (IVF), intrauterine insemination (IUI), and intracytoplasmic sperm injection (ICSI) offer advanced reproductive solutions, particularly for severe cases of male infertility. Doctors should remember its key aspects when attempting to treat infertility. The cause of reproductive difficulties should determine the treatment method. Although many methods are effective, diagnostics and treatment availability remain problematic, and future research should focus on these areas.

Author's Contributions

Conceptualization: Szymon Bienia, Aisha Hassan
Methodology: Sara Hassan, Klaudia Konieczna
Formal analysis: Kamil Hassan, Wafa Al-Batool
Resources, data curation: Izabela Zarecka, Jakub Leicht
Investigation: Paweł Godlewski, Aleksandra Kossakowska
Writing – original draft: Szymon Bienia
Writing – review & editing: Aisha Hassan, Sara Hassan
All authors have read and agreed with the final, published version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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