Male Infertility

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Introduction

Infertility is defined by the WHO as the inability of a non-contracepting, sexually active couple to achieve pregnancy in 1 year, and it affects 15% of the couples in Western industrialized European countries [1]. The prevalence of primary infertility, to conceive a first child, affects one in eight couples, and that of secondary infertility (to conceive a subsequent child) affects one in six. A male-associated factor can be found in ~50% of infertile relationships, mostly in the form of abnormal semen parameters. Recent advances allow to father a child for those men who previously had no chance of this [2].

Main Medical Characteristics

The intact testicular function is essential for male health: production of testosterone and sperm. Spermatogenesis is regulated by the hypothalamic–pituitary–gonadal (HPG) axis: Gonadotropin-releasing hormone (GnRH) controls the anterior

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pituitary gland by secreting the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). LH regulates the function of testosterone production in the Leydig cells, while FSH regulates seminiferous tubule function, the spermatogenesis, which requires complex interactions between Sertoli cells, Leydig cells, and germ cells. The entire process to form elongated spermatids requires 74 days. After the spermatogenetic process, sperm mature and move toward collecting tubules to the storage and maturation area in the epididymis. The maturation process occurs in the epididymis and takes another 14 days. Vas deferens passes through the prostate gland where the sperm is mixed with additional fluid from the seminal vesicles. Sperm then enter the urethra by the ejaculation process. Obstructions or anatomical abnormalities along this pathway can also lead to male infertility.

A significant decreasing trend of the male fertility parameters can be observed in the last decades, theoretically due to gonadotoxic exposures; environmental conditions, toxins, and lifestyle factors (sedentary lifestyle, obesity, smoking, alcohol, etc.). In contrast, physical activity, reduced body weight, and reasonable diet will lead to the improvement of semen parameters and fertility. Quantitative and qualitative (globozoospermia and immotile cilia syndrome) spermatogenic impairment can have genetic, non-genetic, and presumed genetic causes. Genetic alterations [3] (Y chromosome microdeletions, sex chromosome anomalies: e.g., 47,XXY and 46,XX syndromes, partial androgen insensitivity, chromosomal structural anomalies: translocations and inversions) may result in male infertility. Congenital abnormalities can predict later sub/infertility and can enhance the risk of testicular malignancies (testicular dysgenesis syndrome). Endocrine disturbances (e.g., hypogonadisms and delayed puberty) and immunological factors (antisperm antibodies) are also well-known factors of male infertility. Anabolic and androgenic steroid abuse is an increasingly prominent cause of male factor infertility. Reduced male fertility can also be the result of acquired urogenital abnormalities (e.g., previous testicular torsion and previous surgery), infections of the urogenital tract, and increased scrotal temperature (e.g., as a consequence of varicocele). Malignancies (e.g., testicular tumors and hematological malignancies) can cause a major decrease in fertility. Sexual and ejaculatory dysfunctions are also relevant factors. Although a revolutionary improvement has been made in the past decade in both diagnostics and surgical treatment, ~25–30% of the male infertility cases remained idiopathic [4]. The effect of aging on male fertility is not completely clear [5]. Young men have spermatids present in 90% of seminiferous tubules, which decreases to 50% by the age of 50–70 and to 10% by the age of 80. Additionally, 50% of Sertoli cells are lost by the age of 50. In aging men, pregnancy rates are significantly lower, conception often takes longer, and the prevalence of congenital and genetic abnormalities in newborns is even higher (see Table 1).

Table 1 Male conditions, mechanism, and effects on male health

Medical condition	Mechanism	Effect
Environmental conditions, toxins, and lifestyle factors	Toxins, less physical activity, recreational drugs	Spermatogenic and/or sperm function defect
Genetic alterations	Sex chromosomal or autosomal diseases	Spermatogenic failure
Endocrine disturbances	Altered hormonal regulation	Central stimulatory problems, peripheral spermatogenic defect
Testicular maldescent	Testicular dysgenesis, Sertoli and Leydig cell dysfunction	Sub/infertility, hypogonadism, testicular cancer
Malignancies	Oncotherapies	Spermatogenic defect, DNA fragmentation
Acquired urogenital abnormalities	Testicular torsion, prostate surgery	Spermatogenic defect, ejaculatory problems
Infections	Oxidative stress	Sperm membrane damage, DNA fragmentation, sperm function problems
Immune infertility	Autoantibodies	Affected sperm motility, penetration defect
Anabolic and androgenic steroid use	Negative feedback	Spermatogenic impairment, endogenous testosterone production stop
Sexual and ejaculatory dysfunctions	Intercourse problems	Fertilization defect
Aging	Affected sperm function	Less pregnancy rates, higher rate of miscarriages, higher incidence of genetic problems in the offspring

Diagnosis

Medical Examination

First of all, an accurate **medical history** is essential, focusing in particular on lifestyle, any risky work activities, concomitant pathologies, interfering therapies on spermatogenesis, sexual development (if cryptorchidism, puberty disorders), erectile dysfunction, and if there are ejaculate changes in the last period; it is also important to investigate age and pathologies of the partner in order to establish the successive iter for the couple.

The **physical examination** consists of evaluation of BMI, scrotal palpation (testicular volume and consistency, epididymis, vas deferens, possible neoformations, and varicocele), and exclusion of penile malformations [6].

Semen Analysis

- **Spermiogram** is the diagnostic gold standard; it must be interpreted according to WHO 2010 reference values [7] (Table 2) and must be performed at least twice after 3 months, as the seminal parameters are subjected to variability over time.
- **Biological and Functional Tests**: They are second-level tests; the most used are the separation by gradients (to recover the most mobile spermatozoa, also in foresight of assisted fertilization techniques), the DNA fragmentation test (as a possible cause of fertility in the absence of other alterations of the seminal parameters or in case of repeated abortions) [8], the MAR test (to evaluate the presence of antibodies on the surface of the spermatozoon), and the eosin test (in case of immobility or severe asthenozoospermia, it evaluates vitality).
- **Other Examinations**: Based on the diagnostic question, culture tests of spermatic fluid or prostate secretion [9], serological tests, and search for spermatozoa in the urine may be required.

Hormone Levels

The study of hormonal profile is fundamental to assess the extent of testicular damage and if there are endocrine dysfunctions at the base [10].

- **FSH, LH, and total testosterone** are the first-level tests. FSH is the hormone that directly stimulates spermatogenesis, while LH mainly regulates the production of testosterone by the testicle. In the case of testicular insufficiency,

Table 2 Parameters for spermiogram

Parameter	Normal values	Meaning
Volume	>1.5 ml	If reduced (hypoplasia), there may be obstruction, retrograde ejaculation, or hypogonadism
Aspect	Grey-opalescent	If altered, there may be an infection or blood
pH	>7.2	It becomes acidic in case of obstruction of ejaculatory ducts
Viscosity	Normal	Increased if there is infection of the accessory glands
Agglutination	Absent	It is present if inflammation or antisperm antibodies
Leukocytes	$<1 \times 10^6$/ml	Increased if inflammation
Concentration	$>15 \times 10^6$/ml	Oligozoospermia is reduced sperm count per ml; in cryptozoospermia, spermatozoa are present only after centrifugation; azoospermia is the total absence of spermatozoa
Progressive motility	>32%	Asthenozoospermia is reduced sperm motility; akinesia is the complete immobility
Morphology	>4%	Teratozoospermia are the structural changes in the head, central part, or tail

there is often a profile of hypergonadotropic hypogonadism (increased LH and FSH, with reduced or still normal testosterone). Instead, in pre-testicular forms, there are reduced levels of both FSH, LH, and testosterone (hypogonadotropic hypogonadism).

- The assay of **free testosterone** is not currently a reliable method; however, it can be calculated using an equation between total testosterone, albumin, and SHBG.
- As second level, based on particular clinical or anamnestic data, it may be required the study of **metabolic profile** (diabetes mellitus), **thyroid function** (dysthyroidism), **PRL** (hyperprolactinemia), **estradiol** (estrogen-secreting tumors), or **other pituitary hormones** (in case of hypogonadotropic hypogonadism, it is indicated to differentiate isolated forms from multiple pituitary deficits).

Imaging Diagnostics

- **Scrotal ultrasound** [11] is helpful in identifying the main pathological patterns most frequently associated with male infertility: reduced testicular volume or hypoechoic structure (in case of hypogonadism, congenital, or acquired), inhomogeneous ecopattern (testicular tumors, ectasia of rete testis, and microlithiasis), cryptorchidism, enlarged or cystic epididymis (e.g., for epididymitis, traumatic outcomes or obstructive causes), agenesis, or dilation of the vas deferens. The visualization of the spermatic plexus in B mode also allows us to identify the presence of varicocele and the evaluation of the diameter of the intrafunicular sperm veins.

  Usually, the ultrasound study continues with the **color Doppler** investigation in search of spermatic venous refluxes of pathological significance, represented by the presence of basal spermatic venous reflux in orthostatism and/or prolonged response to the Valsalva maneuver [12]. Furthermore, the study of vascularization of the testicular pulp and epididymis is useful for the diagnosis of orchiepididymitis and testicular torsion.
- **Trans-rectal ultrasound (TRUS)** allows the study of the prostate and distal seminal pathways. In addition to excluding mono- or bilateral agenesis of the seminal vesicles, it serves to assess the presence of prostate–vesicular inflammations and to document any ectasias of the seminal vesicles and/or ejaculatory ducts, secondary to functional obstructive pathology, or conditioned by the presence of intraprostatic cysts (originated by Mullerian or Wolffian ducts). TRUS is not performed routinely, but only in case of hypoplasia or suspected inflammatory pathology.

Genetic Analysis

Genetic investigations are indicated in case of azoospermia or severe oligo-asthenoteratozoospermia [13].

- **Karyotype** can be already requested in case of sperm concentration less than ten million per ml, and it allows to highlight alterations of sex chromosomes (the most frequent is correlated with Klinefelter syndrome) or autosomal ones (translocations, etc.)
- Search for **microdeletions of the Y chromosome** is indicated in case of sperm concentration less than five million per ml; in particular, in the AZF region there are several genes involved in spermatogenesis.
- **Mutations of CFTR gene** (cystic fibrosis) are responsible for a condition of agenesis of the vas deferens or ejaculatory ducts (not detectable on physical examination); suspicion criteria may be also a seminal volume less than 1.5 ml and pH less than 7.

Finally, in the presence of documented alterations, adequate genetic counseling is important, also aimed at calculating any risk of transmission to the fetus.

Main Nonsurgical Treatments

Lifestyle

First of all, a healthy lifestyle should be observed [14]. Indeed, overweight, smoking, alcohol, use of anabolics or drugs, stressful conditions, and exposure to high temperatures (sauna, Turkish bath, and some jobs) can cause a significant decrease in fertility potential, which is reversible.

Nutraceutical

Supplements are often used in idiopathic infertility, after a complete diagnostic process, in the presence of documented alterations of seminal parameters and fragmentation of sperm DNA, and repeated failures with assisted reproduction techniques [15]. Their function is to reduce oxidative stress, which leads to a reduction in sperm quality, to supply the amino acids necessary for spermatogenesis, to regulate the mitochondrial energy metabolism or to improve viscosity. However, the evidence is low due to the lack of comparative studies between the individual molecules, their combinations, doses, and optimal duration of treatment. Furthermore, the potential side effects in case of overdose should not be ignored and the physiological oxidative stress necessary for the fertilization of the oocyte by the spermatozoa must not be completely inhibited [16].

The most commonly used active ingredients are listed as follows:

1. **Folic acid**—necessary for the integrity of sperm DNA.
2. **Arginine**—precursor of spermine and spermidic synthesis, antioxidant.
3. **Astaxanthin**—carotenoid that acts as membrane stabilizing, antioxidant.
4. **Carnitine**—essential for mitochondrial beta-oxidation, improves motility and concentration.

5. **Coenzyme Q10**—antioxidant and cofactor for mitochondrial transport chain, improves all parameters.
6. **Glutathione**—antioxidant, improves all parameters.
7. **Myo-Inositol**—FSH second messenger, regulates spermatogenesis and osmotic balance.
8. **N-Acetylcysteine**—mucolytic action, improves viscosity and motility, increases sperm volume.
9. **Selenium**—antioxidant, improves concentration and motility.
10. **Vitamin C**—antioxidant, improves concentration and motility.
11. **Vitamin E**—antioxidant, increases motility.
12. **Zinc**—antioxidant, stabilizes sperm chromatin.

Hormonal Therapy

An effective spermatogenesis requires the action of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Idiopathic Male Infertility

- **FSH therapy** (human or recombinant) can also be considered when there are normal levels of gonadotropins, as numerous data are in favor of an improvement of the seminal parameters in case of oligozoospermia, oligoasthenozoospermia, or high spermatic DNA fragmentation index [17]; on the other hand, a lack of response to treatment occurs when there are already high FSH levels. The most commonly used dosages are 150 IU subcutaneously or intramuscularly three times a week for 3 months.
- **Antiestrogens** (SERMs) increase the endogenous secretion of LH, FSH, and testosterone, as they block the negative feedback of estrogens on the hypothalamic–pituitary axis. Clomiphene 50 mg per day or tamoxifen 10 mg has been proven effective in increasing the pregnancy rate in case of idiopathic infertility; however, they are off-label in men, so they need the signature of the informed consent and their cost is total load of the patient.
- **Aromatase inhibitors** (letrozole, anastrozole) have a mechanism similar to SERMs, but their use is not currently recommended for a possible loss of bone mass [18].

Infertility Due to Hypogonadotropic Hypogonadism

- **Human chorionic gonadotropin** (hCG) has an action similar to LH. The dosage is 1500–2000 IU subcutaneously or intramuscularly three times a week for at least 6 months (dose and duration should be finalized to normalize testosterone levels). If after 6–9 months of therapy the patient still remains azoospermic or

severely oligozoospermic, FSH therapy should be added at a dose of 75–150 IU three times a week.
- **Pulsatile GnRH** can be considered in case of hypothalamic pathology. It is a subcutaneous hormone infusion pump that stimulates the release of gonadotropins (GnRh) every 2 h; the initial dose of 25 ng/kg can be increased up to 600 ng/kg, until normal testosterone levels are reached. This therapeutic option is severely limited by poor compliance and high costs.
- **Testosterone replacement therapy**, instead, is contraindicated in case of desire of paternity because it inhibits the release of FSH and LH.

Other Therapies

The following treatments are aimed at resolving specific causes [19].

Infertility Due to Post-Testicular Causes

- **Antibiotic therapy** is used in case of didymal, epididymal, or accessory glands infections; the choice is guided by semen culture or by cultural examination of expressed prostatic secretion when chronic bacterial prostatitis is suspected. Main antimicrobial agents usually include fluoroquinolones, macrolides, or tetracyclines [20].
- **Anti-inflammatory therapy** can be considered alone or in combination with antibiotics, in order to reduce symptoms of inflammation and oxidative stress, in case of the persistence of leukospermia or autoimmune forms. Belonging to this category, there are NSAIDs, cortisone, and phytotherapy with fibrinolytic and anti-edema action, such as escin or bromelain.

Infertility Due to Extra-Gonadic Hormonal Causes

- Hyperprolactinemias, dysthyroidisms, and diabetes mellitus require the specific pharmacological treatment prescribed by an endocrinologist or diabetologist.

Sexual Dysfunctions

The most commonly used drugs do not seem to interfere negatively on the seminal parameters [21].

- In the case of premature ejaculation, dapoxetine 30–60 mg on demand should be considered.
- For erectile dysfunction, PDE5 inhibitors are indicated in the oral form (sildenafil, tadalafil, vardenafil, and avanafil) or through intra-cavernous administration (alprostadil).

Surgical Treatments

Most important conditions in male infertility with surgical therapeutic consequences are schematized in Table 3.

Varicocele

Surgical correction (**varicocelectomy**) results in semen analysis improvement in ~75% of patients when indicated correctly; that is in the case of long infertile relation (minimally 1, but even 2 years), palpable varicoceles with oligozoospermia in younger male patients (age of the partner is also a significant influencing factor in order to optimize the cost/benefit ratio in infertility setting!). The microsurgical subinguinal approach is the gold standard treatment option to preserve the testicular artery and lymphatics. Then, laparoscopy or open surgical techniques using subinguinal or inguinal incisions are employed. In more countries, radiological interventions are also used for varicocele treatment [22].

Azoospermia

Obstructive Azoospermia

Absence of spermatozoa in the ejaculate despite normal spermatogenesis. Prevalence of OA accounts for ~10% of patients presenting for fertility evaluation. Testicular volume is usually normal with normal gonadotropin levels.

Table 3 Male infertility conditions and related effects on fertility

Disease	Definition	Effects on fertility
Varicocele	Dilated, tortuous veins of the pampiniform plexus in the spermatic cord, reported in about 15% of the fertile male population and ~40% of infertile males	Decreased testicular arterial blood flow, increased level of vasoconstrictor agents, temperature elevation. Decreased Leydig cell function may cause spermatogenetic defect and decreased sperm function
Azoospermia	Total absence of sperm in the ejaculate	Infertility
Obstructive azoospermia (OA)	Absence of spermatozoa in the ejaculate despite normal spermatogenesis—Testis volume is usually normal with normal gonadotropin levels	Reversible infertility
Non-obstructive azoospermia (NOA)	Spermatogenic failure due to either a lack of appropriate stimulation by gonadotropins or a testicular impairment (primary testicular failure), usually presents with low testicular volume and elevated FSH (except of hypogonadotropic hypogonadism)	Irreversible infertility, 50% chance of focal spermatogenesis

Table 4 Sites of obstructions and related treatment

Site of obstruction	Definition	Treatment
Rete testis	Sperms cannot enter the epididymis, loss of the maturation process	TESE
Epididymis	Due to infectious etiology	Tubulo-vasectomy, MESA, TESE
Vas deferens	Congenital uni/bilateral absence	MESA, TESE
Ejaculatory duct	Due to infectious etiology	TURED

Surgical treatment of obstructive azoospermia [23] (see also Table 4):

- Vasectomy reversal (vasovasostomy); after a vasectomy operation (mostly performed for birth control), microsurgical reconstruction of the vas deferens for fertility potential restoration.
- Tubulo-vasectomy; modern microsurgical reconstruction of congenital or post-inflammatory occlusions at the epididymal level. New anastomosis between one dilated epididymal tubule and the vas deferens to bypass the obstructed part of the seminal ways.
- Microsurgical epididymal sperm aspiration (MESA); in the case when microsurgical reconstruction is not possible or failed. Sperms from the epididymis can be used for in vitro fertilization with a higher success rate compared to testicular sperms.
- Testicular sperm extraction (TESE or testicular biopsy) [24]; in obstructive azoospermia TESE is applied to retrieve testicular sperm for assisted reproductive technique (intracytoplasmic sperm injection—ICSI). Indicated when reconstruction or MESA cannot be used or failed and can be performed also less invasively with percutan methods.
- Transurethral Resection of the Ejaculatory Duct (TURED) [25]; for the treatment of ejaculatory duct obstruction.

Non-obstructive Azoospermia (NOA)

A failure of spermatogenesis is caused by either a lack of appropriate stimulation by gonadotropins (usually primary or secondary hypogonadism) or a testicular impairment (primary testicular failure). Possible etiologies show a wide palette from genetic disorders or local testicular insults resulting in dysfunction of the hypothalamic–pituitary–testis axis. NOA is usually present with low testicular volume and elevated FSH (except of hypogonadotropic hypogonadism).

At about 50% of non-obstructive azoospermia cases, spermatogenesis may be focal; spermatozoa (or elongated spermatids) can be surgically found and used for assisted reproduction, intracytoplasmic sperm injection (ICSI). This is the only option in NOA to father a child. Multiple random bilateral testicular sperm extraction (TESE) is the method of choice. Microsurgical TESE increases retrieval rates

[26]. ICSI results are significantly weaker in NOA compared to obstructive azoospermia (18% vs. 28%).

Non-Palpable Testicular Masses: Organ-Sparing Surgery

With the widespread use of scrotal ultrasound for male infertility, a greater number of incidental testicular lesions are being identified. Recently, there has been an increasing trend toward organ-sparing microsurgery to prevent fertility and androgen substitution and improve health-related quality of life. The majority (~80%) of small non-palpable testicular masses are benign lesions.

Semen Cryopreservation

It allows sperm storage at temperatures below 0 °C for an indefinite time, although current techniques may still cause damage and deterioration over time. It is recommended in the case of [27]:

- Any kind of surgical sperm retrieval (MESA, TESE, microTESE), in order to avoid further sperm-finding procedures for assisted reproduction.
- Neoplastic or autoimmune diseases that must be treated with therapies capable of altering the reproductive function (e.g., chemo/radiotherapy).
- Progressive diseases that can affect fertility.
- Progressive and serious deterioration of the quality of the seminal fluid over time.
- Spinal cord injured men.
- Surgical interventions that may alter the mechanisms of ejaculation (e.g., prostatectomy, vasectomy) or fertility.
- Sperm donation.

Sexuality and Quality of Life

Male infertility appears to be a pathology that causes much suffering to both patients and their partners. The initial astonishment at the diagnosis of infertility soon gives way to anxiety and feelings of inadequacy: a sense of guilt toward the partner and obsessive behavior while waiting for the result of treatment, such as daily exercise (morning run) and diet (weight loss) [28].

A study by Irisawa et al. [29] evaluated the sexual behavior of 156 infertile patients by interview. It was found that the intensity of sexual desire of infertile patients was weaker than that of fertile males in the corresponding age groups, especially between 34 and 40 years of age. The frequency of morning erection in

infertile patients was highest between the ages of 24 and 30 and decreased with age. On the other hand, there was no significant reduction in the intensity of erection during sexual intercourse. While 6% of infertile patients reported disturbance of arousal and ejaculation, 16% of partners expressed dissatisfaction with their sex life. This was often accompanied by anxiety and mood disorders.

Erectile dysfunction is often associated with male infertility [30]: a 2013 study evaluating 22,682 interviews with men and women aged 15–44 years reported that, in the United States, up to 12% of men have fertility problems [31]. It seems that sexual dysfunction in men is often present in the general population, with 20–30% of adult men worldwide reporting at least one sexual disorder, with prevalence increasing with age. The estimated prevalence of erectile dysfunction and premature ejaculation in men of reproductive age ranges from 12% to 19% and 8% to 31%, respectively [32–35].

The types of sexual dysfunction that lead to male infertility include erectile dysfunction and ejaculation disorders, such as anejaculation, retrograde ejaculation, and severe premature ejaculation, with organic, iatrogenic, relational, and/or psychogenic causes. It should be noted that male fertility may be impaired by sexual dysfunction per se, as in the case of psychogenic erectile dysfunction, or, more often, infertility may be caused by the negative effect exerted on sperm parameters by a systemic disease or the drug used to treat such diseases, which may also lead to sexual dysfunction [36].

In particular, ejaculation disorders affecting male fertility are mainly those that lead to aspermia (dry ejaculation), which can occur [37] either due to the inability to transport sperm (anejaculation) or the inability to ejaculate in an anterograde direction (retrograde ejaculation).

The simultaneous presence of sexual dysfunction in the female partner of an infertile couple may contribute to the deterioration of erectile function.

Women with secondary infertility had lower female sexual function index scores in orgasm, satisfaction, arousal, and desire than women with primary infertility [38–40].

Hassanzadeh et al. [41] found that in 300 infertile Iranian men, 129 suffered from premature ejaculation, of which 74% had the permanent form and 26% had acquired premature ejaculation. These results are similar to those reported by Serefoglu et al. [42] in a study of 261 Turkish men attending an outpatient urology clinic with a self-reported complaint of premature ejaculation (62.5% with the permanent form and 16.1% with the acquired form). By contrast, in an Italian study [43] Lotti et al. reported that of 244 men seen consecutively, with couple infertility, 38 had premature ejaculation, of which 38.5% had the permanent form and 61.5% had the acquired form. These data were similar to those reported by Basile Fasolo et al. [44] in 2658 Italian men with premature ejaculation admitted to outpatient clinics for free andrological examination (21.4% with permanent premature ejaculation and 69.8% with acquired premature ejaculation).

The study by Ramezanzadeh et al. [45] showed that sexual desire was negatively associated with the duration of infertility and positively associated with the frequency of coitus. Furthermore, no significant difference in sexual desire was

observed between subjects with a recent (<3 months) or long-term (3–180 months) diagnosis of infertility ($P = 0.075$).

Similar results have been reported by others using the validated IIEF-15 instrument [46].

Reduced sexual desire in infertile couples has been related to the fact that sexual activity is focused on procreation rather than on the playful aspects and that intrusive medical requirements affect intimacy [47].

But What of the Couple: How Do They Experience This Pathological Situation?

Most publications have also analyzed the relationship between male infertility and marital instability. Some studies report low sexual satisfaction following the diagnosis of infertility. Drosdzol and Skrzypulec [48] found that male infertility became more intolerable for the couple depending on the duration of infertility (3–6 years). Andrews et al. [49] found a weak association between male fertility-related stress and sexual dissatisfaction in 157 infertile couples (but the duration of infertility was not indicated).

Smith et al. [50] investigated sexual satisfaction among 357 men in infertile couples (duration of infertility: 1.4–2.3 years) and found a low-to-medium value.

Monga et al. [51] suggested that perceived male infertility leads to feelings of inadequacy, decreased self-esteem, and increased stress levels, which affect sexual satisfaction. A 2014 study investigating sexuality, self-esteem, and partnership quality [52] in 153 males from infertile couples showed that infertility is associated with reduced sexual and general relationship satisfaction, self-esteem, and confidence, using the Self-Esteem and Relationship Questionnaire (SEAR).

With regard to orgasmic function: Jain et al. [53] reported male orgasm failure in 8% of a sample of 175 infertile men (using a questionnaire not validated according to ICD-103), while Saleh et al. found [54] that 11% of 405 men undergoing infertility evaluation revealed problems with orgasm (using the IIEF-15). In particular, these patients failed to collect sperm for a second analysis, by masturbation or during sexual intercourse at home, after abnormalities in one or more sperm parameters were detected. They also reported severe anxiety.

Rabo et al. [55] reported that the average sexual activity of 110 men with Klinefelter's syndrome examined for infertility was significantly lower than that of 325 normozoospermic and functional men.

Yoshida et al. [56] found a prevalence of sexual dysfunction in 67.5% of 40 men with Klinefelter syndrome who complained of infertility (39 with azoospermia and one with severe oligoasthenospermia). However, men with Klinefelter syndrome showed no significant difference in the frequency of sexual dysfunction compared with a control group of 55 infertile non-azoospermic men. The average monthly frequency of sexual intercourse in patients with Klinefelter syndrome was significantly higher than in the control group, probably because they wanted to continue

to have sexual relations after the diagnosis of azoospermia. Corona et al. [57] found severe erectile dysfunction in 22.7% of 23 men with Klinefelter syndrome, while 60.9% had hypoactive sexual desire, 9.5% suffered premature ejaculation, and 9.5% delayed ejaculation.

It is now clear that couples' infertility involves significant psychological stress: the European Society of Human Reproduction and Embryology (ESHRE) has developed guidelines for clinical practice. These guidelines provide recommendations to improve the quality of psychosocial care for couples with infertility and during ART. ESHRE guidelines [58] report that patients starting first-line infertility treatment or ART do not have worse marital and sexual relationships than the general population and that patients receiving fertility treatment do not have higher prevalence rates of sexual dysfunction than the general population.

Everyday clinical evidence also shows that, in infertile men, erectile dysfunction is associated with mood disorders and generalized anxiety (assessed by questionnaires: IIEF-15-EFD—the MHQ), especially in patients with azoospermia compared to other categories of infertile men. In addition, men with azoospermia show higher rates of premature ejaculation and sexual desire with reduced orgasmic function (due to depressive and somatized anxiety) than fertile men.

Conclusion

Erectile dysfunction and male infertility are considered early indicators of poor general health. Men with azoospermia show the highest rates of psychological and general health disorders associated with a higher prevalence of sexual dysfunction. Finally, drugs commonly used for general health problems can lead to sperm abnormalities and sexual dysfunction, and therefore, adequate information must be provided to patients. There is no doubt, in all of this, that knowing the sexual history of the couple and of individuals would offer clinicians and the sexologist better references to understand: the patient's and partner's compliance, the couple's relationship, the obsessiveness regarding the parental project, the conditioning of social networks (friends who have already had children), and families (families of origin pressing for a grandchild).

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