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Sandro C. Esteves MD., PhD.

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Who cares about oligozoospermia when we have ICSI

Approach to oligozoospermia in the ICSI era

Sandro C. Esteves, MD., PhD. [1,2,3]

[1]ANDROFERT, Andrology and Human Reproduction Clinic, Campinas, Brazil.
[2]Department of Surgery (Division of Urology), Faculty of Medical Sciences, University of Campinas (UNICAMP), Campinas, Brazil.
[3]Faculty of Health, Aarhus University, 8000 Aarhus C, Denmark.

Correspondence to: SC Esteves. Medical Director, ANDROFERT – Andrology & Human Reproduction Clinic, Av. Dr. Heitor Penteado 1464, Campinas, SP, 13075-460, Brazil, Email: s.esteves@androfert.com.br
ORCID: https://orcid.org/0000-0002-1313-9680

ABSTRACT

The value of assessing subfertile males with oligozoospermia is controversial due to prevailing notions that therapies are limited and ICSI may provide the couple with a baby without the need to explain the nature or cause of underlying male infertility. This article highlights that offering ICSI to oligozoospermic men indiscriminately is not free of potential adverse effects and does not grant subfertile men the best fertility pathway. Recent data support associations between oligozoospermia and poor male reproductive health, DNA and epigenetic damages in spermatozoa, and possible adverse health consequences to offspring. Many conditions directly or indirectly affecting the testicles are capable of causing oligozoospermia (varicocele, genital infections, congenital and genetic defects affecting the reproductive system, testicular torsion/trauma, chronic diseases, inadequate lifestyle, occupational/environmental exposure to toxicants, drugs, cancer and related treatments, acute febrile illness, endocrine disorders, and iatrogenic damage due to surgical interventions in the genitourinary system). If oligozoospermia is detected, a range of therapeutic interventions can improve sperm quantity/quality and the overall male health, ultimately resulting in better pregnancy outcomes even when ICSI is used. Fertility clinics are urged to engage male infertility specialists in diagnosing and treating oligozoospermia as a matter of best clinical practice. A well-conducted male infertility evaluation represents a unique opportunity to identify relevant medical and infertility conditions,

many of which may be treated or alleviated. The andrological assessment may also help guide the optimal application of ICSI. The final goals are to positively impact the overall patient health, the couple's pregnancy prospects, and the offspring's wellbeing.

Keywords: Intracytoplasmic sperm injection; Male health; Male infertility; Oligozoospermia; Offspring health; Semen analysis; Sperm DNA damage; Spermatozoa; Therapeutics.

INTRODUCTION

The merit of proper male evaluation and treatment has been questioned because intracytoplasmic sperm injection (ICSI) may provide the couple with a baby without the need to explain the nature of oligozoospermia. In real-life settings, a remarkable proportion of couples undergo assisted reproductive technology (ART) without ever being subjected to an andrological evaluation, a trend that seems to persist over time (Pozzi et al., 2021). Although it is commonplace to recommend ICSI for oligozoospermic men indiscriminately, this practice is not free of potential adverse effects and does not grant subfertile men the best fertility pathway, as highlighted in this article.

OLIGOZOOSPERMIA: WHAT DOES IT MEAN?

Oligoozoospermia refers to sperm concentrations below established reference limits (e.g., 16 million per ml, 95% confidence interval: 15-18) (WHO 2021). Qualifiers such as ‘severe’, ’moderate’, and ‘mild’ are frequently applied based on arbitrarily defined thresholds, none of which imply an underlying etiology. Notably, an oligozoospermia verdict always results from a semen analysis, a complex laboratory test that should be carried out following the rigor recommended by the WHO manual (WHO 2021). However, even when the semen is analyzed following standardized protocols and rigid quality control, there is marked intra-individual variation in sperm concentration (Alvarez et al., 2003). For this reason and because semen analysis is frequently a gateway test from which expensive and invasive treatments, like ICSI, are based, clinicians should request at least two semen analyses to establish the diagnosis of oligozoospermia.

Clinically, many conditions directly or indirectly affecting the testicles are capable of causing oligozoospermia. They include congenital (e.g., cryptorchidism, spermatogenic failure, vas

deferens defects, ejaculatory cysts) and genetic (e.g.,) defects affecting the reproductive system, varicocele, testicular trauma or torsion, hormonal disturbances (e.g., hypogonadism, hyperprolactinemia, thyroid diseases), genital tract infections (e.g., sexually transmitted diseases, chronic prostatitis), acute febrile illness, chronic diseases (e.g., diabetes, metabolic syndrome, autoimmune diseases, kidney diseases), cancer and related treatments (e.g., testicular cancer), occupational or environmental exposure to toxicants (e.g., endocrine-disrupting chemicals, pesticides, ionizing radiation), inadequate lifestyle (e.g., smoking, obesity, illicit drug abuse), medication-induced (e.g., serotonin-reuptake inhibitors, 5α-reductase inhibitors, testosterone replacement therapy, anabolic steroids, sulfasalazine, azathioprine, methotrexate, mycophenolate mofetil, opioids, antipsychotics), and iatrogenic damage due to surgical interventions (e.g., scrotal surgery hernia repair) (**Figure 1**). These factors may also cause other semen abnormalities (e.g., reduced sperm motility and/or morphology, increased rate of sperm exhibiting chromatin damage), which might or might not be detected by a routine semen analysis.

TIP OF THE ICEBERG

There is growing awareness that male fertility is a marker of overall health (Chen et al., 2021). Oligozoospermia, particularly, is linked with relevant health conditions that deserve medical attention, as mentioned above. Furthermore, many studies show that oligozoospermia has solid genetic and epigenetic backgrounds. The interaction of thousands of genes, the epigenetic control of gene expression, and environmental and lifestyle factors, which influence genetic and epigenetic variants, determines the spectrum and magnitude of the anomalies seen in the human semen (Gunes and Esteves, 2021).

Numerical (e.g., 47,XXY/46,XY mosaicism) and structural (e.g., inversions and translocations) chromosomal aberrations are more frequently found in oligozoospermic men (4% vs. 0.7% in normozoospermic controls) (Krausz and Riera-Escamilla, 2018). These abnormalities increase the risk of having unbalanced gametes and abnormal offspring. The frequency of Yq microdeletions is also higher in oligozoospermic men (6%-8% vs. 0.025% in the general population) (Krausz and Riera-Escamilla, 2018). Transmission of AZFc microdeletions from oligozoospermic men to their progeny via ICSI is real, invariably leading to infertility in male progeny. Besides, submicroscopic structural variations of the genome (copy number variations)

are increased in oligozoospermic men (Tüttelmann et al., 2011). While there is currently no treatment for these genetic anomalies, diagnosis can help counsel the affected couples most optimally.

Contemporary research has also highlighted the essential role of epigenetic processes for spermatogenesis and sperm function and the association between epigenetic defects (e.g., germ cell-specific methylation defects, protamine abnormalities, histone modifications) and oligozoospermia (Darbandi et al., 2019). The sperm nuclear genome has a central compact toroid of protamine-bound DNA and a peripheral compartment of histone-bound DNA. The latter contains promoters for developmentally crucial genes, microRNAs, and signaling factors, highly susceptible to environmental insults, particularly oxidative harm (Gunes and Esteves, 2021). Spermatozoa of oligozoospermic men may harbor specific epigenetic dysregulation caused by intrinsic or modifiable extrinsic factors (e.g., nutrition, smoking, chemical exposures).

Along these lines, seminal oxidative markers are overall increased in men with oligozoospermia. Sperm DNA fragmentation (SDF), a marker of oxidative stress, is found in 40-50% of these individuals (Aktan et al., 2013). The fertilization of oocytes by sperm carrying DNA and/or epigenetics defects through ICSI may increase the risk of fertilization failure, embryo arrest, miscarriage, congenital malformations, childhood cancer, and perinatal morbidity (Esteves et al. 2021). It has been suggested that ICSI offspring, mainly among cases involving male factor infertility, has increased risks of congenital and urogenital malformations, epigenetic disorders, chromosomal abnormalities, infertility, childhood cancer, delayed psychological and neurological development, and impaired cardiometabolic profile compared with naturally conceived children (Esteves et al., 2018). Parental sperm defects have been suggested as primarily responsible for the conditions above.

On this basis, the overall and reproductive health of oligozoospermic men seeking fertility should not be disregarded in an attempt to create a pregnancy by ICSI at any cost. Offering ICSI to all oligozoospermic men is like prescribing expensive antipyretics to all febrile individuals: both may resolve the ‘symptom’, but none of them tackle the underlying causative factor and its potential adverse consequences.

THE SOLUTION

The diagnosis of oligozoospermia should initiate an objective and transparent patient (couple)-physician discussion about its implications, treatment options and outcomes, and alternatives. It is critical to offer the affected patient a complete andrological assessment by a specialist. A detailed medical and reproductive history and a physical examination are the minimum standards, but further investigations such as hormonal assessment (e.g., FSH, testosterone, prolactin, estradiol, and thyroid hormone levels), sperm functional tests (e.g., SDF testing), genetic analysis (e.g., Karyotype, Y chromosome microdeletion, cystic fibrosis gene mutation), and imaging studies (e.g., scrotal ultrasound, transrectal ultrasound) may be required depending on the initial findings (Esteves et al., 2012).

The male evaluation brings many benefits. First, it can identify correctable conditions such as varicocele, genital tract infections, obstructions in the reproductive tract, and endocrine disorders. Second, it may help determine the cases where oligozoospermia is untreatable but appropriate for ICSI using the patient's sperm. For example, genetic-related oligozoospermia, which requires parental counseling about the risks and sequelae to offspring health, and oligozoospermia associated with other sperm defects (e.g., pathological SDF), where consideration for sperm retrieval and ICSI with testicular sperm may be considered (Esteves et al. 2017). Third, the assessment can uncover health-threatening conditions or related coexistent diseases requiring medical care (e.g., obesity, metabolic syndrome, erectile dysfunction, hypogonadism, kidney diseases, and malignancies). Lastly, it can provide a unique opportunity to address lifestyle conditions that might affect the patient or offspring's health (e.g., smoking, bad nutrition habits, chemical exposures, use of licit or illicit drugs with potential gonadotoxic and/or teratogenic effects).

TREATMENT OPTIONS

Therapeutic interventions should be considered for subfertile oligozoospermic men before ICSI is contemplated. **Table 1** summarizes the existing options and outcomes. Although many proposed therapies lack robust evidence for improved live birth rates, the primary focus should be to improve the male germline, possibly enhancing fertility and reproductive success as well as the offspring's health and wellbeing. Treatment effects are generally seen 3-9 months later. Although it has been argued that couples whose partners have advanced maternal age or poor ovarian reserve cannot tolerate such a delay, recent data indicate that this time frame is unlikely

to impact reproductive outcomes of most couples even when ICSI is used (Romanski et al., 2020; Bhattacharya et al. 2021).

Varicocele repair

The negative effect of varicocele on sperm quantity and quality is well established. Among subfertile males with abnormal semen parameters, varicocele is found in approximately 25% of the individuals. The testis responds to varicocele-associated cell stressors by generating excessive free radicals, which might lead to oligozoospermia and other sperm abnormalities, like chromatin damage (Hamada et al., 2013). Treatment is recommended to subfertile men with clinical (i.e., palpable) varicoceles and abnormal semen parameters and aims to occlude the dilated veins of the pampiniform plexus. Varicocele repair is carried out using open (with or without magnification) or laparoscopic surgical techniques or through percutaneous embolization of the internal spermatic vein. Many studies show that varicocele repair alleviates oxidative stress and ameliorates sperm parameters in ~two-thirds of treated individuals as early as 3 to 5 months postoperatively; total sperm count, in particular, increases by ten million overall (Hamada et al., 2013; Agarwal et al., 2007).

Moreover, a 2021 meta-analysis of RCTs provided updated evidence that varicocele repair improves natural pregnancy rates compared to delayed or no treatment in subfertile men with clinical varicocele and abnormal semen parameters (Persad et al., 2021). Varicocele repair in oligozoospermic men may also allow couples to use less invasive assisted conception techniques (e.g., IUI) (Samplaski et al., 2017) or lead to improvements in ICSI outcomes (Esteves et al., 2016; Kirby et al. 2016). Sperm DNA quality enhancement has been suggested as a critical factor explaining the beneficial effect observed after varicocele repair among couples undergoing ICSI (Esteves et al., 2020; Lira Neto et al., 2021).

Lifestyle interventions and antioxidants

Obesity and inadequate lifestyle (e.g., smoking, alcohol abuse, illicit drugs) have been postulated to contribute to poor semen quality, oligozoospermia, and probability of achieving a live birth (Guo et al., 2017; Bian et al., 2021). Although the effects of lifestyle interventions on semen quality and pregnancy outcomes are poorly studied, good dietary habits (e.g., Mediterranean diet, Prudent diet) have been associated with better semen quality than the typical Western diet rich in saturated and trans-fatty acids, processed foods and sugared beverages (Salas-Huetos et al.,

2017). Additionally, limited data indicate that smoking cessation, regular physical activity, and weight loss through diet and exercise may improve semen parameters and reproductive outcomes of couples seeking infertility care (Faure et al., 2014; Vanegas et al., 2017; Ibañez-Perez et al. 2019).

Oxidative stress has also been a critical contributor to male infertility and a marker of inadequate lifestyle. Oral antioxidants might counteract, to some extent, the adverse effects of elevated ROS on sperm quality and translate into an increased probability of achieving pregnancy compared to placebo (Smits et al., 2019). Improvements in sperm chromatin integrity and other semen parameters, including sperm concentration, have been reported with various antioxidant formulations (Smits et al., 2019; Esteves et al., 2020). Still, the evidence remains mixed as some recent RCTs did not show significant advantages (Steiner et al., 2020). A recent pilot trial conducted in Denmark demonstrated that a combination of dietary changes and oral antioxidants improved semen parameters in male partners of subfertile couples with a history of failed ART (Humaidan et al., 2022). An assessment of lifestyle and dietary patterns may be an opportunity for nutrition and lifestyle re-education.

Infection

Urethritis, prostatitis, orchitis, and epididymitis are male accessory gland infections (MAGI). The infectious agents include bacteria, viruses, and protozoa, and in many cases, they are sexually transmitted. These pathogens activate seminal leukocytes, which generate a significant amount of reactive oxygen species. These free radicals may damage sperm membranes and sperm DNA, thus affecting sperm quality potentially. MAGI prevalence ranges between 3-20% in the infertile male population and can be asymptomatic. It has been reported that *Ureaplasma urealyticum* and *Mycoplasma hominis* in the semen are associated with decreased semen parameters, increased SDF, and elevated levels of antisperm antibodies (Gallegos et al., 2008). Human papillomavirus is also linked with male infertility, altered semen parameters, and decreased pregnancy outcomes (Depuydt et al., 2019). In a study including 285 couples undergoing ART, the presence of *Enterococcus faecalis* and/or *U. urealyticum* and/or *M. hominis* in genital samples of male partners was predictive for a negative ART outcome (Ricci et al., 2018). Bacterial MAGI should be treated with antibiotics to eradicate micro-organisms and

reduce the inflammatory response, potentially improving semen parameters and fertility. Notably, the female partner should be evaluated and treated as well.

Hormonal modulation

Several agents have been used as empirical treatments for idiopathic oligozoospermia, including selective estrogen receptor modulators (SERM), aromatase inhibitors, bromocriptine, and gonadotropins. Through different mechanisms of action, treatment aims to stimulate spermatogenesis by modulating the endogenous levels of reproductive hormones or exogenous gonadotropin administration. SERM and aromatase inhibitors increase sperm concentration and testosterone levels (vs. placebo or no treatment) in men with idiopathic oligozoospermia, but the effects on natural or medically assisted conception are equivocal (Cannarella et al., 2019). By contrast, limited data indicate that this patient population benefits from exogenous FSH therapy. It has been reported that FSH injections –administered to infertile males with idiopathic oligozoospermia– increased sperm concentration and natural pregnancy rates (Omar et al., 2019). The effect seems to be related to the anti-apoptotic and pro-survival actions of FSH on germ cells, ultimately resulting in improved sperm chromatin integrity (Santi et al., 2018; Esteves et al., 2020). However, evidence concerning the effect of male FSH therapy on ICSI outcomes is lacking.

FUTURE DIRECTIONS: A COUNTERCURRENT MOVEMENT

Accumulating evidence indicates that the ability to diagnose and treat male infertility may improve the patient's reproductive health, the couple's pregnancy prospects, and progeny's long-term health trajectory, even when ICSI is used. On these grounds, we should question ourselves whether we are providing the best reproductive care to our patients (and the children yet to be born) by ignoring the health of oligozoospermic males. Also, we must honestly confront the financial incentives driving the decision to bypass a complete male infertility evaluation and recommend ICSI to oligozoospermic men indiscriminately.

Although we need more data about the clinical utility of medical and surgical interventions for oligozoospermic males, fertility clinics are urged to engage male infertility specialists in diagnosing and treating oligozoospermia as a matter of best clinical practice. The complexity of oligozoospermia requires a multidisciplinary approach that involves andrology, urology,

reproductive endocrinology, genetics, ART, nutrition, and psychology. It provides an unparalleled opportunity to treat both the underlying male subfertility and associated health issues while aiming to produce a viable pregnancy and healthy offspring through natural conception or safe utilization of ICSI. We must take sides and intervene because neutrality on this matter will never help the affected male. We urgently need more reproductive endocrinologists/gynecologists open for collaborations and qualified reproductive urologists/andrologists to be effective collaborators.

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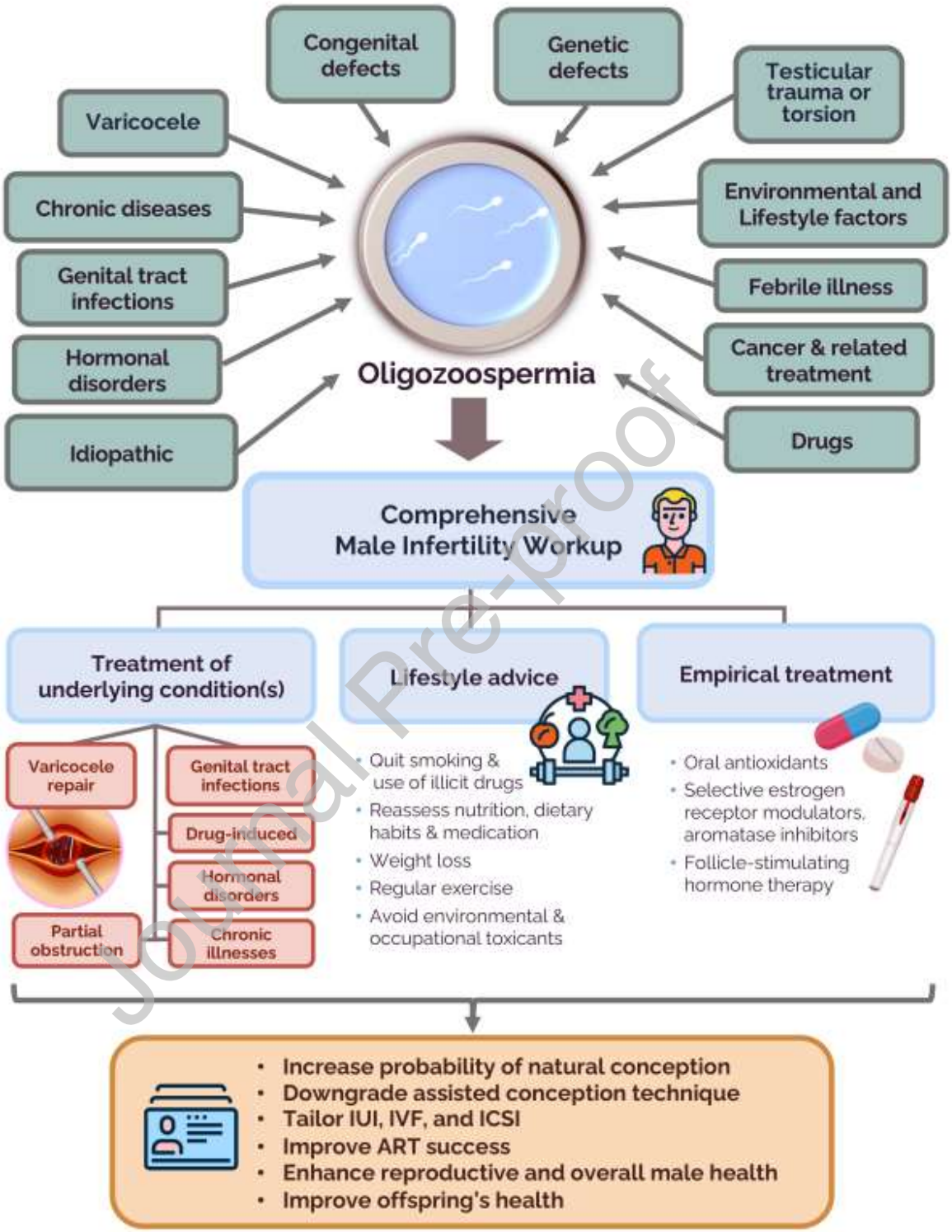

FIGURE LEGEND. **Proposed clinical practice pathway for oligozoospermic men seeking fertility: causes, andrological assessment, treatment options, and goals**. In the upper part, the diagram depicts the main conditions causing oligozoospermia. In the middle part, the box highlights the importance of a complete andrological assessment, which must include a detailed medical and reproductive history, physical examination, routine semen analysis. Other investigations (e.g., hormonal assessment, sperm functional tests, genetic analysis, and imaging studies) may be necessary based on the clinical and semen analysis findings. In the lower part, the diagram depicts the main treatment options. Lastly, the bottom box lists the primary treatment goals before ICSI is contemplated.

Table 1. Summary evidence of main treatment options with potential clinical utility for oligozoospermic males seeking fertility

Varicocele repair	
Varicocele repair improves natural pregnancy rates compared to delayed or no treatment in subfertile men with clinical varicocele and abnormal semen parameters (RR: 1.94, 95% CI 1.23, 3.05; p=0.004; 7 RCTs; 693 participants). On average, six patients would have to receive varicocele repair (instead of delayed or no treatment) for one additional couple to achieve a pregnancy.	Persad et al. 2021
Varicocele repair increases TMSC and may allow couples needing ICSI to use a less invasive assisted conception modality (e.g., IUI) or attempt natural pregnancy. The most evident increase was with baseline TMSC <5 million, from 2.3 ± 1.5 preoperatively to 15.9 ± 32.9 milion postoperatively (p=<0.0001); 58.8% of men were upgraded from IVF-ICSI candidacy to IUI or natural pregnancy.	Samplaski et al. 2017
Pregnancy rates by ICSI were increased in couples whose oligozoospermic male partners had a varicocele repair compared to those who did not (Clinical pregnancy: OR = 1.59, 95% CI 1.19, 2.12, p=0.002, 4 observational studies, 852 patients; Live birth: OR = 2.17, 95% CI 1.55, 3.06, p<0.00001, 3 observational studies, 622 patients). On average, five patients would have to receive varicocele repair before ICSI (vs. no treatment) for one additional couple to achieve a pregnancy.	Esteves et al. 2016
Varicocele repair increased the likelihood of achieving a live birth by ICSI in men with either oligozoospermia or azoospermia (five observational trials including 786 oligozoospermic participants (OR 1.76, 95% CI 1.22–2.53, p=0.002).	Kirby et al. 2016
SDF rates are reduced as early as three months after varicocele repair in subfertile men with abnormal semen parameters and clinical varicocele (WMD: 7.2%, 95% CI -8.9%, -5.6%, p<0.0001; 19 observational studies, 1070 patients). The improvement in sperm chromatin quality translated into improved pregnancy rates as couples who conceived naturally or with ART had lower postoperative SDF rates than those who did not.	Lira Neto et al. 2021
Lifestyle interventions and antioxidant therapy	
Healthy dietary patterns (e.g., Mediterranean diet, Prudent diet) have been linked to better semen parameters than diets rich in processed foods and saturated fats.	Salas-Huetos et al., 2017
A prospective study including 176 couples reported that higher male waist circumference was a risk factor for poor ART outcomes. For each 5 cm increase in male waist circumference, the odds of live birth per initiated cycle decreased by 9.0% (95% CI 1.1, 16.4%) after accounting for several anthropometric and demographic characteristics of both partners.	Bian et al. 2021
A study including 225 couples undergoing ART found that among past male smokers, every additional year since the patient had quit smoking reduced the risk of failing ART by 4% (HR: 0.96; 95% CI: 0.91, 1.00), particularly between clinical pregnancy and live birth (HR: 0.86; 95% CI: 0.76, 0.96).	Vanegas et al. 2017

A nutritionist-led dietary program coupled with exercise helped reduce weight loss and improve semen parameters, translating into improved pregnancy outcomes.	Faure et al. 2014
A 3-month lifestyle intervention program combined with oral antioxidant therapy using vitamins, coenzyme Q10, omega 3, and oligo-elements reduced SDF rates in infertile men with elevated baseline SDF (mostly oligozoospermic) and a history of failed IVF/ICSI.	Humaidan et al. 2021
Male genital infection	
Microbiological analysis of 285 couples undergoing ART showed that 35.8% of male partners presented with an asymptomatic genital tract infection. A positive semen specimen was associated with impaired semen parameters and reduced pregnancy outcomes by ICSI.	Ricci et al. 2018
In a study involving 95 men with MAGI caused by chlamydia or mycoplasma, antibiotic therapy using a macrolide, a tetracycline, or a quinolone, combined with a course of anti-inflammatory agents, improved SDF rates in 91% of patients (37.7% ± 13.6% to 24.2% ± 11.2%; $p<0.0001$. A total of 86% of couples that attempted pregnancy succeeded 3-6 months after therapy. When couples with and without pregnancy success were compared, the main difference was lower SDF rates in the pregnant couples.	Gallegos et al. 2008
FSH therapy	
Recombinant FSH injections (50–300 IU administered daily or on alternate days for 3–4 months (vs. placebo) were associated with higher sperm concentration (MD: 3.17 x 10^6/ml, 95% CI 2.44–3.91x10^6/ml; 444 participants; seven studies; $p<0.0001$; very low certainty) and natural pregnancy rates (OR: 3.30, 95% CI 1.39–7.82; 343 participants; five studies; $p=0.007$; low certainty).	Omar et al., 2019
A systematic review and meta-analysis demonstrated that FSH injections given to men with idiopathic infertility for three months reduced SDF values (MD: 4.24%, 95% CI 0.24-8.25%; $p=0.04$; five prospective observational trials and one RCT; 383 participants).	Santi et al. 2018

TMSC: total motile sperm count; IUI: intrauterine insemination; IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; RR: relative risk; CI: confidence interval; HR: Hazard ratio; RCT: randomized controlled trial; ART: assisted reproductive technology; SDF: sperm DNA fragmentation; LBR: Live birth rate.