In the name of GOD

Male Infertility

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Definition

- Infertility in a couple is usually defined as the inability to achieve conception despite one year of regular, unprotected intercourse
- When the female partner is >35 years old, infertility is defined as failure to conceive within six months of unprotected intercourse

Epidemiology

- Up to 40 to 50 percent of young, healthy couples that fail to conceive in the first 12 months will conceive in the subsequent 12 months with no specific treatment
- In some circumstances, delay in extensive evaluation and treatment is reasonable
- In approximately 35 percent of couples with infertility, a male factor is identified along with a female factor
- In approximately 10 percent, a male factor is the only identifiable cause

- While many men with male infertility have oligozoospermia (a low number of sperm cells in the ejaculate compared with reference ranges) or azoospermia (no sperm cells in the ejaculate), some infertile men have normal sperm counts
- Over 80 percent of infertile men have low sperm concentrations and poor sperm quality (a decrease in sperm motility [asthenozoospermia] and/or an increase in spermatozoa with abnormal morphology [teratozoospermia])
- A small percentage of infertile men have normal sperm concentrations but poor sperm quality, and another small percentage of infertile men have normal sperm concentrations and normal motility and morphology

Pathophysiology

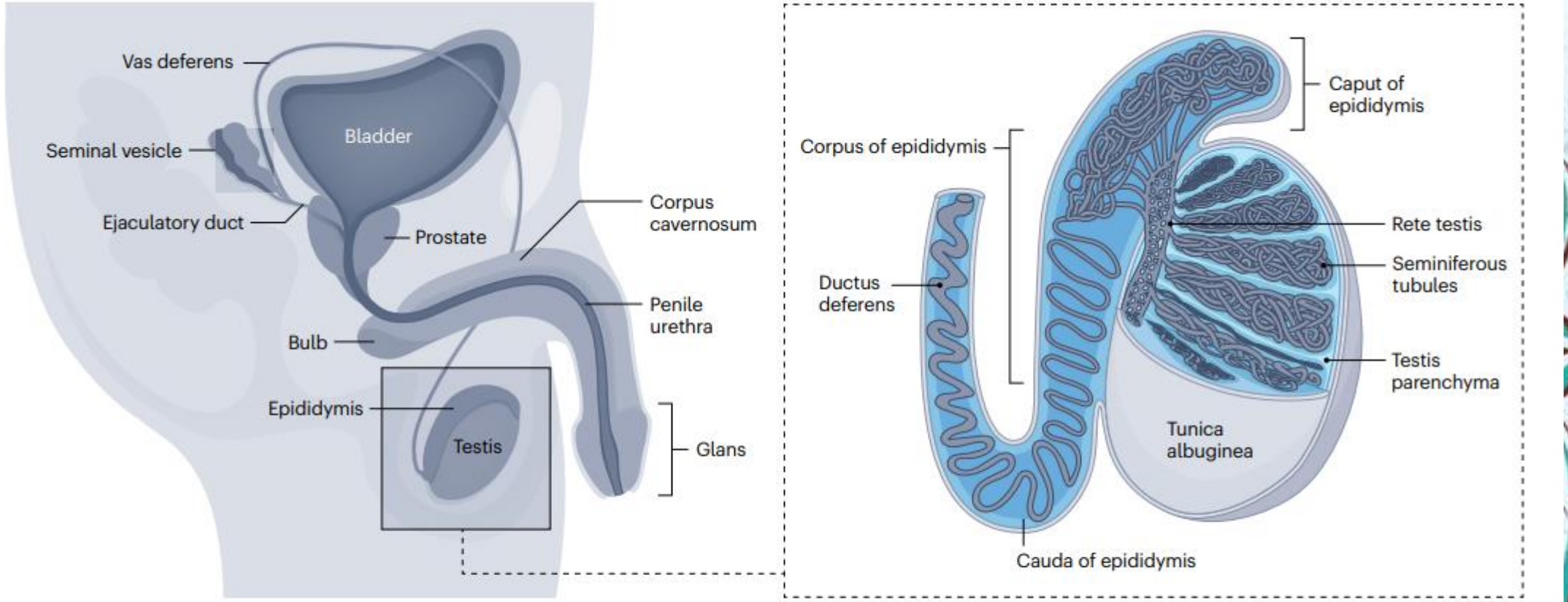


Fig. 2 | Anatomy of the male reproductive tract. Spermatogenesis occurs in the testis. Sperm then moves through the rete testis to the epididymis where sperm maturation is completed. Sperm then traverses the vas deferens against gravity into the pelvis. Sperm is stored in the ampulla of the vas deferens until ejaculation. On ejaculation, fluid from the vasa deferentia and prostate are expelled into the posterior urethra followed by fluid from the seminal vesicles. The ejaculate is then expelled from the urethra.

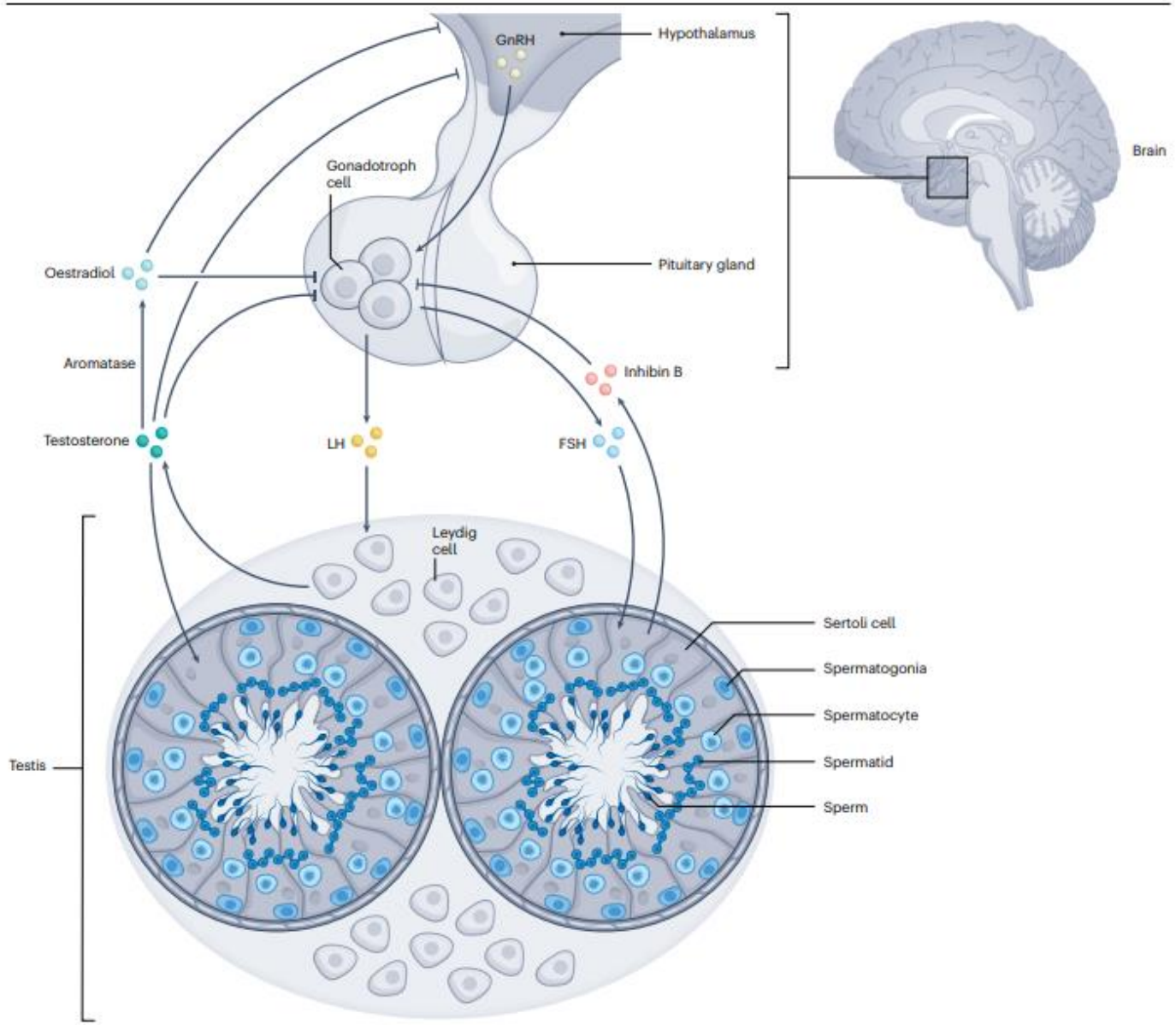

GnRH
Hypothalamus
Brain
Gonadotroph cell
Pituitary gland
Oestradiol
Aromatase
Inhibin B
Testosterone
LH
FSH
Leydig cell
Sertoli cell
Spermatogonia
Spermatocyte
Spermatid
Sperm
Testis

Table 1 | The major organs, cell types, hormones, paracrine factors and receptors that regulate human spermatogenesis

Organ	Cell type	Receptor	Major hormones produced
Hypothalamus	GnRH-producing neurons	GnRH receptor	GnRH
Hypothalamus, pre-optic nucleus, amygdala	GnRH-producing neurons	Androgen receptor Oestrogen receptor	GnRH
Pituitary gland	Gonadotrophs	GnRH	Follicle-stimulating hormone Luteinizing hormone
Testis	Sertoli cells	Follicle-stimulating hormone receptor Androgen receptor Oestrogen receptor, thyroid hormone receptor, relaxin receptor	Inhibin B Mullerian inhibiting substance
	Leydig cells	Luteinizing hormone receptor Prolactin receptor Growth factor receptor Insulin and insulin-like growth factor receptors Fibroblast growth factor receptors Platelet-derived growth factor receptor-α (fetal)	Testosterone Insulin-like growth factor 3

Categories of male infertility

- Endocrine and systemic disorders with hypogonadotropic hypogonadism – 5 to 15 percent
- Primary testicular defects in spermatogenesis – 70 to 80 percent
- Sperm transport disorders – 2 to 5 percent
- Idiopathic male infertility – 10 to 20 percent

Endocrine and systemic disorders (hypogonadotropic hypogonadism)
Congenital disorders
▪ Congenital GnRH deficiency (Kallmann syndrome) ▪ Iron overload syndromes ▪ Multiorgan genetic disorders (Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, familial cerebellar ataxia)
Acquired disorders
▪ Pituitary and hypothalamic tumors (pituitary macroadenoma, craniopharyngioma) ▪ Pituitary and hypothalamic infiltrative disorders (sarcoidosis, histiocytosis, tuberculosis, fungal infections) ▪ Pituitary and hypothalamic lymphocytic infundibulitis or hypophysitis ▪ Head trauma, intracranial radiation, or surgery ▪ Vascular (pituitary infarction, aneurysm) ▪ Hormonal (hyperprolactinemia, androgen excess, estrogen excess, cortisol excess) ▪ Drugs (exogenous androgens, opioids and psychotropic drugs, GnRH agonists or antagonists)
Systemic disorders
▪ Severe systemic illness ▪ Nutritional deficiencies ▪ Morbid obesity

Primary testicular defects in spermatogenesis

Congenital disorders

- Klinefelter syndrome (XXY) and its variants (XXY/XY, XXXY)
- Cryptorchidism
- Myotonic dystrophy
- Functional prepubertal castrate syndrome (congenital anorchia)
- Androgen insensitivity syndromes
- 5-alpha-reductase deficiency
- Estrogen receptor or synthesis disorders

Acquired disorders

- Varicocele (large, palpable without Valsalva maneuver)
- Infections – Viral orchitis (mumps, echovirus, arbovirus), granulomatous orchitis (leprosy, tuberculosis), epididymo-orchitis (gonorrhea, chlamydia)
- Drugs – Alkylating agents, alcohol, marijuana, antiandrogens, ketoconazole, spironolactone, histamine-2 receptor antagonists, ionizing radiation
- Environmental toxins – Dibromochloropropane, carbon disulfide, cadmium, lead, mercury, environmental estrogens, and phytoestrogens; smoking; hyperthermia
- Immunologic disorders, including polyglandular autoimmune disease and antisperm antibodies
- Trauma
- Testicular torsion

Systemic illness

- Idiopathic dysspermatogenesis
- Renal failure, hepatic cirrhosis, cancer, sickle cell disease, amyloidosis, vasculitis, celiac disease

Genetic causes of dysspermatogenesis

- Y-chromosome microdeletions and related disorders
- Autosomal and X-chromosome defects
- Mutations causing severe defects in sperm morphology

Sperm transport disorders

- Epididymal dysfunction (drugs, infection)
- Abnormalities of the vas deferens (congenital absence, Young syndrome, infection, vasectomy)
- Seminal vesicles and prostate
- Ejaculatory ducts disorders

Sexual dysfunction

- Infrequent vaginal intercourse, erectile dysfunction, and premature ejaculation

Diagnostic approach

- History
- Physical examination
- Semen analysis

History

- Sexual developmental history, including testicular descent, pubertal development, loss of body hair, or decrease in shaving frequency
- Chronic severe systemic illness or history of major head trauma, surgery, or irradiation that could result in hypogonadotropic hypogonadism
- Infections, such as mumps orchitis, sinopulmonary symptoms, sexually transmitted infections, and genitourinary tract infections

- Surgical procedures or significant trauma involving the pelvis and genital area.
- Drugs and environmental exposures that can adversely impact the hypothalamic-pituitary-testicular axis, including alcohol, tobacco, marijuana, opioids, radiation therapy, **anabolic steroids**, corticosteroids, cytotoxic chemotherapy (current or past), drugs that cause hyperprolactinemia, and exposure to toxic chemicals
- Sexual history, including libido, frequency of intercourse, and previous fertility assessments of the man and his partner

Physical examination

- The physical examination should include a general medical examination to determine overall health, obesity, and overt signs of endocrinopathies that are uncommon causes of male infertility (eg, thyroid dysfunction or Cushing syndrome)
- Because some infertile men have combined defects in testosterone and sperm production, the examination should also focus on findings suggestive of androgen deficiency.
- The clinical manifestations of androgen deficiency depend upon the age of onset. Androgen deficiency during early gestation presents as atypical genitalia; in late gestation as micropenis; in childhood as delayed pubertal development; and in adulthood as decreased sexual function, infertility, and, eventually, loss of secondary sex characteristics

Semen analysis

- The standard semen analysis consists of the following:
- Semen volume and pH
- Microscopy for:

  -Sperm concentration, count, motility, and morphology

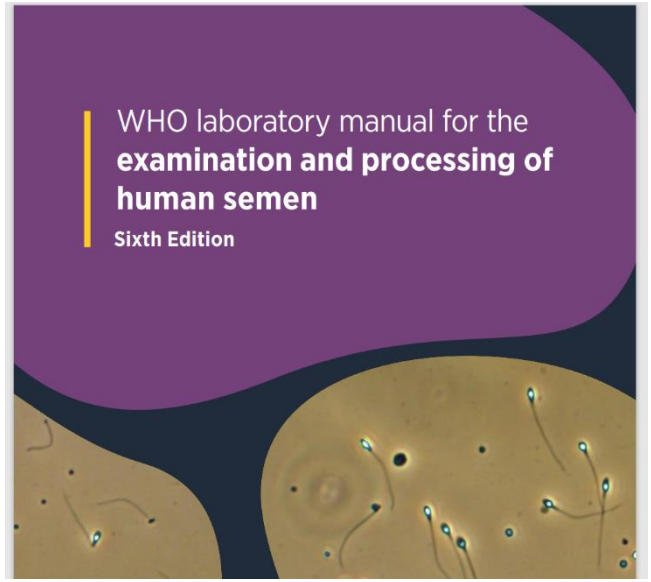
  -Debris and agglutination

  -Leukocyte count

  -Immature germ cells

Sampling

- The semen sample should be collected after two to seven days of ejaculatory abstinence
- If possible, the patient should collect the sample by masturbation at the doctor's office
- If not possible, then the sample may be collected at home and delivered to the laboratory within an hour of collection



Volume – 1.4 mL (95% CI 1.3-1.5)

Total sperm number – 39 million spermatozoa per ejaculate (95% CI 35-40)

Morphology – 4 percent normal forms (95% CI 3.9-4)

Vitality – 54 percent live (95% CI 50-56)

Total motility – 42 percent (40-43)

Progressive motility – 30 percent (95% CI 29-31)

Men with a normal semen analysis

- Male partners in an infertile couple may have idiopathic male infertility. Other possibilities include infertility of the female partner or a couples' infertility factor (including **insufficient** frequency or duration of unprotected vaginal intercourse that should occur at least **one to two** times weekly for optimal conception rates). After complete evaluation of the female partner and treatment of reversible causes of female infertility, the couple should consider referral to a specialist in ART, such as in vitro fertilization (IVF).

Men with an abnormal semen analysis

- Most infertile men with abnormal semen analyses have abnormalities in sperm concentrations, morphology, and motility
- **Normal sperm concentration, abnormal morphology and/or motility→**

❖ In an infertile couple with a male partner who has a normal sperm concentration but abnormal sperm morphology and/or motility, referral to a specialist in ART, such as intracytoplasmic sperm injection (ICSI), might be useful

Sperm concentration <5 million/mL→

- Because Klinefelter syndrome is common in men presenting with infertility and sperm concentrations <5 million/mL, serum total testosterone (on a blood sample obtained between 8 and 10 AM), serum follicle-stimulating hormone (FSH), and luteinizing hormone (LH) measurements should be performed in these men. The results of the endocrine testing and details from the history and physical examination can help identify the cause of the infertility

Severe oligozoospermia or azoospermia →

- Men with azoospermia or severe oligozoospermia also need endocrine testing; further evaluation also depends upon the results. In addition to undergoing endocrine testing, men with severe oligozoospermia or azoospermia require genetic testing

Endocrine evaluation

- Low testosterone, and high FSH and LH → Primary (hypergonadotropic) hypogonadism (affecting both spermatogenesis and Leydig cell function)
- Normal testosterone and LH and high FSH → Primary (hypergonadotropic) hypogonadism (seminiferous tubule damage without Leydig cell dysfunction)
- Low testosterone, but FSH and LH not elevated (normal or low) – Secondary (hypogonadotropic) hypogonadism

Endocrine evaluation

- High testosterone and LH, but normal FSH → Partial androgen resistance
- Normal testosterone, LH, and FSH → Further evaluation depends upon findings on semen analysis (eg, azoospermia, oligozoospermia, asthenozoospermia, or teratozoospermia)
- Low sperm count and very low LH in a man who is very muscular → Suspicious for androgen abuse

Semen analysis interpretation

❖ Low volume

- Low semen volume with normal sperm concentration
- Low semen volume and low sperm concentration
- A low volume with azoospermia (no sperm) or severe oligozoospermia

Semen analysis interpretation

❖ Low concentration

- The lower reference limit for sperm concentration has been 15 million/mL
- Some men with sperm counts considered to be low can be fertile, while others above the lower limit of normal can be subfertile
- For the purposes of in vitro fertilization (IVF), 10 million/mL or even less can be satisfactory

Semen analysis interpretation

❖ Abnormal morphology

- Length, width, width ratio, area occupied by the acrosome, and neck and tail defects
- Round cells in the seminal fluid may be leukocytes, immature germ cells, or degenerating epithelial cells

❖ Poor motility

- In general, motility is not an important factor in independently predicting the probability of natural pregnancy, unless a very high percentage of sperm in ejaculate are immotile

- **The standard semen analysis provides descriptive data that do not always distinguish fertile from infertile men**
- In one prospective study of 430 couples, among those with a sperm concentration ≥40 x 106/mL, 65 percent achieved pregnancy compared with 51 percent of those with lower sperm concentrations
- In a study of male partners in 765 infertile couples in which the female partners had normal infertility workup and in 696 control fertile couples recruited from prenatal classes, there was extensive overlap between fertile and infertile men in sperm concentration, motility, and morphology
- However, men who have a **"triple"** defect of low sperm concentrations, low percentage of normal morphology, and low percentage of motile sperm have a high probability of infertility

Management

Table 4 – European Association of Urology guideline recommendations for noninvasive treatments for male infertility[a]

Recommendation	Strength rating
For men with idiopathic oligoasthenoteratozoospermia, lifestyle changes, including weight loss, increased physical activity, smoking cessation, and a reduction in alcohol intake, can improve sperm quality and the chances of conception.	Weak
No clear recommendation can be made for the treatment of patients with idiopathic infertility using antioxidants, although antioxidant use may improve semen parameters.	Weak
No conclusive recommendations can be made regarding the use of selective oestrogen receptor modulators in men with idiopathic infertility.	Weak
No conclusive recommendations can be made regarding the use of either steroidal (testolactone) or nonsteroidal (anastrozole and letrozole) aromatase inhibitors in men with idiopathic infertility, even before testis surgery.	Weak
Hypogonadotropic hypogonadism (secondary hypogonadism), including congenital causes, should be treated with combined hCG and FSH (recombinant FSH; highly purified FSH) or pulsed GnRH via pump therapy to stimulate spermatogenesis.	Strong
In men with hypogonadotropic hypogonadism, induce spermatogenesis with an effective drug therapy (hCG; human menopausal gonadotropins; recombinant FSH; highly purified FSH).	Strong
The use of GnRH therapy is more expensive and does not offer any advantages when compared to gonadotropins for the treatment of hypogonadotropic hypogonadism.	Strong
In men with idiopathic oligozoospermia and FSH values within the normal range, FSH treatment may ameliorate spermatogenesis outcomes.	Weak
No conclusive recommendations can be given regarding the use of high-dose FSH in men with idiopathic infertility before (microdissection) testicular sperm extraction and therefore cannot be routinely advocated.	Weak
Do not use testosterone therapy for the treatment of male infertility.	Strong

FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin.

[a] Amended table from the European Association of Urology guidelines on sexual and reproductive health [6].

Approach based upon diagnosis

- Endocrine and systemic disorders

  - Secondary (hypogonadotropic) hypogonadism: Induction of spermatogenesis

    Gonadotropin replacement therapy

  - Hyperprolactinemia

Primary testicular defects in sperm production

- Low serum T, elevated FSH and LH
- Normal serum T and LH, high FSH
- Normal serum T, normal LH and FSH

} ART

Intracytoplasmic Sperm Injection (ICSI)

Ovarian stimulation

A) Stimulation
The ovaries are stimulated with medication to promote the growth of follicles containing the eggs.

Control
The response of the ovaries is monitored with ultrasounds and/or blood tests, to control the size and quantity of follicles.

Egg release
To assist with the final maturation of the egg and loosening of the egg from the follicle wall, an injection of Human Chorionic Gonadotrophin (hCG) - the trigger- is administered.

Egg retrieval

B) Egg retrieval
The egg retrieval is performed 35-38 hours after 'the trigger' under ultrasound guidance, and takes place while you are sedated.

Fertilisation

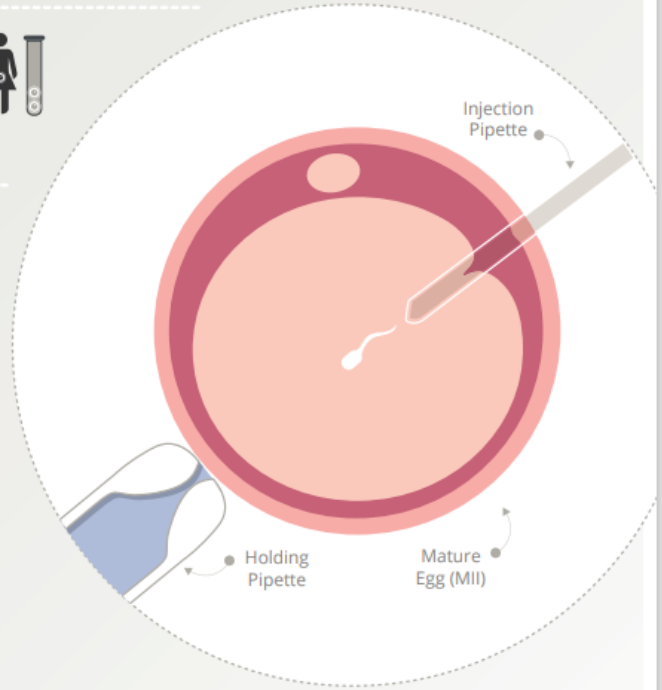
C) Sperm selection
The motile sperm are prepared and selected for insemination.

During sperm selecion a medium called Sperm Slow ™ is used. This medium contains hyaluronan (HA) which binds sperm that are more likely to have intact DNA and thus allows selection of these bound sperm for injection.

By selecting the sperm that are bound to HA and using them for ICSI, the embryologists are preferentially using the better quality, more mature sperm.

D) Egg maturity assessment
The cumulus cells surrounding the egg are removed by a gentle enzyme so maturity of the eggs can be clearly observed.

Only gentically mature eggs (MII) can be inseminated using ICSI.



ICSI

E) Insemination
Involves the injection of a single sperm directly into a mature egg.

F) Fertilisation
The dishes are placed in an incubator and checked for fertilisation 16-18 hours after insemination.

G) Culture
Embryos are grown in the lab for 2-5 days.

Embryo transfer

H) Embryo transfer
The embryo chosen for transfer is loaded into a transfer catheter which is passed through the cervix into the uterus, and gently released. Generally, only one embryo is transferred, in exceptional cases two.

I) Vitrification
The good quality embryos that are not transferred are frozen and stored. Frozen embryos can be used in subsequent cycles if the first cycle is not successful or for a sibling pregnancy.

Luteal phase & pregnancy test
The luteal phase is the two-week period between embryo transfer and the pregnancy test.

You will be encouraged to limit your activity for 24 hours after the embryo transfer.

Your pregnancy blood test will be approximately 14 days after embryo transfer.

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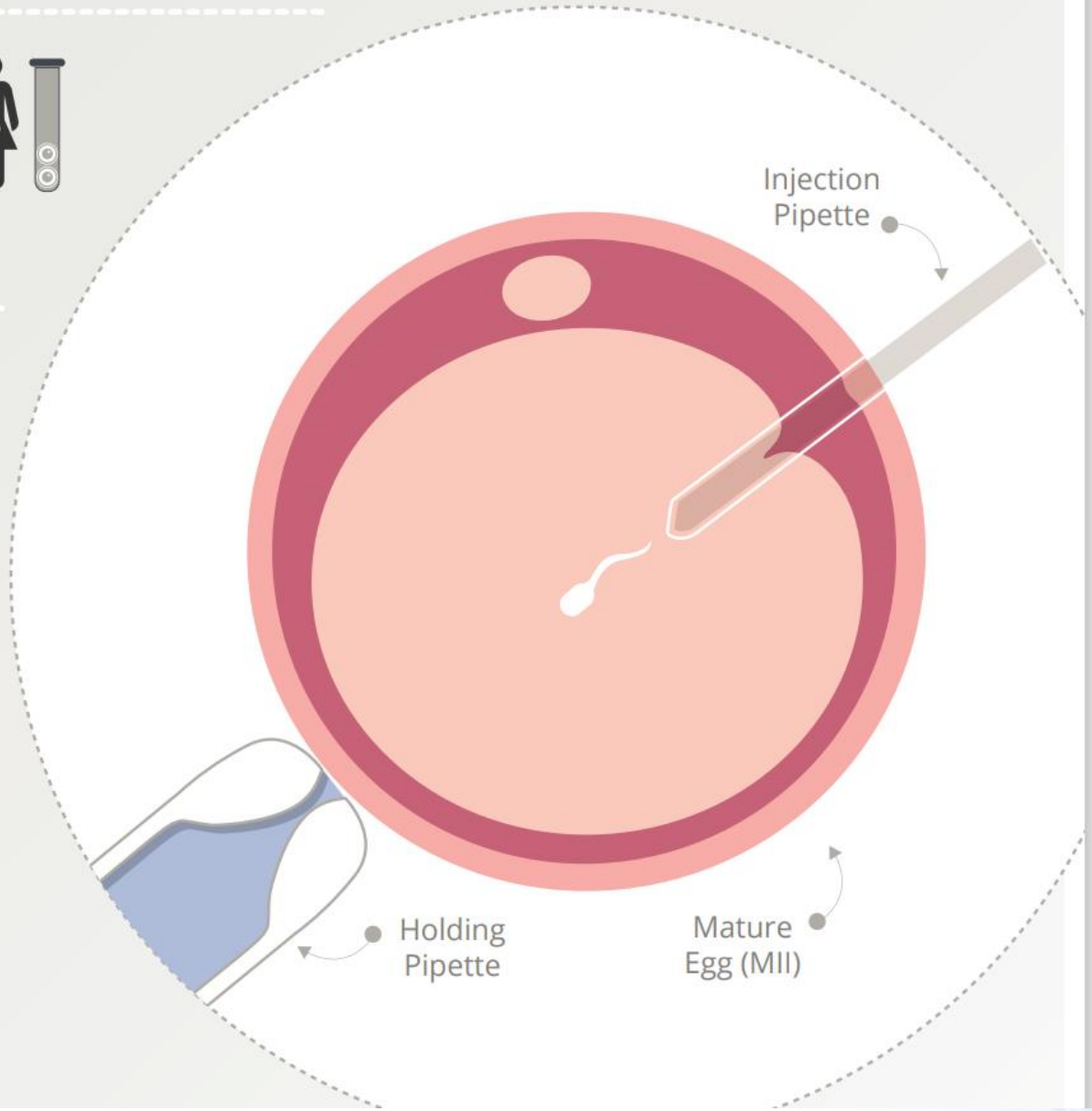

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Unproven therapies

- Surgical repair of varicocele→ **Surgery** only in infertile men with abnormal semen analyses and large, grade 3 varicoceles
- Treatment of leukospermia → Antibiotics and NSAIDs ×
- Medical therapies to increase circulating gonadotropin concentrations → **We recommend against** using clomiphene, aromatase inhibitors, or gonadotropin therapy for idiopathic dysspermatogenesis or idiopathic male infertility

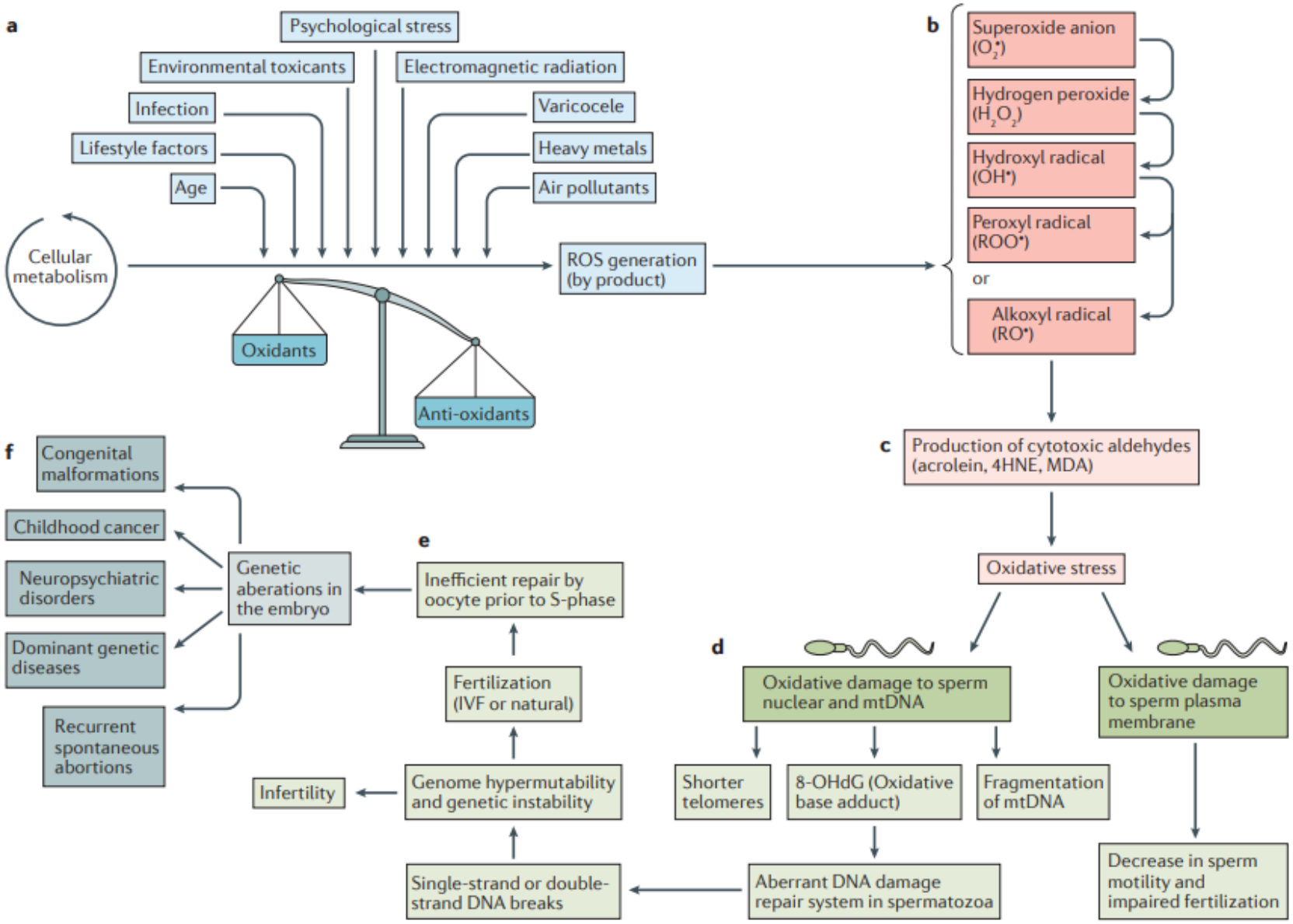
Lifestyle changes

- Avoiding tobacco, marijuana, excessive alcohol intake, and obesity
- Dietary supplements
  - Fish oil
  - Antioxidants (carnitines, carotenoids, coenzyme Q10, cysteine, folate, selenium, zinc, vitamin C, and vitamin E)

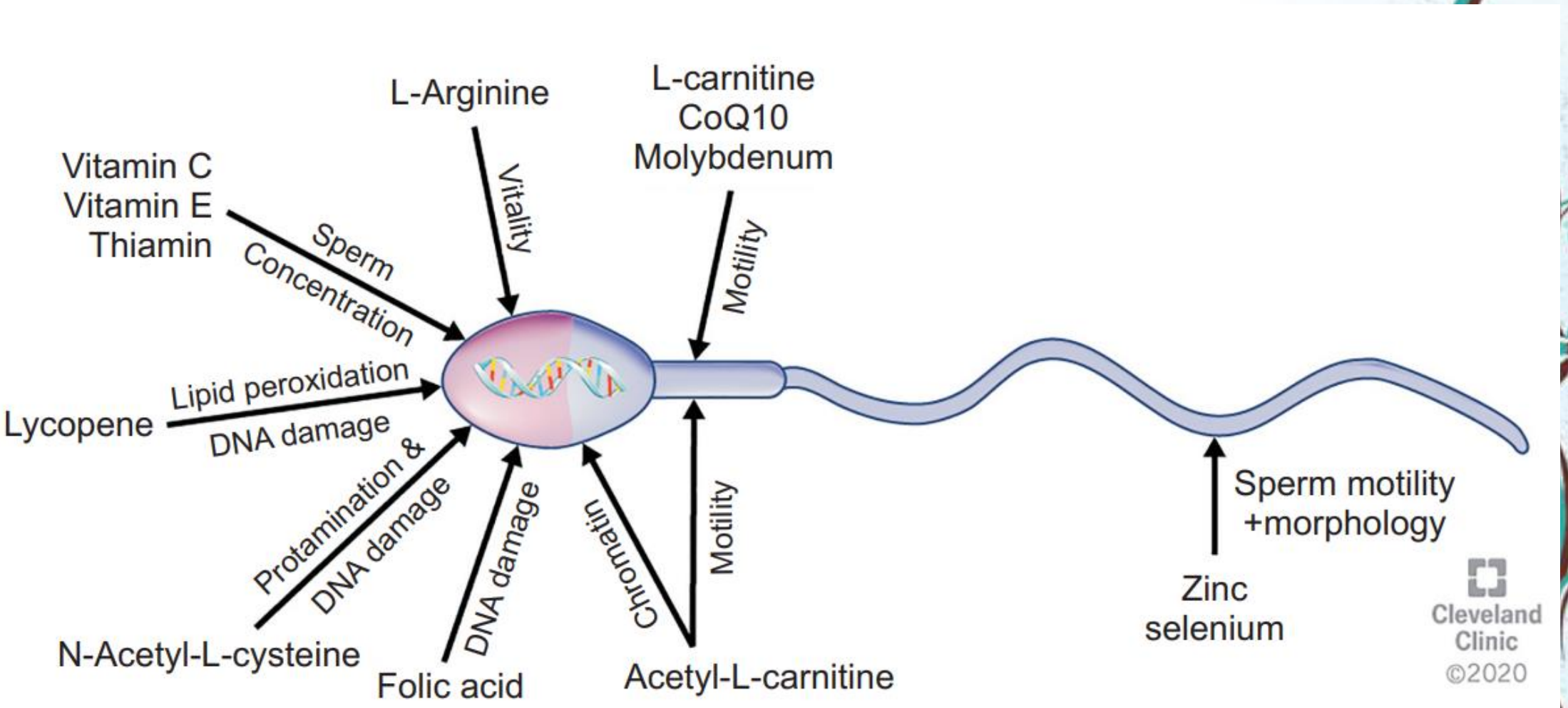
Sperm transport disorders

- Sexual disorders
- Retrograde ejaculation
- Obstructive azoospermia

Oxidative stress

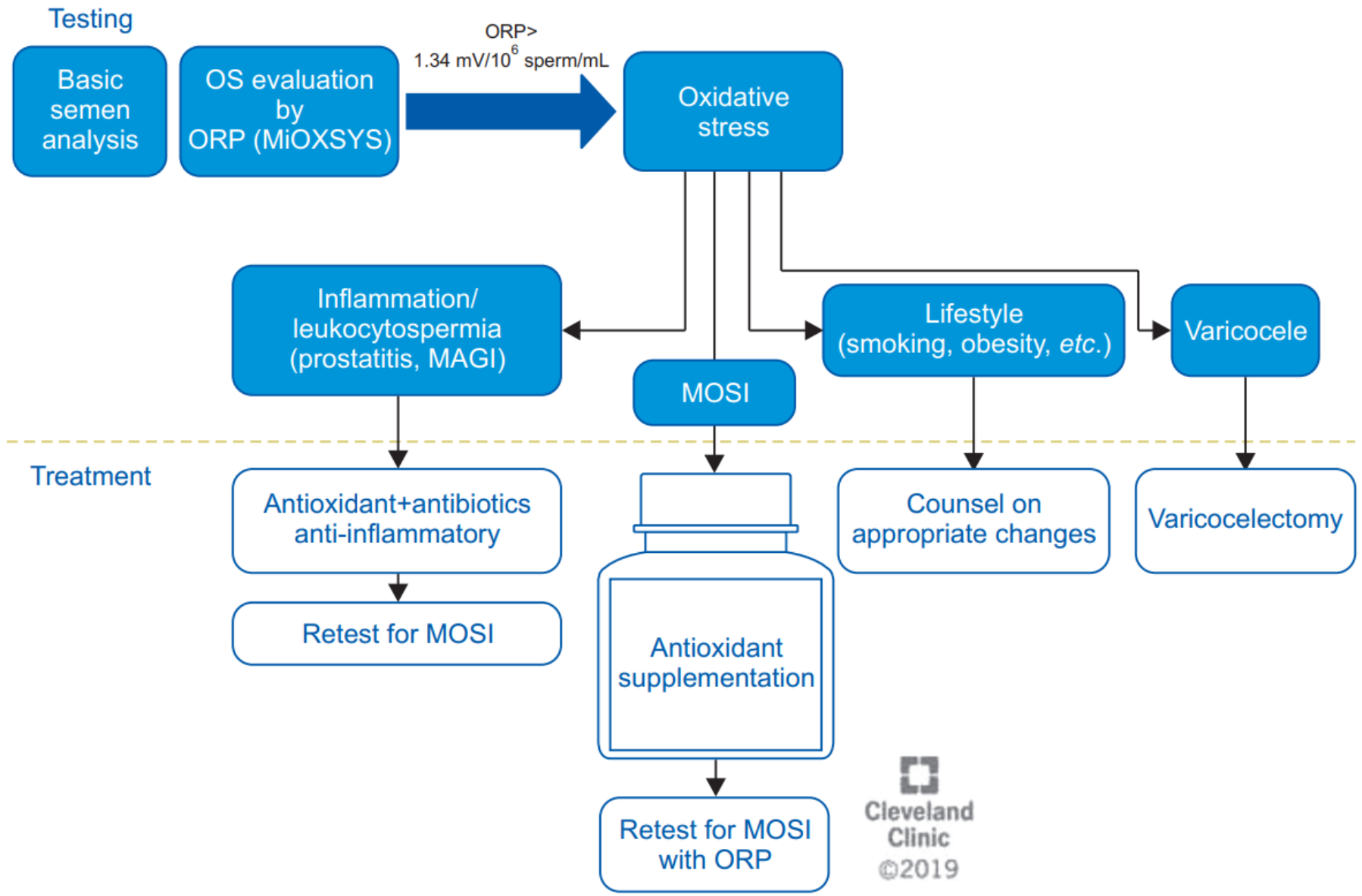


Antioxidants



Antioxidants

- While antioxidant supplementation is frequently utilized for the treatment of male factor infertility, no clear recommendations exist endorsing their use for specific clinical indications
- Looking at the diverse groups of conditions where oxidative stress is significantly involved and an anti-oxidant treatment would make sense, it is clear that in absence of prior testing for oxidative stress and without proper identification of suitable patient groups, the treatment will fail


Testing
Basic semen analysis
OS evaluation by ORP (MiOXSYS)
ORP> 1.34 mV/10^6 sperm/mL
Oxidative stress
Inflammation/ leukocytospermia (prostatitis, MAGI)
MOSI
Lifestyle (smoking, obesity, etc.)
Varicocele
Treatment
Antioxidant+antibiotics anti-inflammatory
Retest for MOSI
Antioxidant supplementation
Retest for MOSI with ORP
Counsel on appropriate changes
Varicocelectomy
Cleveland Clinic ©2019

Antioxidants

❖ Abnormal semen quality

●Antioxidants can improve conventional semen parameters and measures of sperm function (**grade C** recommendation)

❖ Varicocele

●Antioxidants in addition to varicocele ligation result in further improvement in semen parameters (**grade C** recommendation).

Antioxidants

❖ Unexplained male infertility and idiopathic male infertility

●Antioxidants significantly increase sperm quality in men with IMI and UMI (**grade B** recommendation)

Antioxidants

❖ Despite the safety and efficacy of the antioxidant therapy, five main factors have hindered its wide acceptance and implementation in the treatment of male infertility:

●Lack of randomized placebo-controlled Studies that show the safety and efficacy of antioxidants in improving pregnancy rates in infertile couples

●Type of antioxidant to be used

●Dose

●Duration of treatment

●Costs

Table 3. Preparations with potential positive effect on male infertility.

Substance	Dosage
vitamin E	400 mg
carnitines	500–1000 mg
vitamin C	500–1000 mg
CoQ10	100–300 mg
NAC	600 mg
zinc	25–400 mg
folic acid	0.5 mg
selenium	200 mg
lycopene	6–8 mg

Strengths

- Extensive interest in the use of antioxidants for the tratement of male infertility.
- Antioxidants have been associated with improvement in semen parameters and advanced tests of sperm function.
- Minimal side effects reported with antioxidant use.
- Current evidence suggest the effectiveness of antioxidants in idiopathic and unexplained male infertility.

Weaknesses

- Contradictory results have been reported with regards to the impact of antioxidant treatment on reproductive outcomes.
- Several studies did not adjust for confounding factors when examining the effect of antioxidant treatment on reproductive outcomes.

Opportunities

- Oral antioxidants are an easy and cost effective alternative for infertile couples who want to avoid ART.
- Recent efforts proposed tailoring antioxidant therapy towards patients with evidence of oxidative stress.
- Recent proteomic studies offered a better understanding of the molecular pathways involved with antioxidant supplementation.

Threats

- The exaggerated use of antioxidants may cause reductive stress.
- The evidence supporting the use of antioxidants is of low quality.
- Antioxidants therapy may unnecessarily delay treatment in certain circumstances (varicocele, severe male factor and couples of advanced age).