

In the name of God

The guidelines on male infertility

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Failure to conceive within 12 months of attempted conception is due in whole or in part to the male in approximately one-half of all infertile couples.

Although many couples can achieve a pregnancy with assisted reproductive technologies (ART), evaluation of the male is important to most appropriately direct therapy.

Some male factor conditions are treatable with medical or surgical therapy, and others may only be managed with donation or adoption.

Some conditions are life threatening, while others have health and genetic implications for the patient and potential offspring.

Without a male evaluation it is not possible to adequately design management of the patient and the couple.

varicocele

- Surgical varicocelectomy should be considered in men attempting to conceive who have palpable varicocele(s), infertility, and abnormal semen parameters, except for azoospermic men. (Moderate Recommendation; Evidence Level Grade: B)
- Clinicians should not recommend varicocelectomy for men with non-palpable varicoceles detected solely by imaging. (Strong Recommendation; Evidence Level Grade: C)
- For men with clinical varicocele and NOA, couples should be informed of the absence of definitive evidence supporting varicocele repair prior to ART. (Expert Opinion)

varicocele

- For men with NOA undergoing sperm retrieval, microdissection testicular sperm extraction (TESE) should be performed. (Moderate Recommendation; Evidence Level Grade: C) In men undergoing surgical sperm retrieval, either fresh or cryopreserved sperm may be used for ICSI. (Moderate Recommendation; Evidence Level Grade: C)
- A recent meta-analysis evaluating the use of sperm from men with NOA observed no differences in fertilization, pregnancy, or live birth rates from ICSI in men for whom sperm was extracted and used with or without cryopreservation, as long as there were sperm of adequate number and survived cryopreservation and thawing.

Azoospermia

- In men with azoospermia due to obstruction undergoing surgical sperm retrieval, sperm may be extracted from either the testis or the epididymis. (Moderate Recommendation; Evidence Level Grade: C)
- While the available studies are of low quality, fertilization, pregnancy, and live birth rates were similar for epididymal and testicular derived sperm in men with azoospermia due to obstruction.

Aspermia

For men with aspermia, surgical sperm extraction or induced ejaculation(sympathomimetics, vibratory stimulation or electroejaculation) may be performed depending on the patient's condition and clinician's experience. (Expert Opinion)

Male infertility may be managed with ART. (Expert Opinion)

One of the greatest advances in the management of male infertility has been the use of IVF and, subsequently, ICSI as ART.

Although sperm number and quality affected the results of treatment with IVF, ICSI appeared to abrogate any adverse effects of sperm “quality” as measured by sperm concentration, motility, and morphology as long as viable sperm are present to inject into all oocytes.

With IVF, abnormal sperm motility and morphology adversely affect fertilization rates. The application of ICSI during IVF treatment provided fertilization rates comparable to that observed with otherwise normal sperm.

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- Studies to date show limited known differences in birth defect rates between naturally occurring pregnancies, IVF, or ICSI-derived pregnancies.
- IVF treatment requires more than a week of ovarian stimulation, procedures for oocyte retrieval and intrauterine embryo transfer; each attempt typically allows for a 33% live delivery rate per initiated IVF cycle.

Pregnancy and live birth results are closely related to female age, with progressively lower success with increased female age (over 35 years). Approximately 19% of all deliveries involve twins, and additional pregnancies may result from one IVF cycle if additional embryos are available for cryopreservation.

hypogonadotropic hypogonadism

The patient presenting with hypogonadotropic hypogonadism (HH) should be evaluated to determine the etiology of the disorder and treated based on diagnosis. (Clinical Principle)

AIs,hCG, SERMs

Clinicians may use aromatase inhibitors (AIs), hCG, selective estrogen receptor modulators (SERMs), or a combination thereof for infertile men with low serum testosterone .

Each agent may be used separately or in combination in an effort to increase serum testosterone concentrations without impairing spermatogenesis.

hCG isFDA-approved for use in men with HH

Clinicians may consider use of AIs for men with testosterone deficiency and elevated estradiol levels.

Clinically, either hCG or SERMs may be considered for testosterone optimization in men with low or normal serum LH. Men who exhibit an elevated LH, consistent with primary hypogonadism, may have a limited serum testosterone response to these medications due to inherent testicular dysfunction.

Als,hCG, SERMs

- Clinicians should inform the man with idiopathic infertility that the use of SERMs has limited benefits relative to results of ART.(Expert Opinion)
- SERMs induce increased LH and FSH production by the pituitary gland.
- Although not FDA-approved for use in men, SERMs such as clomiphene or tamoxifen are often prescribed in infertile men who have normal serum testosterone levels with the therapeutic aim of improving semen parameters and fertility outcomes.

Als,hCG, SERMs

- One meta-analysis reviewed 11 studies that compared either clomiphene or tamoxifen with either placebo or no treatment in men with oligozoospermia or asthenoteratospermia. Collectively, the findings suggested that SERMs may improve sperm concentration, sperm motility, and spontaneous pregnancy rate.

A more recent systematic review published in 2019 included 16 studies that compared clomiphene or tamoxifen to placebo, no treatment, or other treatments (e.g., supplements, other medications) in men with oligozoospermia. As anticipated based on mechanism of action of SERMs, gonadotropin and serum testosterone levels increased.

Data suggested an improvement in sperm morphology and pregnancy rate with SERM administration, but no consistent impact on other semen parameters.

Antioxidants, vitamins

Clinicians should counsel patients that the benefits of supplements (e.g., antioxidants, vitamins) are of questionable clinical utility in treating male infertility. Existing data are inadequate to provide recommendation for specific agents to use for this purpose.

There are no clear, reliable data related to the variety of supplements (vitamins, antioxidants, nutritional supplement formulations) that have been offered to men attempting conception. Current data suggest that they are likely not harmful, but it is questionable whether they will provide tangible improvements in fertility outcomes.

A recent RCT by the NIH Reproductive Medicine Network of 174 men did not show adequate effect on semen parameters or DNA integrity in the initial screening arm to proceed to full patient accrual.

FSH analogue

For men with idiopathic infertility, a clinician may consider treatment using an FSH analogue with the aim of improving sperm concentration, pregnancy rate, and live birth rate. (Conditional Recommendation; Evidence Level Grade: B)

To this end, some clinicians have employed exogenous FSH in infertile men without HH (i.e., baseline FSH in or slightly above the normal range) with the therapeutic goal of improving fertility outcomes despite limited published data to date.

Typical treatment doses were 150 IU given daily over a 12-week period of therapy.

FSH analogue

One comprehensive meta-analysis reviewed 15 trials and described impacts of FSH administration versus placebo or no treatment on semen parameters and pregnancy rates. Overall, sperm concentrations and pregnancy rates, both unassisted and via ART, appeared to improve in the FSH-treated men.

A subgroup metaanalysis from this study looked at the 9 trials of FSH administration in 389 men compared to 308 controls and related unassisted pregnancy rates, with a resultant overall OR of 4.50 (CI 2.17 to 9.33, $P < 0.001$).

A second subgroup meta-analysis assessed pregnancy rates after ART; 322 men were treated with FSH compared to 275 controls, with a resultant overall OR of 1.60 (CI 1.08 to 2.37, $P = 0.002$)

FSH analogue

Another systematic review included 6 RCTs (225 men on FSH, 231 controls) assessing FSH versus placebo or no treatment and impact on pregnancy rate and live birth rate.

FSH therapy prior to medically-assisted treatments (one study on IUI, one study on IVF-ICSI) did not conclusively affect pregnancy rates with ART.

Clinicians should be aware that FSH is not FDAapproved for use in men. Additionally, the cost-to-benefit ratio of this treatment is questionable.

NOA

Patients with NOA should be informed of the limited data supporting pharmacologic manipulation with SERMs, AIs, and gonadotropins prior to surgical intervention. (Conditional Recommendation; Evidence Level Grade: C)

- One single-center, prospective, non-randomized comparative study assessed men with NOA who received CC prior to micro-TESE. Of the 372 men receiving CC, 11% had sperm recovery in the ejaculate, obviating the need for microTESE. SRR at the time of micro-TESE in the remaining 331 men was 57.7%, as compared with 33.6% in the control group.
- A double-blind, multi-center RCT published in 2013 compared treatment with letrozole, an aromatase inhibitor, to placebo in men with NOA. Although all NOA men in the treatment arm did have recovery of sperm in the ejaculate (and none in the placebo group), there were no unassisted pregnancies in either the treatment or placebo groups

NOA

Two studies used gonadotropin treatment in men with NOA. One retrospective comparison study explored the effects of hCG to no treatment in men with NOA undergoing surgical sperm retrieval; men were in the treatment arm, and 49 did not receive hCG. For all patients, conventional TESE was the initial surgical approach. If no sperm were identified, the procedure was converted to micro-TESE. There was no statistically significant difference in SRR, pregnancy rate, or live birth rate between groups.

A second prospective, non-randomized comparative study of 108 men with NOA compared FSH treatment to no medication prior to TESE. Neither group had recovery of sperm to the ejaculate. Surgical SRR in this small study was 64% in the men who received FSH versus 33% in the no treatment group.

Fertility preservation

Clinicians should inform patients undergoing chemotherapy and/or radiation therapy to avoid pregnancy for a period of at least 1 months after completion of treatment. (Expert Opinion)

Clinicians should encourage men to bank sperm, preferably multiple specimens when possible, prior to commencement of gonadotoxic therapy or other cancer treatment that may affect fertility in men. (Expert Opinion)

Clinicians should consider informing patients that a SA performed after gonadotoxic therapies, should be done at least 12 months (and preferably 24 months) after treatment completion. (Conditional Recommendation; Evidence Level Grade: C)

THE END

