# USI Male Infertility Guidelines

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## Aim

These guidelines cover the subject of male infertility and have been prepared by the USI Male infertility guidelines panel. The guidelines are intended for urologists to help them in their evaluation and management of patients with Male infertility and are not intended to replace clinical judgment.

## Material and Methods

Various topics under Male infertility were given to individual panelists for literature review and draft preparation . The draft prepared by the member was then discussed thoroughly by all members in almost 50 online meetings extending for four consecutive months from May to August 2020. Literature search was conducted on Pubmed, Cochrane, Index copernicus, Medline and Embase. Trials in India were separately searched. Secondary evidence sources included various society guidelines and reviews. The keywords used for the search included etiology OR causes, epidemiology OR prevalence, infertility OR subfertility, male, Male infertility, semen, obstructive azoospermia, vasovasostomy, vasoepididymostomy, non-obstructive azoospermia, sperm retrieval, hypogonadotropic hypogonadism, secondary hypogonadism, male accessory gland infection or MAGI, epididymitis, prostatitis, genetics, varicocele, testicular microlithiasis, unconsummated marriage, testicular cancer, fertility, cryopreservation, idiopathic and unexplained.

English language and Human filters were used and a total of 135775 abstracts were screened. After removing the duplicate and irrelevant articles the final remaining articles formed the basis of the written draft. A total of shortlisted 843 studies we included as evidence to frame the guidelines. Level of evidence was evaluated by the Center of Evidence based medicine method and the strength of recommendation was made. Each section starts with Guideline statements followed by a draft with references to substantiate the statements. Each chapter ends with a practical algorithmic flow chart for easy understanding of the practicing urologists. The panel made its final recommendations based on available global data with special reference to Indian studies as well as the socio economics of healthcare in India. Grades of recommendation ( strong/moderate/weak) are the strength of mandate based on the extent of risk-benefit ratio of either taking or not taking an action. Clinical principal(CP) is a statement that is widely agreed upon by clinicians for which there may or may not be evidence in medical literature. Expert opinion(EO) is a statement agreed upon by the guidelines panel in the absence of clear evidence.

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# Introduction:

Infertility has an immense psychosocial impact in Indian society. It is now a leading issue in the reproductive agenda of our government's policy.
The problems related to management of infertility specific to our country include poor availability of dedicated laboratories for semen analysis and other tests related to male infertility, mushrooming of fertility/ IVF centres and bypassing of male partner evaluation in majority of infertile couples, very few dedicated andrology centres with facilities for microsurgery , low affordability of patients for advanced tests and management by assisted reproductive techniques and a lack of well structured training programme on this subject in the curriculum of our medical teaching. All these factors have lead to lack of awareness and poor management of this problem. Creation of these guidelines will partly help to alleviate this important health issue.

# Etiology and Epidemiology

It is a worldwide problem and it affects 15% of married couples worldwide [1]. The prevalence of infertility in the general population is 15-20%, and of this, the male factor is responsible for 20-40%[2,3].In Indian couples seeking treatment, the male factor is the cause in approximately 23% [4]. A recent report on the status of infertility in India, states that nearly 50% of infertility is related to the reproductive anomalies or disorders in the male. In over 25% of infertility cases, no detectable cause can be traced after routine tests, which leaves the case as unexplained infertility[5]. The estimates of infertility vary widely among Indian states from 3.7% in Uttar Pradesh, Himachal Pradesh, and Maharashtra [6], to 5% in Andhra Pradesh [7], and 15% in Kashmir [8]. Causes of Male infertility can be grouped into three major groups [9] namely non obstructive, obstructive and coital. The Panel endorses the WHO definition of Infertility as the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in one year [10].

# Evaluation and Diagnostics

Evaluation should be performed with thorough history and detailed examination including focus on sexual dysfunction [11] and timing of performing intercourse. Sexual intercourse may be performed every other day beginning 5 days before expected ovulation until 5 days after [12]. Socio-economic status must be ascertained in our population as a part of evaluation [13]. Examination should help to rule out infections [14] such as genito-urinary tuberculosis [15]. Semen Analysis is the first investigation needed and due to significant variability in semen analysis reports of the same individual, it is suggested to do two semen analyses at least 2 weeks apart [16,17]. No clear recommendations can be made regarding ideal abstinence due to the conflicting nature of current evidence [18] but for all practical purposes, 2-5 days would be the ideal abstinence period for semen analysis [19]. The panel would like to emphasize that fructose is not a definitive marker to differentiate between obstructive and non-obstructive cause for abnormal semen parameters [20]. It is recommended to obtain blood endocrine profile as the second line investigation when semen analysis is abnormal. An initial blood endocrine profile shall include FSH, LH and total testosterone. Additional blood endocrine workup that may be done as second-line investigation includes Estradiol, SHBG and Prolactin [21]. FSH still remains the preferred test to evaluate spermatogenesis due to higher cost of inhibin B estimation [22].
Advanced Semen tests like evaluation of DNA fragmentation, Reactive oxidative species and antisperm antibody evaluation [23] are optional due to unclear consensus on cutoff values [24], availability and role.
The latest WHO Manual (6th Edition ) published recently emphasises the fact that Semen examination itself can not categorically differentiate between fertile and infertile males. The

normal reference ranges based on 5th percentile in the 5th edition of WHO manual has been replaced by decision limits. The introduction of decision limits is to stress upon the fact that the purpose of semen examination is not to label a man as fertile or infertile but rather to decide the next steps in terms of further evaluation and treatment. Both borderline and pathological reports are eligible for therapeutic intervention [25].

| Semen | Normal | Borderline | Pathological |
|---|---|---|---|
| Count | >20 mill./ml | 10-20 mill./ml | <10 mill./ml |
| Motility(Progressive) | >50% | 35-49% | < 35% |
| Morphology | >14 % | 4-13% | <4% |
| Sperm antibody binding(Agglutination) | <50% | 50-79% | >80% |

Evaluation of Sperm DNA fragmentation(SDF) constitutes an important addition in the workup as an extended test. Reactive Oxygen species(ROS) has been included as an advanced test though still considered more of a research tool.

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|---|---|---|
| Both the partners should be investigated simultaneously | CP | Moderate |
| Relevant reproductive clinical history and focused clinical examination should be done | CP | Strong |
| Perform semen analysis as per the WHO Laboratory Manual for the Examination and Processing of Human Semen (6th edn) reference criteria [26] | CP | Strong |
| Offer blood endocrine profile only if semen analysis is abnormal on at least two occasions | EO | Strong |
| Offer ultrasound scrotum for patients who are obese, with previous scrotal surgery or have tight small scrotum | EO | Weak |
| Transrectal ultrasound is offered only when ejaculatory duct obstruction is suspected | CP | Strong |
| For patients with Nonpalpable Vas, CBAVD must be suspected and CFTR mutation tested for both partners | 2a | Strong |
| Diagnostic testicular biopsy should be done preferably in a center where there is facility of sperm retrieval and cryopreservation | 1b | Strong |
| Vasography should not be used as diagnostic procedure alone and only to be used intraoperatively before reconstructive surgery | 2a | Strong |

Table 1: Recommendations for diagnosis and evaluation of male infertility

## Azoospermia and Management

Azoospermia is the absence of spermatozoa in the sediment of a centrifuged sample of ejaculate due to obstruction which is corroborated by a second sample. Obstructive azoospermia is less common than NOA and occurs in 20-40% of men with azoospermia [27]. The examinations and evaluation must aim at finding the level of obstruction in obstructive azoospermia and when partner has a good ovarian reserve surgical correction should be offered to the couple whenever feasible [28].

Low volume ejaculate, acidic pH and absent fructose suggests obstructive azoospermia, most commonly due to congenital bilateral absence of vas deferens (CBAVD) or ejaculatory duct obstruction (EDO). CBAVD is a clinical diagnosis, made by absence of bilateral vasa on palpation. The genetic test for CBAVD is CFTR gene mutation evaluation and Comprehensive testing in the couple is necessary to avoid CF child. Sperm retrieval is usually successful in men with CBAVD by epididymal aspiration or testicular sperm aspiration.

In patients with suspected non-obstructive azoospermia (NOA) serum FSH elevated more than 2.5 times strongly predicts NOA, However normal value does not rule out NOA. Inhibin B below 170 pg/mL (IQR 125–215 pg/mL) may suggest NOA [29] and 17 Hydroxyprogesterone assessment may indicate levels of intratesticular testosterone production [30] which have a greater clinical significance. Karyotype analysis [31] and Screening of Y-chromosome microdeletions [32] must be performed before invasive sperm extraction.Treatment with clomiphene [33] and hCG can lead to an increase in intratesticular testosterone (ITT) [34] and Leydig cells within the testis.

Male hypogonadotropic hypogonadism (HH) is the failure of the testes to produce androgens and sperms secondary to congenital or acquired diseases affecting the hypothalamus and /or the pituitary gland. Its diagnosis is confirmed by low serum FSH,LH and Testosterone levels. HH is one of the rare conditions in which specific medical treatment can reverse infertility. Treatment requires Androgen replacement therapy till/when fertility is not desired [35]. For fertility Gonadotropins are started to stimulate spermatogenesis.

In patients with undescended testis a Testicular biopsy should be done during orchiopexy to rule out malignancy [36]. Early orchiopexy should be offered as Orchiopexy done after 12 months has resulted in significant reduction of spermatogenesis, compared to those done before 12 months. Sperm retrieval with TESE may be done in cryptorchidism with azoospermia. In men with Klinefelter syndrome the chances of sperm retrieval at microdissection TESE is around 22-50%.

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|---|---|---|
| Men with female partners having good ovarian reserve should be offered microsurgical vasovasostomy or epididymovasostomy for azoospermia due to obstruction in epididymis and vas [37] | 3a | Strong |
| In CBAVD [38] or When the ovarian reserve of the partner is limited use Sperm retrieval techniques like MESA, TESE, PESA, TESA | 3a | Strong |
| Sperm retrieval techniques must be used in adjunct to reconstructive surgery | 2a | Strong |
| Patients with irreparable reproductive tract should be offered sperm retrieval techniques and ICSI/IVF | 2a | Strong |
| Men with EDO and dilated ejaculatory ducts may benefit from Trans-urethral resection of the ejaculatory ducts (TURED) | 2a | Moderate |

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|---|---|---|
| Men with suspected EDO but normal TRUS findings are likely to have a fibrous type of ejaculatory duct obstruction (post-infective). They are not candidates for TURED and will need PESA-ICSI | CP | Strong |
| NOA patients and those with counts <5 million/ml should undergo a comprehensive assessment including hormonal profile and genetic tests (Karyotyping and Y ch microdeletion) for assessing the aetiology | 1b | Strong |
| In men with complete AZFa and AZFb microdeletions surgical sperm retrieval is contraindicated | 2a | Strong |
| Young men with AZFc deletions require genetic counseling regarding transmission to offsprings and have better chances of sperm retrieval (up to 55%) on microdissection TESE | 2b | Moderate |
| Microdissection TESE (mTESE) is the most efficient method for surgical sperm retrieval in NOA [39] | 2b | Strong |
| Testosterone replacement therapy must not be done for management of infertility | 1a | Strong |

Table 2: Recommendations for management of Azoospermia

## Infections in Infertility

Infections have been associated with male infertility but direct causation has not been proven. Infections can lead to various defects in semen parameters [40] with increase in oxidative stress being a major contributing factor [41]. Leukocytospermia (LCS) or pyospermia is defined as $>10^6$/ml WBCs but there is no available reference for the number of Peroxidase positive cells [42]. WBCs should be differentiated from round cells (Precursors of Sperms) which are peroxidase negative and other cells like macrophages. Semen leukocytes are not a correct marker of infection in the reproductive tract and their presence is independent of detected of microorganisms [43]. Treatment of leukocytospermia in the absence of any documented pathogen does not improve the fertility rates [44]. Antibiotics and Anti-inflammatory agents (NSAIDs) for upto 3 - 6 weeks may have a role in management of Male Accessory Glands Infection (MAGI) especially in cases of Prostatitis, Vesiculitis, and epididymitis. Antioxidant therapy in presence of epididymitis to restore ROS balance after resolving infections and inflammation may also be used. Fluoroquinolones are first choice for 28 days to 42 days. However with increasing resistance to Fluoroquinolones, other pertinent options like 3rd generation cephalosporins, Trimethoprim, Azithromycin and Doxycycline may also be suggested.

## Varicocele,Microlithiasis and Male Infertility

The presence of varicocele has been implicated in the development of male factor infertility, testicular hypotrophy and abnormal semen parameters [45,46].The role of ultrasound and colour doppler imaging in the diagnosis of varicocele remains controversial and subclinical varicocele have poor concordance with those detected on physical examination [47].Subclinical varicoceles are seldom of clinical significance in patients with male factor infertility and so is the repair thereof [48,49]. Surgical varicocelectomy significantly improved

semen parameters in men with abnormal semen parameters including men with non-obstructive azoospermia [50]. In few cases of non-obstructive azoospermia especially those with hypospermatogenesis or late maturation there may be a return of low numbers of sperms in the ejaculate after varicocele repair [51].The treatment of the varicocele should be considered in a male partner where male factor infertility is present, when the varicocele is palpable on physical examination of the scrotum; the couple has known infertility; the female partner has normal fertility or a potentially treatable cause of infertility and the male partner has abnormal semen parameters.

Testicular microlithiasis is an uncommon condition characterized by calcifications within the seminiferous tubules . As per literature its incidence is between 0.7 to 6% but the true prevalence in a normal population has not been defined .

Testicular cancer can affect fertility both by virtue of its presence and its treatment rendering as many as half the patients subfertile [52]. After the administration of gonadotoxic chemotherapeutic agents, a patient can develop oligospermia, or even azoospermia and a number of factors both hormonal and non-hormonal play a role in regeneration [53]. Similarly, radiation exposure can damage spermatogenesis, while higher doses lead to azoospermia [54].

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| There is no proven direct causation of infections on infertility | 3 | weak |
| Antibiotics and anti-inflammatory agents can be given in patients with leukocytospermia, clinical evidence of male accessory gland infections and abnormal semen parameters | 3 | Weak |
| Only clinically palpable varicoceles require treatment | 1a | Strong |
| Microsurgical varicocelectomy is the preferred modality of treatment | 1b | Strong |
| Microlithiasis is associated with abnormal semen parameters but direct causation cannot be proven | 3 | Weak |
| Testicular Self Examination must be taught and encouraged in patients with Microlithiasis | 2 | Moderate |
| Cryopreservation is mandatory and counselling should be done for all cases regarding Fertility Options. | 2 | Strong |
| Orchidectomy should not be delayed in the process of fertility preservation | 3 | Moderate |
| Risk of Hypogonadism should also be explained and baseline hormones should be established | 3 | Moderate |

Table 3 - Conditions causing abnormal semen parameters and their management.

Unconsummated marriage (UCM) is an important but neglected cause of male infertility, accounting for up to 17% of outpatient visits in clinics treating sexual health. These couples

have been unable to achieve peno-vaginal penetration due to male, female or combined factors [55].

## Unexplained and Idiopathic infertility

Unexplained Infertility refers to those persons with normal seminal parameters and no known associated conditions that impart male infertility , have normal findings on physical examination and endocrine laboratory testing and a definitive female infertility factor has not been identified in the couple [56]. Idiopathic infertility is defined as abnormal semen parameters without a known cause.Before labelling an infertile male as unexplained or idiopathic infertility all other causes should be excluded . Idiopathic and unexplained infertility doesn't have definitive treatment. Empirical medical treatment (EMT) consists of two broad categories, hormonal and antioxidants which can be offered to these patients [57]. Such Empirical Medical treatment should be offered initially for at least four to six months (two spermatogenic cycles) before going for Assisted reproductive techniques. Clomiphene Citrate is a widely used medication in patients with normal testosterone to estradiol ratio of more than 10 [58]. Patients with an abnormal T/E2 ratio less than 10 may benefit from a treatment with aromatase inhibitors like Anastrozole and letrozole [59]. 30% to 80% of infertile men have elevated seminal ROS levels, a potentially treatable condition [60]. Oxidation–reduction potential (ORP) is a better representative for oxidative stress(OS) as it provides an overall measure of the activity of both oxidants and reductants.

## Conclusion

The present text represents a summary of the USI guidelines on male infertility. For approximately 50% of couples with infertility, the cause will be related to a male factor and therefore all infertile men should undergo urological evaluation . The latest WHO Manual (6th Edition ) emphasises that Semen examination itself can not categorically differentiate between fertile and infertile males. It has replaced the reference range in semen analysis with decision limits in order to decide further management and not label them as fertile or infertile. Amongst various causes of male infertility, Hypogonadotropic hypogonadism and infections are amenable to medical management and varicocele and obstructive azoospermia to surgical management.
In India because of socio economic reasons donor insemination and adoption remain important options in management of infertile couples. Idiopathic and unexplained infertility still affects one third of the infertile couples. Currently, there is insufficient evidence to support the plethora of empirical treatments and interventions being used in clinical practice. Detailed information with full text ,supporting references and practical algorithms are available on the USI website.

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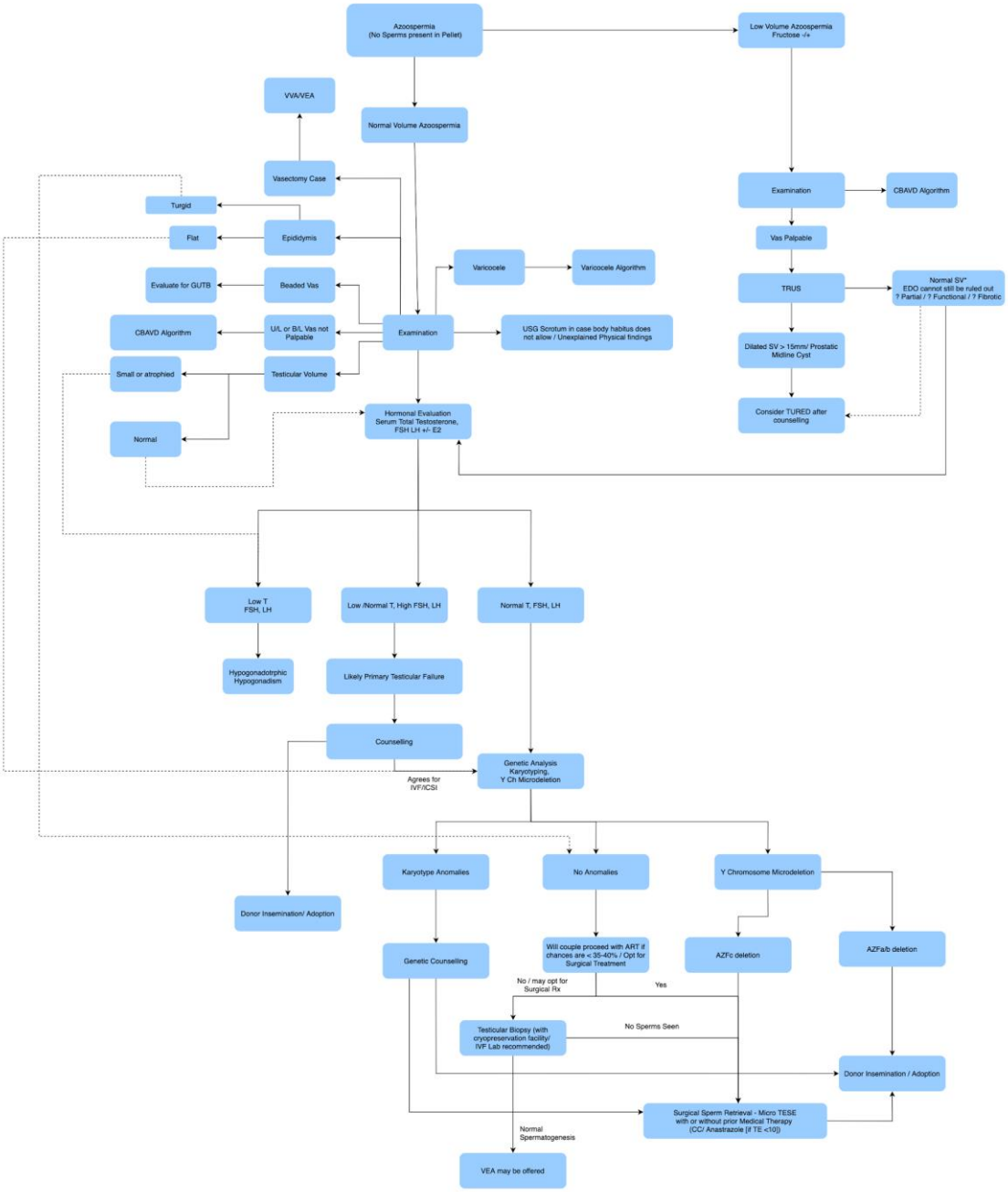
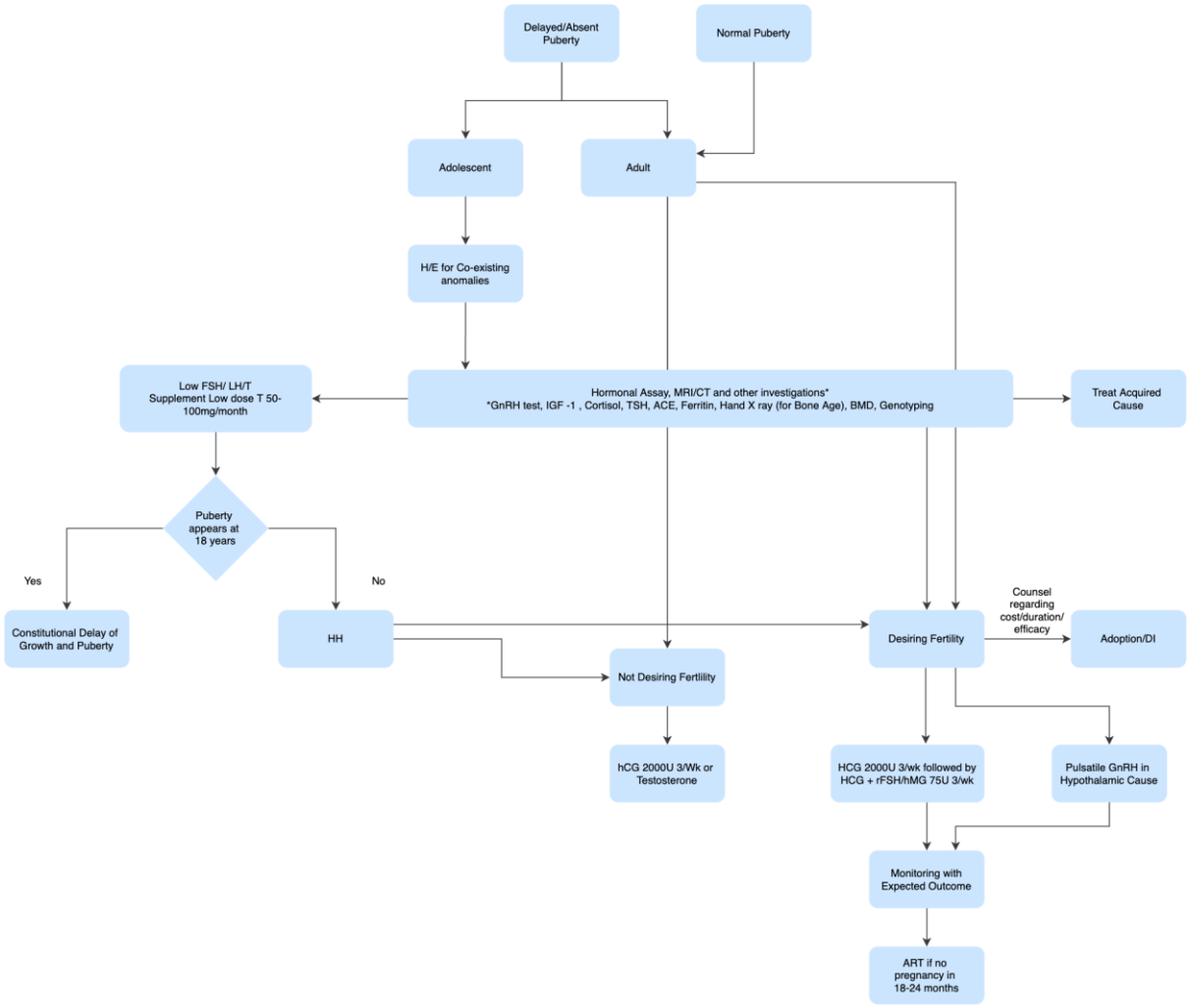
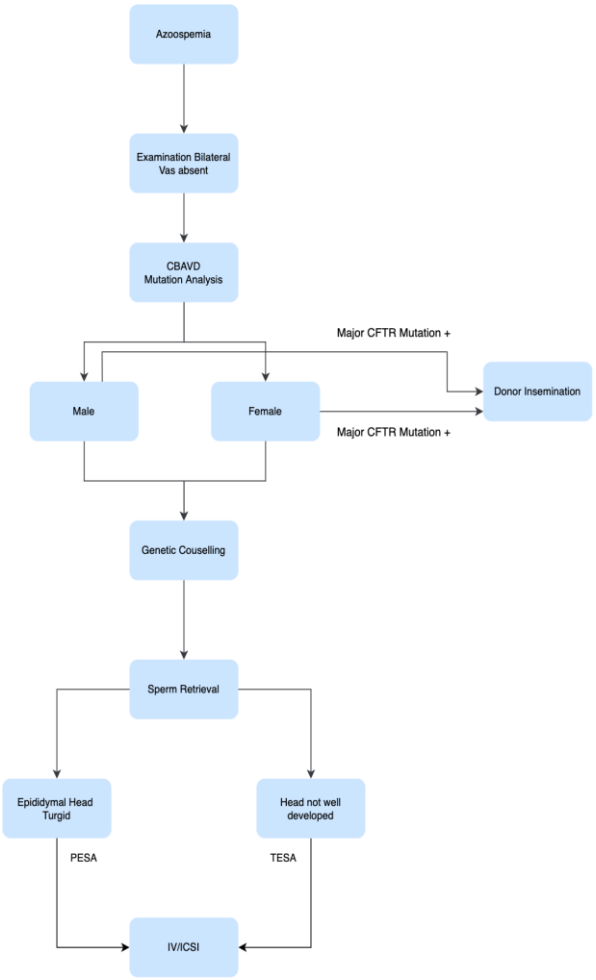
1.Algorithm for management of Azoospermia



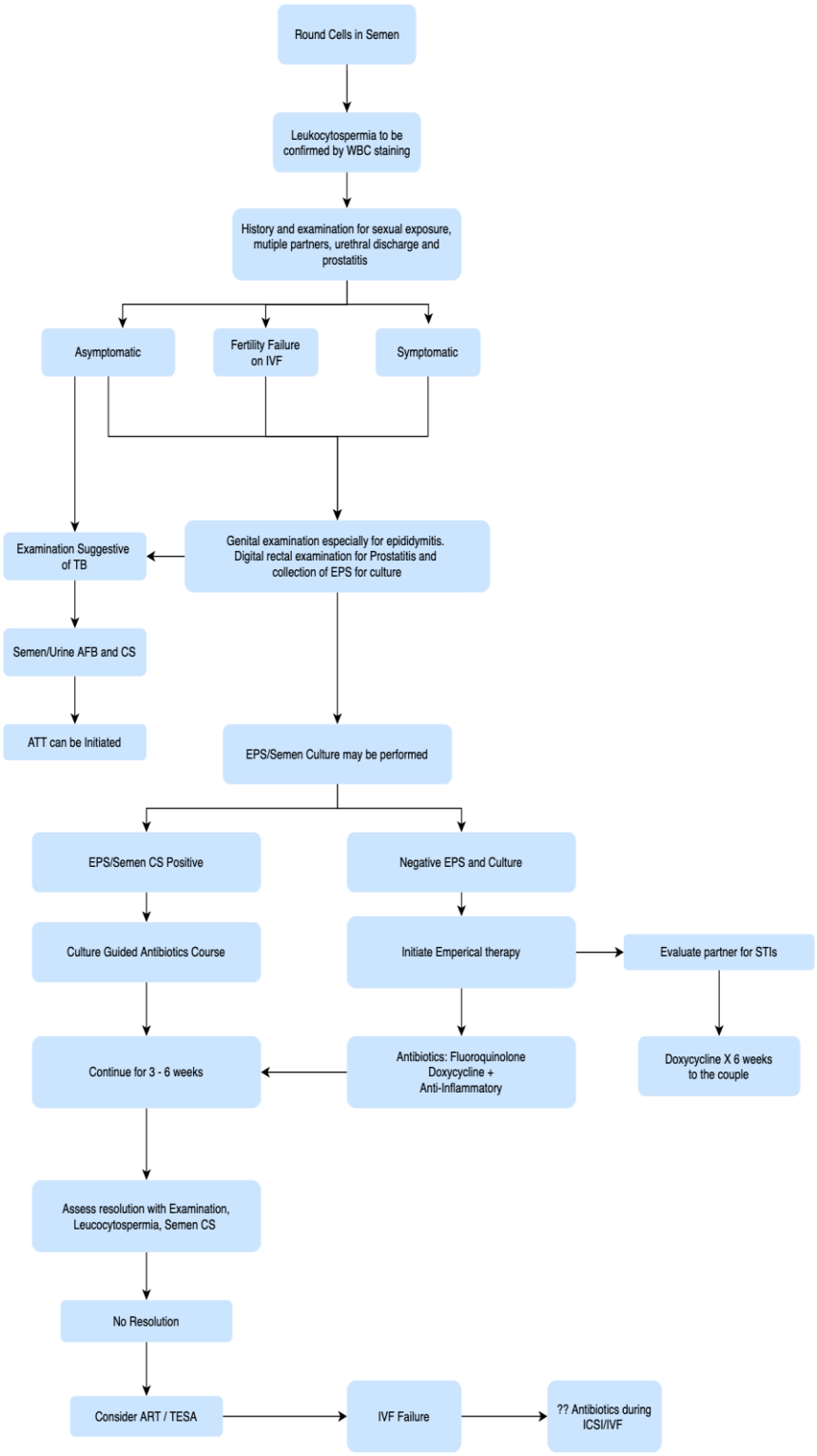
2.Algorithm for management of Hypogonadotropic hypogonadism



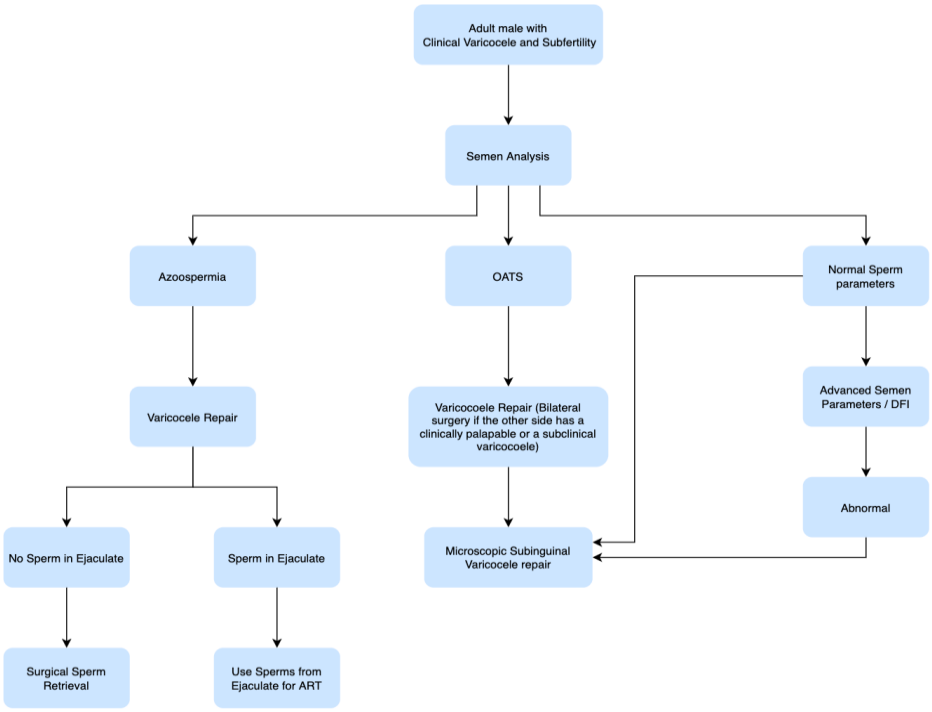
3. Algorithm for management of CABVD



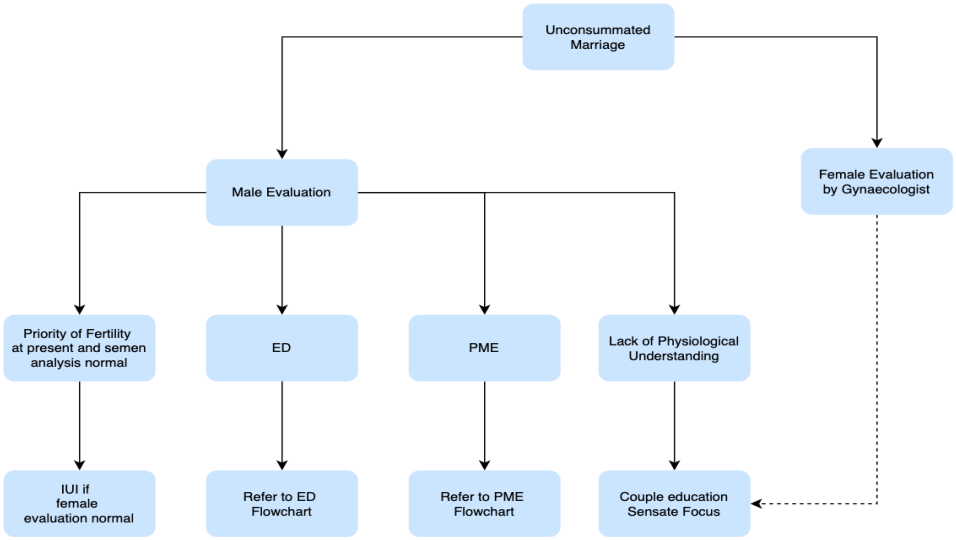
4.Algorithm for management of Leucocytospermia



## 5. Algorithm for management of Varicocele




## 6. Algorithm for management of Unconsummated marriage



7. Algorithm for management of Idiopathic and unexplained infertility