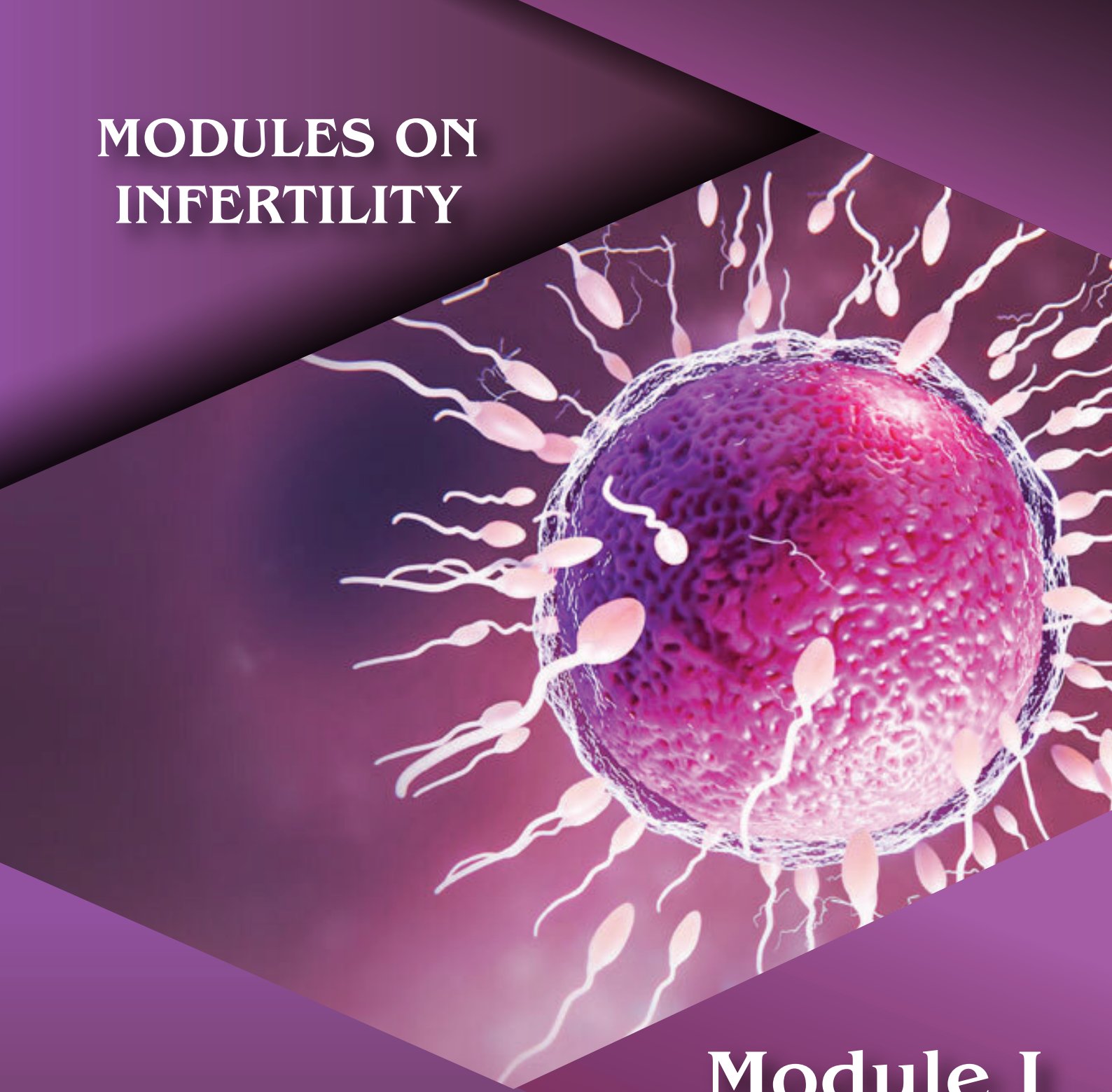
MODULES ON INFERTILITY



Module I

Overview of Infertility and Diagnostic approaches in Infertility

CONTENT

Overview of Infertil ity

Human beings are remarkably fertile. Most females are capable of conceiving and bearing children beginning in their mid-teen years. While women in industrialized societies usually bear children in their 20s and 30s, women can give birth well into their 40s and beyond. Men can be fertile into extreme old age. Unlike most mammals, humans can mate successfully year round; fertility is not restricted to a particular season of the year or to brief episodes of female heat.

But the process of reproduction is immensely complex. For conception to take place and pregnancy to begin, hundreds of individual hormonal, chemical, and physical events must take place in a precise order. For example, a sperm must form in the testicle, mature in the epididymis, be released into the female vagina, "swim" through the cervical opening, continue through the uterus and into a fallopian tube. In the tube, it must encounter a viable egg within 12 hours or so of its monthly release, attach itself to the egg, penetrate its outer vestments and fertilize the ovum within. After staying in the fallopian tube for about two days, the fertilized egg must descend into the uterus, grow and divide for a few more days, and then implant itself on the uterine wall.

A single disruption, small or large, in any of these events and conditions can cause infertility. The sperm may not be viable-it may be dead, it may contain the wrong number of chromosomes, it may have been stored too long after its formation. Or it may be viable but immotile, meaning that it cannot "swim" correctly. It may be perfectly healthy but not accompanied by enough other sperm, for although only one sperm is ultimately required for fertilization, men whose semen contains less that 20 million sperm per milliliter frequently have infertility problems. The sperm ducts may be blocked, because of past infection or injury. The man may not be able to ejaculate, or his ejaculation may propel the sperm backward into his bladder rather than out through the penis. Once inside the cervix, the sperm may meet mechanical or chemical roadblocks. A muscle spasm may eject the sperm, the cervical mucus may be too thick to penetrate, or chemically hostile to the sperm. The fallopian tube may be blocked by scar tissue. If the sperm does manage to reach the egg, it may not be able to penetrate its defenses to fertilize it. A fertilized egg may become stuck in the fallopian tube. Or it may not be able to implant successfully in the uterus.

In the late 20th century, medical science has made great advances in understanding each stage of the reproductive process and in identifying the problems that can occur at each step. In an increasing number of cases these barriers can be corrected or worked around in order to achieve fertility for about 65% of couples who seek the help of fertility specialists. Although most of the biological work of creating children must still be done by the human body-the gestation bottles depicted in Aldous Huxley’s 1946 novel Brave New World are still impossible-science can provide substitutes for a few key processes.

Is infertility becoming more common? Despite public worry and discussion, the actual incidence of infertility has remained fairly stable over the years. One American couple out of 5 or 6 currently experiences infertility. Infertility grows more common with increasing age; about 33% of couples in their late 30s are infertile. The age factor has taken on new importance as many people in the United States and similar industrialized countries have put off marriage and children until certain educational or career goals are reached. For some time during the "sexual revolution" of the 1960s and ‘70s, doctors did see higher incidence of infertility caused by tubal blockages left by untreated venereal diseases such as gonorrhea and chlamydia. But this trend seems to have reversed since the appearance of AIDS has forced the adoption of barrier methods of contraception, which prevent most venereal diseases. Another social factor, the increasing difficulty of adoption (a result of improved birth control and the availability of legal abortion) has increased the demand for medical answers to infertility, regardless of their complexity and high cost.

Overview on Diagnosis of Infertility

Even the most fertile human couple does not necessarily conceive the first time sexual intercourse takes place. In fact, the chance of conception in any given month among fertile couples attempting to conceive is about 20%, or one chance in five. To avoid unnecessary testing and treatment, most doctors will not make the diagnosis of infertility until one year of unprotected intercourse has failed to result in pregnancy. Some cases, involving older couples or existing evidence from previous marriages, may be diagnosed sooner and treated more aggressively.

Once the diagnosis is made, examinations, testing and history-taking begin to find the cause(s) of infertility. In about 30% of infertility cases, the problem can be found solely in a medical problem of the woman's; in another 30%, male factors alone cause the infertility; and in another 30% of cases, both partners have conditions which render the couple infertile. In the remaining 10% of cases, no clear cause can be found.

Women are given a physical and pelvic examination, laboratory tests, and one or more imaging procedures to locate the problem which may be causing infertility. Testing may include exploratory surgery, using laparoscopy. In this technique, a small fiber-optic tool is inserted through a "keyhole" incision to allow the physician to inspect the reproductive system. Advanced ultrasound imaging may also reveal structural or functional problems. One commonly found condition during the infertility evaluation is endometriosis. In this disorder, cells from the endometrium, which normally line the uterus, spread in patches and cysts throughout the female reproductive system. Additionally, some women do not ovulate regularly or at all. Others may produce eggs regularly that are prevented from being fertilized, descending or implanting.

Men are tested for the presence, quantity and quality of their sperm. The most common problem affecting male sperm levels is a varicocele, a tangle of veins surrounding the testicle. Surgical correction of large varicoceles restores fertility in about two-thirds of cases. Other causes of male infertility include insufficient hormone levels (which may be supplemented); blocked tubes which carry sperm (which can sometimes be surgically repaired or bypassed), untreated diabetes or prostate disease and other conditions.

Assessment of Infertile Couples

The pathway to pregnancy in infertile couples is usually long and requires a high level of resilience owing to several factors including medical procedures, economic costs and psychological stress. In order to minimize the impact and to maximize the results, a well-integrated and multidisciplinary approach including all the different specialists of reproduction is necessary. In fact, it is mandatory to identify the most appropriate procedure with a gradual approach to both partners to obtain a precise diagnosis and the most effective therapeutic option, reducing invasive procedures that are not necessary.

For this reason, the first step should be a preliminary evaluation of both the male and female partner, drawing up the medical history and performing a clinical examination, taking into account the main issues listed in Tables 2 and 3 for male and female respectively. In addition to the medical history and clinical examination, semen analysis, endocrine assessment, and ultrasound scanning should be performed in order to have a more comprehensive picture.

Infertile Couple Pathway

Health workers dealing with infertility should be able to guide couples through a clear, standardized and operative flow, reducing unnecessary burden on couples and optimizing the output of the diagnostic and treatment pathway. In Figure 1, we reported the results of an Italian consensus recommending a comprehensive approach to infertile couples. Based on WHO definition, couples should firstly be divided based on the time of offspring search (< or >12 months). The threshold chosen for the duration of pregnancy seeking is crucial and can impact on the prevalence of the disease, avoiding couples to undergo unnecessary diagnostic tests or to the risk of overdiagnosis (47). The WHO recommends preconception care between 3 and 6 months before trying for a baby because of its positive impact on maternal and child health outcomes (https://apps. who.int/iris/handle/10665/78067). As medical history, physical examination and ultrasound for women are part of routine preconception counselling, the gynecologic and whole health evaluation of the woman seeking pregnancy can be started independently of the diagnosis of infertility (http://www.undp.org/content/undp/en/home/librarypage/mdg/the-millenniumdevelopment-goals-report-2015.html). Possible factors involved in determining female infertility can be investigated as early as this stage (Table 2). For males, medical history, physical examination, sperm analysis, and ultrasound should be performed as shown in Table 3 (48).

If no alteration or risk factors are highlighted by this first level examination, couples are recommended to have free intercourse waiting till 12 months. If any alteration or risk factor emerges, the affected partner should undergo further analyses as described below.

Couples with more than 12 months infertility, should undergo the same preliminary approach. If no alteration is highlighted in both partners, expectant management is acceptable. Indeed, no significant differences in live birth rates between expectant management and other interventions for unexplained infertility have been recently reported, at least excluding patients at poor prognosis of natural conception (49). However, alongside a waiting strategy, further diagnostic investigations are advisable: males should perform a comprehensive microbiological screening (see Andrological Specific Flow-Charts). If any infection is detected, it should be treated and checked after the end of treatment. On the other hand, if any alteration or risk factor emerges from the preliminary examination, the affected partner should undergo further analyses. In particular, targeted examination should be performed for women based on specific risk factors as alterations observed at trans-vaginal ultrasound (Figure 2) or clinical conditions (Figures 3–5 explained below). For men, microbiology tests (Figure 6) or targeted flow charts (Figures 7–9 explained below) should be followed based on sperm parameters.

Gynecological Specific Flow Charts

Second Level Diagnostic Investigation

In a couple with > 12 months infertility, where the male partner has normal sperm parameters and woman has no known risk factors, second level investigations should start with the antral follicle count (AFC) and anti-mullerian hormone (AMH) dosage. If the woman was diagnosed as "poor responder", the couple should be recommended to undergo in-vitro fertilization (IVF) independent of age (Figure 3). As the number and the quality of oocytes are directly related to the probability of obtaining a live birth through IVF, a waiting policy in these couples could be excessively penalizing if spontaneous conception was not obtained (50, 51). Indeed, the age-related decline in ovarian reserve has been shown greater in infertility patients than fertile women (52). Likewise, women older than 40 years old should be directed to IVF independently from the ovarian reserve because in older women with no other risk factors the immediate access to IVF demonstrated superior pregnancy rates compared to other ART treatments (53). However, several key issues in reproductive physiology cannot be accurately investigated by means of the ordinary diagnostic work up. Thus, in women older than 40 years, unexplained infertility cannot be diagnosed easily and women encountering a physiological "age-related infertility" could be treated without a true indication (54). Although an immediate IVF strategy in these couples has theoretical advantages, there is no strong evidence in support of treatment versus a waiting policy (55).

If AFC and AMH are normal (i.e. patients cannot be defined as poor responders) further steps depend on the time of infertility (< or >2 years) and on female age. If the time of infertility is < 2 years, the management depends on the age: in women with less than 35 years (Figure 4), an hysterosalpingosonography (HSSG) should be performed. In case of tubal patency, it can be suggested intrauterine injection (IUI) as first approach, as the chance of achieving a live birth are higher than expectant management (56). VF should be recommended after 3 IUI attempts (57), as the same chance to have a pregnancy by IVF (about 30% per attempt) are achieve at the seventh cycle of IUI (58). We do not consider all these attempts acceptable, as time to pregnancy and the couples' compliance could be compromised after such numbers of failures. Furthermore, previous evidence suggests that the number of IUI attempts should be limited up to four (59–61).

If the HSSG highlights no tubal patency, a diagnostic and/or operative laparoscopy could be proposed, as laparoscopy in women with unexplained infertility may reveal previously undiagnosed pathologies that could require ART, and in those without abnormal surgical finding, ART does not improve pregnancy rate (62). If laparoscopy show tubal patency or it is possible to perform an operative laparoscopy, 6 months of free intercourses or IUI, can be suggested. If laparoscopy confirms tubal occlusions, the couple should be directed to IVF.

If a female age is between 35–40 years (Figure 5) HSSG could be performed. In case of tubal patency, IUI can be suggested as first approach. IVF should be recommended after 3 IUI attempts. If the HSSG highlights no tubal patency, IVF should be recommended. Independently from the ovarian reserve, in presence of hydrosalpinxes (often related to a PID history) a diagnostic and operative laparoscopy should be proposed before IVF (63–66). In case of dysmenorrhea/dyspareunia or others signs suggesting for mild endometriosis or IVF refusal (67, 68), a diagnostic laparoscopy within 3 months could be proposed, because undiagnosed or subtle pelvic abnormalities may be a significant cause of IVF failure (69).

If the time of infertility is >2 years and women age is <40 years, IVF should be proposed. Laparoscopy must be limited to few selected cases (IVF refusal, history of PID/hydrosalpinxes, dysmenorrhea/dyspareunia) after a careful risk benefit assessment. Male partner of couples candidate to IVF could be tested for sperm aneuploidy and nuclear integrity tests.

Andrological Specific Flow Charts

Microbiological Assessment

The WHO guidelines for the management of male infertility include microbiological investigation and the diagnostic examinations of male accessory gland infection (MAGI) (70).

MAGI comprise orchitis, epididymitis, vesiculitis, prostatitis, and urethritis, which are potentially reversible causes of male infertility (71). Following the WHO's recommendations (70), medical history, physical examination and sperm analysis play a crucial role to suggest a microbiological assessment to the male partner of an infertile couple. In particular, leukocytospermia (leukocytes >1 million/ml), more frequently occurring in infertile patients compared to fertile men (72), deserves microbiological investigation, as suggested by the American Society for Reproductive Medicine (ASRM) Practice Committee (73).

There is a lack of consensus about the specific microbiological analysis that should be requested in infertile patients with MAGI. Although the WHO guidelines (70) indicate sperm culture, more recent research suggests that the urethral swab, which could more accurately detect intracellular microorganisms such as mycoplasmas (71, 74), may be useful. Accordingly, a systematic review with meta-analysis carried out on cohort and case-control studies found an association between Mycoplasma hominis and Urea plasma urealyticum and male infertility, underlining the importance of their identification (75). If the culture is negative, the specialist could decide, case by case, both to treat the male with anti-inflammatory or to request second level tests. In the case of positive culture, the female partner should also be tested and tailored treatment should be prescribed to patients with infection. A microbiological re-evaluation at the end of the treatment may be useful because of the relatively high persistence rate at the end of the antibiotic treatment (71).

The microbiological assessment of infertile couples should include the search for Papillomavirus (HPV) DNA, especially in case of current or anamnestic presence of condylomatosis, or in recurrent pregnancy loss. Accordingly, HPV infection shows a significantly higher prevalence in infertile patients compared to fertile men (20.4% vs. 11.4%), as indicated by a meta-analysis (76). Also, results from 5203 men revealed significantly worse conventional sperm parameters in HPV-positive than HPV negative patients, with the motility being the parameter more strongly associated with HPV-infection. Importantly, a significantly higher miscarriage rate has been reported in HPV-positive patients compared to controls (77). Finally, if the HPV DNA test is positive, both male and female should be counselled for possible HPV vaccination and followed-up at 3 and 6 months after counselling.

Azoospermia, Cryptozoospermia, and Severe

Oligozoospermia (< 5 Total Million) The first step for men with azoospermia, cryptozoospermia and severe oligozoospermia (<5 total million sperm), should be the assessment of testicular volume and sex hormones levels (48, 73, 78). If both, testicular volume and FSH, LH, and total testosterone (T) are normal, further analyses are performed based on semen volume: on one hand, if it is reduced or absent, a trans-rectal ultrasound (TRUS) and the search of sperm in the urine sample should be performed to evaluate the possibility of retrograde ejaculation (79–82) or vas deferens obstruction. In the latter case, the CFTR gene mutations should be investigated (83). On the other hand, if the semen volume is normal, TRUS could highlight genital tract obstruction and vas deferens pathologies and should be investigated as above described (84). At the same time scrotal ultrasound should exclude epididymal abnormalities (85, 86). If no alteration is found, histological/cytological evaluation may be performed to highlight spermatogenic function, distinguishing obstructive forms from primary testiculopathy (87, 88). In case of spermatogenic impairment, it makes sense to perform genetic screening for karyotype and Y microdeletions (89–91).

If the testicular volume is normal or reduced, hormonal levels lead to further investigation: in case of increased FSH and normal LH and testosterone levels, genetic screening for karyotype and Y microdeletions should be performed (92) and histological/cytological evaluation procedure could be performed aimed to clarify the tubular status. When LH is increased, testosterone normal or increased and FSH normal or reduced, the genetic screening for androgen receptor (AR) mutations should be performed (93) and also in this case, histological/ cytological evaluation option may be considered.

Lastly, if the testicular volume is reduced, FSH and LH and testosterone are normal or reduced, pituitary-testicular axis should be assessed by both, hormonal tests for hypopituitarism and pituitary imaging to assess the abnormalities (94). In addition, if pituitary imaging doesn't reveal any alteration, genetic screening for KAL, DAX1, LHbeta, and GNRH-R gene mutations should be performed (95–97).

Moderate Oligozoospermia (5–39 Total Million)

Also for men with moderate oligozoospermia (from 5 to 39 total million sperm), the first approach should be the assessment of testicular volume and hormonal asset (48, 73, 78).

If both, volume and hormones are normal, testicular doppler ultrasound should be performed aimed to exclude the presence of varicocele (98–100). Also based on semen volume, pH, and TRUS, four conditions should be considered: MAGI (see the section Microbiological Assessment—Figure 6), partial genital tract obstruction (101), retrograde ejaculation, and idiopathic oligozoospermia (102).

In the last scenario, a genetic screening for karyotype should be performed (92) and, in case of sperm count below 10 million, histological/cytological evaluation, could highlight the cause of oligozoospermia (88, 103).

In presence of normal or reduced testicular volume, normal or increased FSH and LH and normal T and PRL, the presence of varicocele or idiopathic infertility should be investigated as described above (99, 100).

Finally, if testicular volume, FSH, LH and T are normal or reduced and PRL is normal or increased, pituitary-testicular axis should be assessed by both, imaging and further hormonal test for hypopituitarism as previously described (94) (see Figure 7).

Asthenozoospermia

In presence of isolate asthenozoospermia, first of all genital tract infections should be excluded (see the section Microbiological Assessment—Figure 6) and a further semen analysis should be performed after 3 months from the end of treatment to re-evaluate such condition. If confirmed, a scrotal doppler ultrasound, a TRUS and test for anti-sperm antibodies (ASA) test should be performed (104). Based on the results, we could face three scenarios: i) immunological infertility (105); ii) testicular or post-testicular infertility, including epididymal deferential alterations, prostate chronic abnormalities or varicocele (106, 107) and iii) idiopathic infertility. In the case of idiopathic infertility, mutation of dynein gene should be investigated (108, 109). In case of presence of possible environmental or lifestyle causes of semen alteration, asthenozoospermia should be confirmed after 3 months from removal of risk factors (frequent saunas, smoking, workactivities, tight sportswear) (108, 110, 111).

Andrological Specific Flow Charts

TABLE 2 | First gynecological approach.

Medical history	Physical examination	Ultrasound
Iatrogenic causes	BMI	PCO
Ovulation	Hirsutism-hyperandrogenism	Ovarian Reserve
Ovaria reserve	Galactorreha	Ovarian masses
Age	Pelvic masses	
Metabolic factors	Cervical-vaginal disorders	
Poliabortivity		
Lifestyle		
Metrorrhagia	Fibroids	Fibroids
VIP	Malformations	Malformations
IUD		Endometrial polyps
Poliabortivity		Endometrial thickness abnormalities
Malformations		
Previous surgery		
PID	Sacto/hydrosalpinx	Sacto/hydrosalpinx
Dysmenorrhea/Dyspareunia	Adhesions syndrom	Adhesions syndrom
Recurrent cystitis/vaginitis	Endometriosis	Endometriosis
IUD		
Previous surgery		

BMI, Body mass index; IUD, intrauterine contraceptive device; PCO, Polycystic ovary; PID, pelvic inflammatory disease; VIP, voluntary interruption of pregnancy.

TABLE 3 | First andrological approach.

Medical history	Physical examination	Ultrasound	Sperm parameters
Family history of infertility	Anthropometric measures Androgenization	Testicular evaluation (morphology, size, masses	Volume
Testicular trauma	BMI/WC	presence)	Total
Previous infectious diseases	Testicular evaluation (morphology, size, position, masses	Varicocele/hydrocele	number
Iatrogenic factors	presence)	Microlithiasis	pH
Endocrine diseases	Varicocele/hydrocele		Morphology
Using of anabolic steroids	Penis evaluation		Motility
Puberty disorders	Gynecomastia		Vitality
Infertility with previous			Swelling
partner			Antibody
Occupational factors			Viscosity
Lifestyle			

BMI, Body mass index; WC, waist circumference.

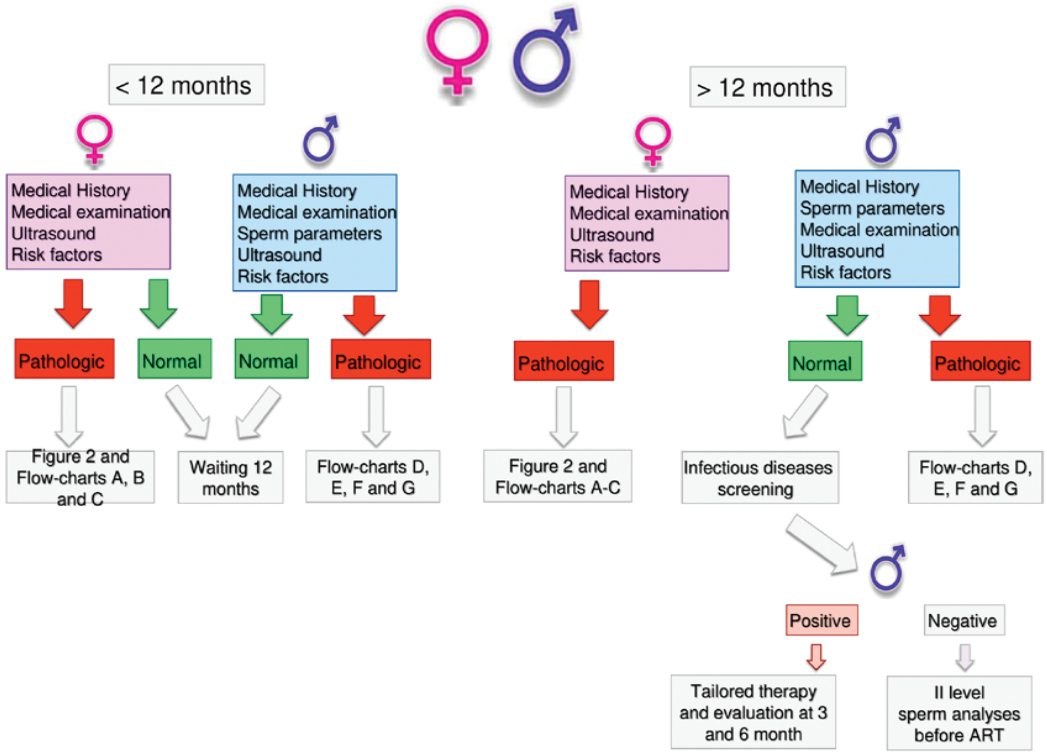


FIGURE 1 | Infertile couple flow chart.

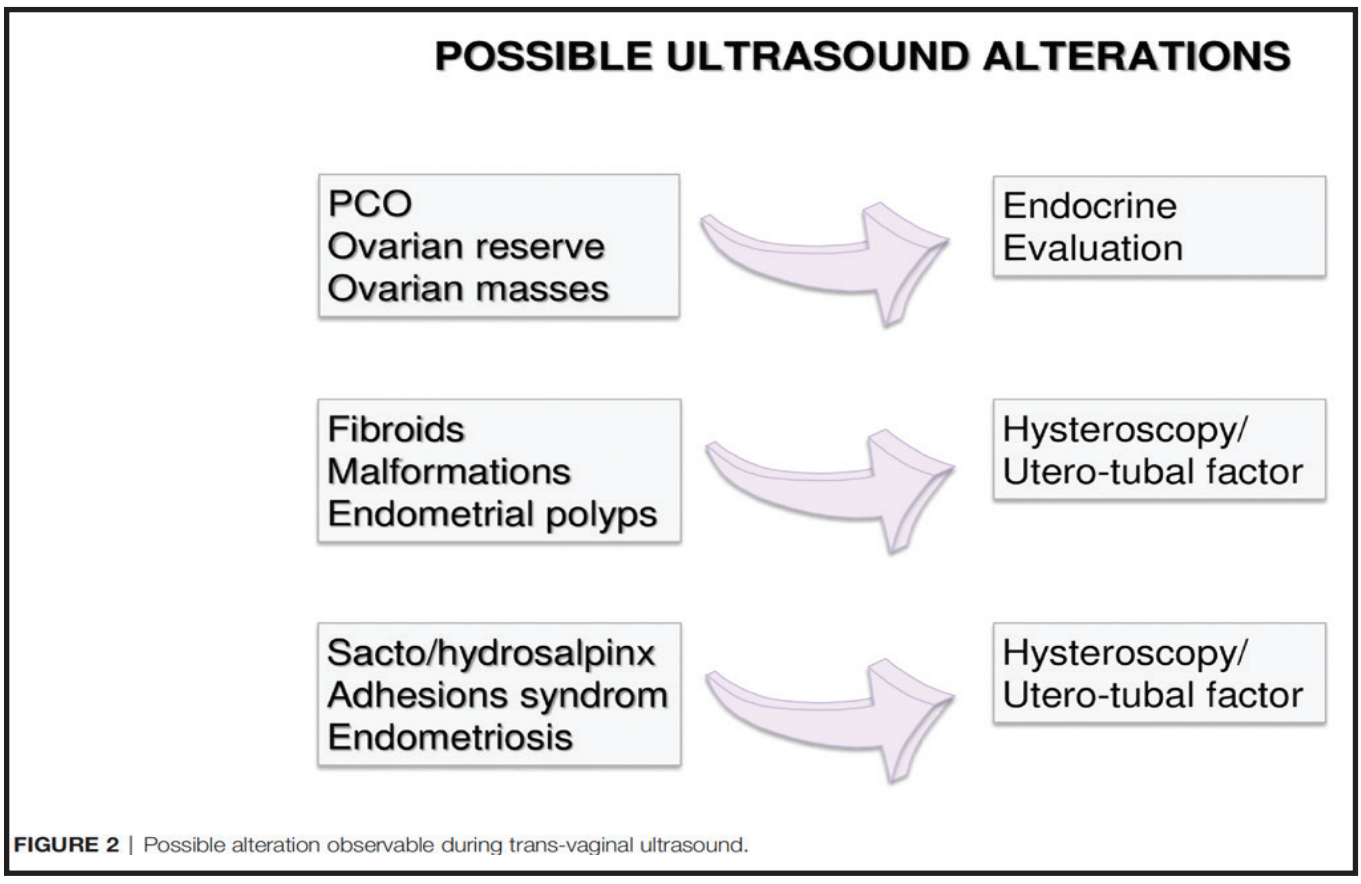


FIGURE 2 | Possible alteration observable during trans-vaginal ultrasound.

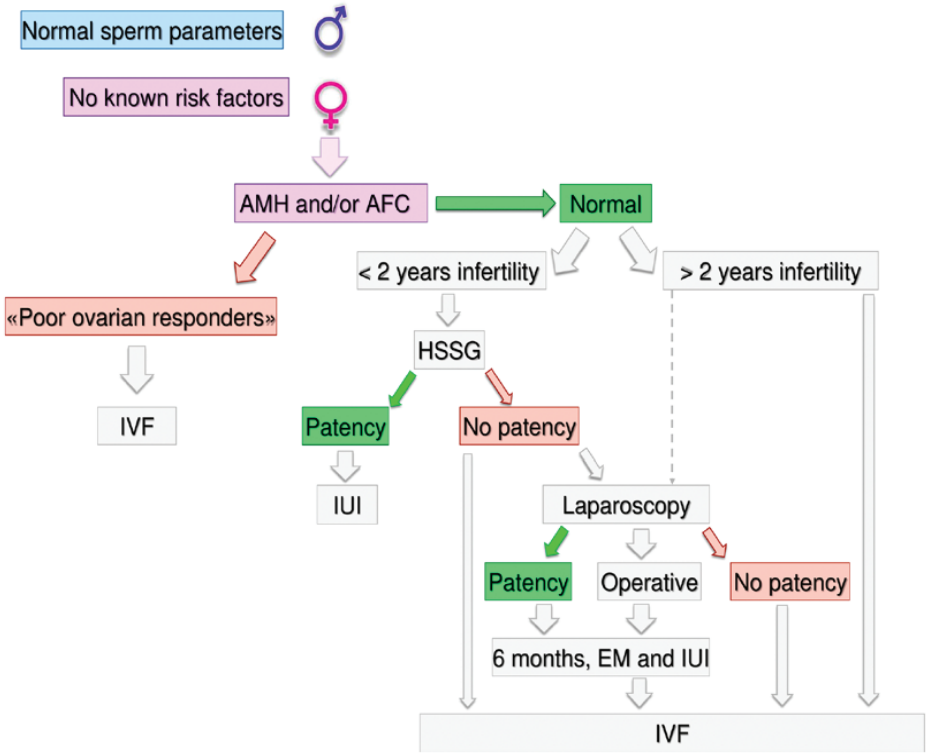


FIGURE 3 | Gynecological specific flow chart: second level diagnostic investigation and possible therapeutic approach for woman with no known risk factors.

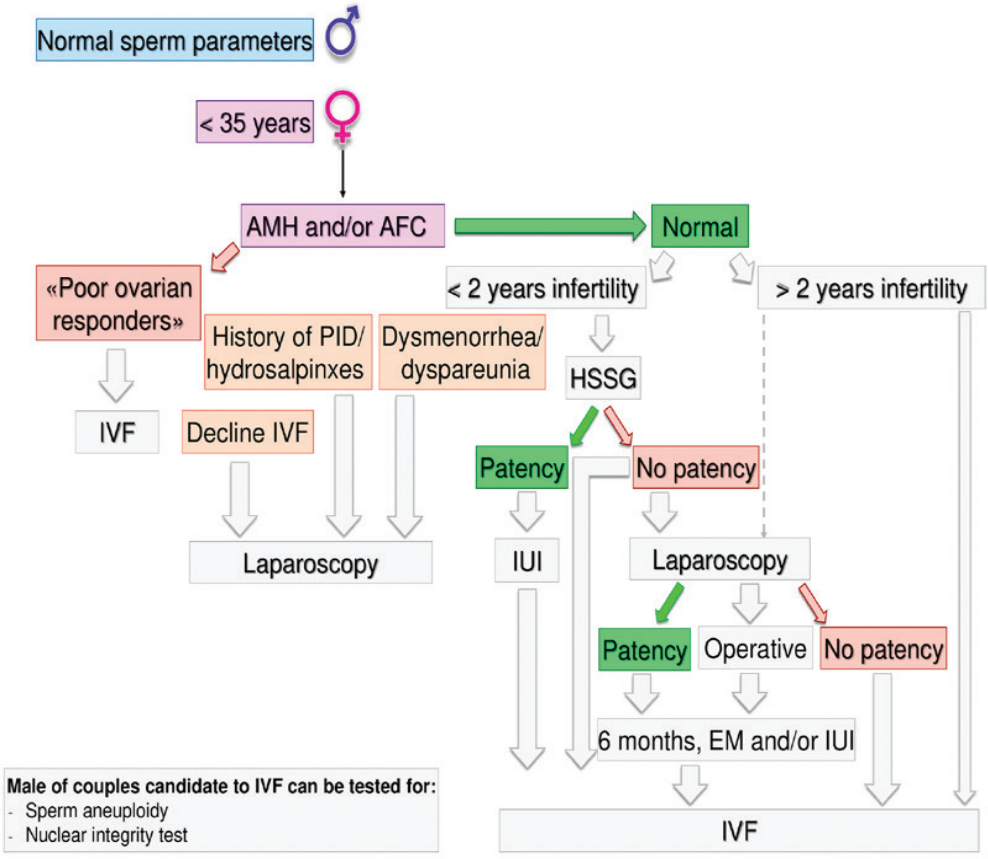


FIGURE 4 | Gynecological specific flow chart: second level diagnostic investigation and possible therapeutic approach for woman with <35 years.

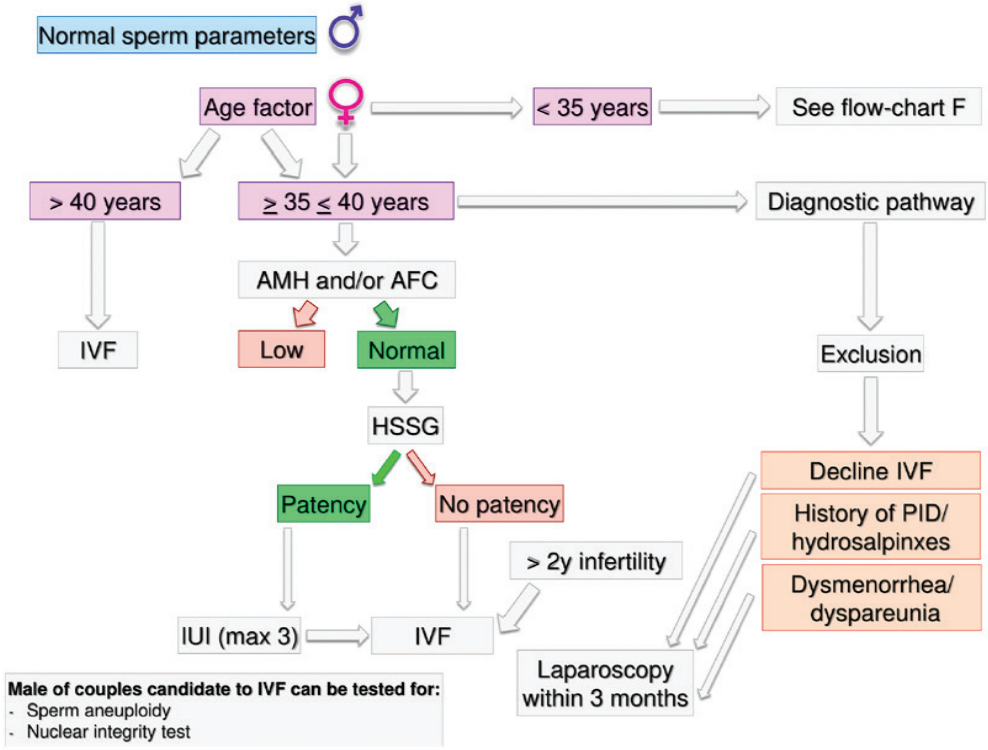


FIGURE 5 | Gynecological specific flow chart: second level diagnostic investigation and possible therapeutic approach for woman with >35 years.

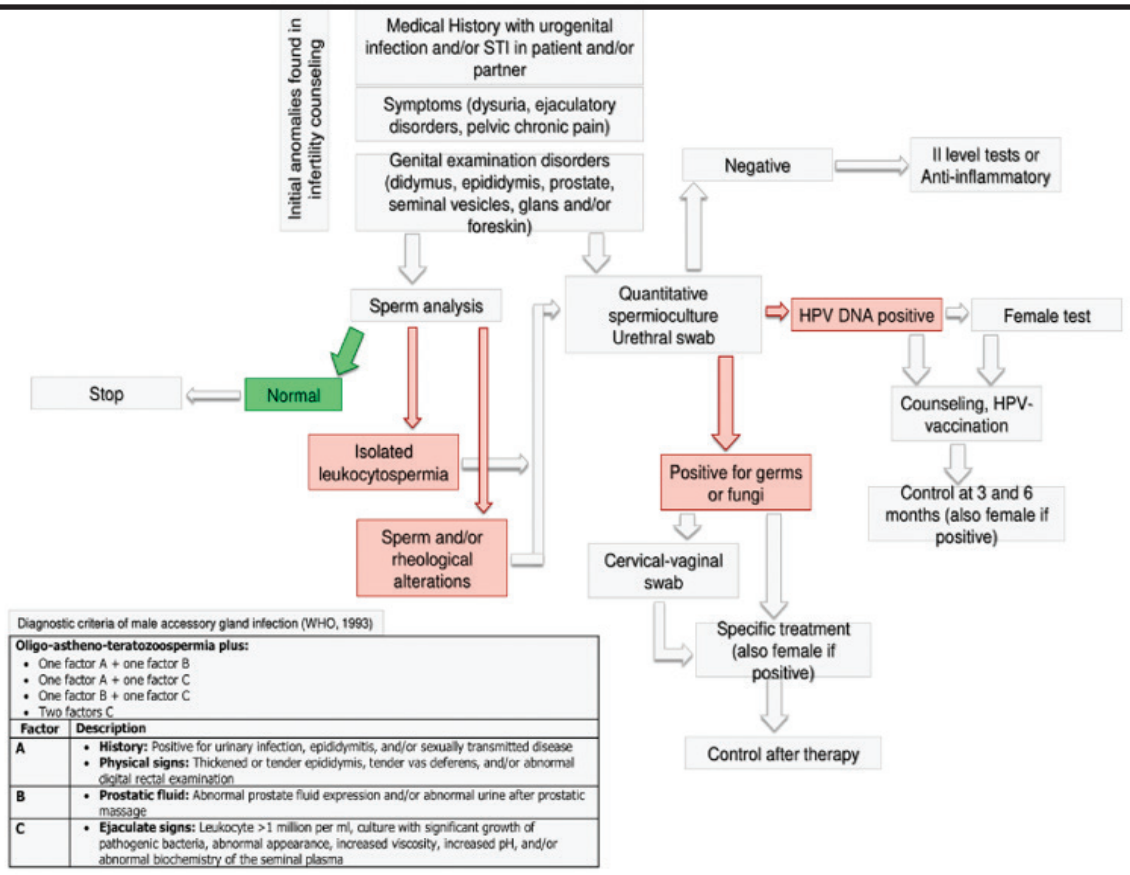


FIGURE 6 | Andrological specific flow chart: microbiological assessment in male with anomalies found in infertility counseling.

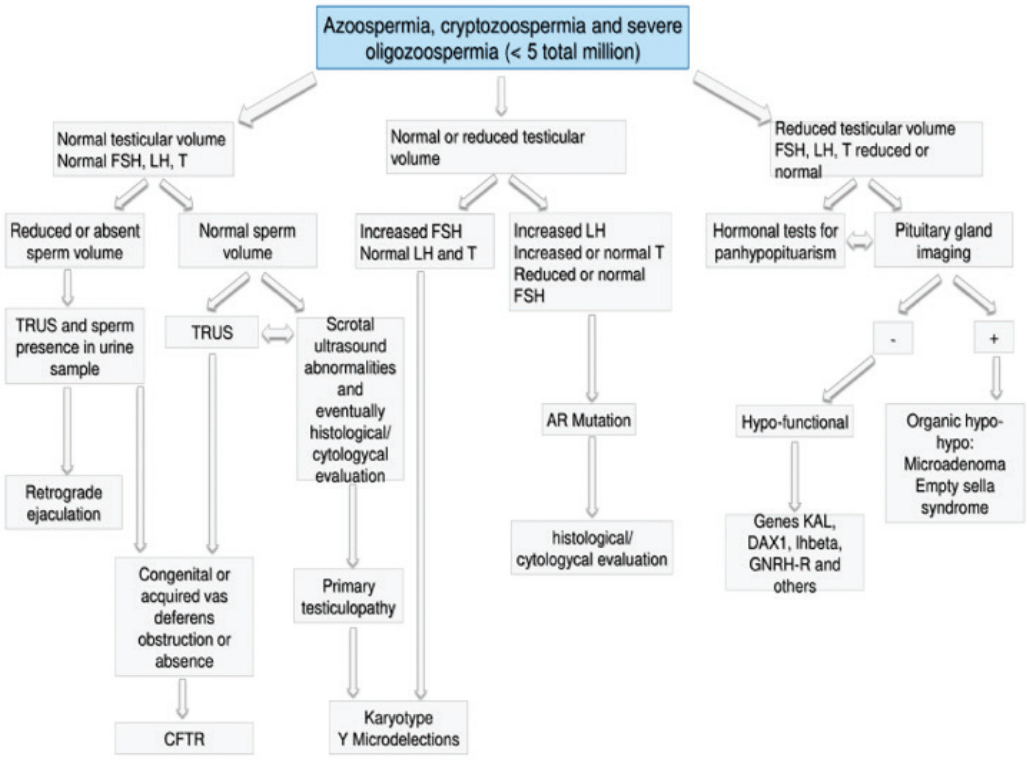


FIGURE 7 | Andrological specific flow chart: diagnostic investigation for man with azoospermia, cryptozoospermia, and severe oligozoospermia (<5 total million).

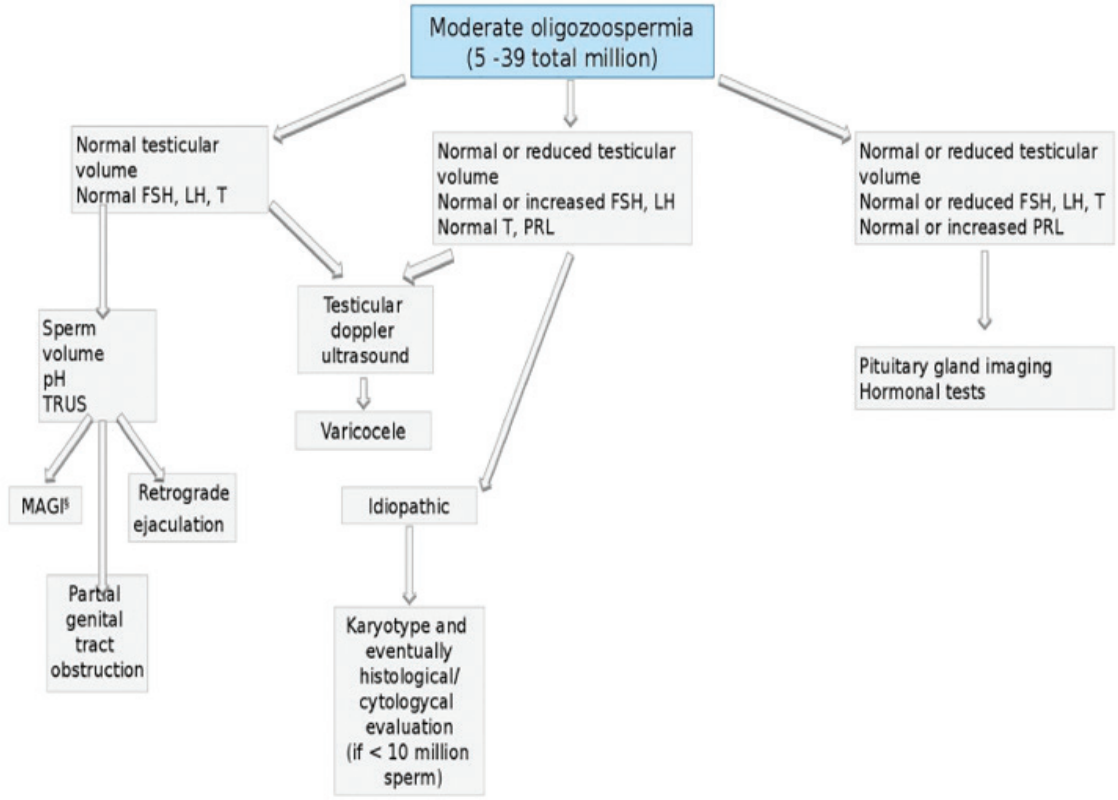


FIGURE 8 | Andrological specific flow chart: diagnostic investigation for man with moderate oligozoospermia (5–39 total million).

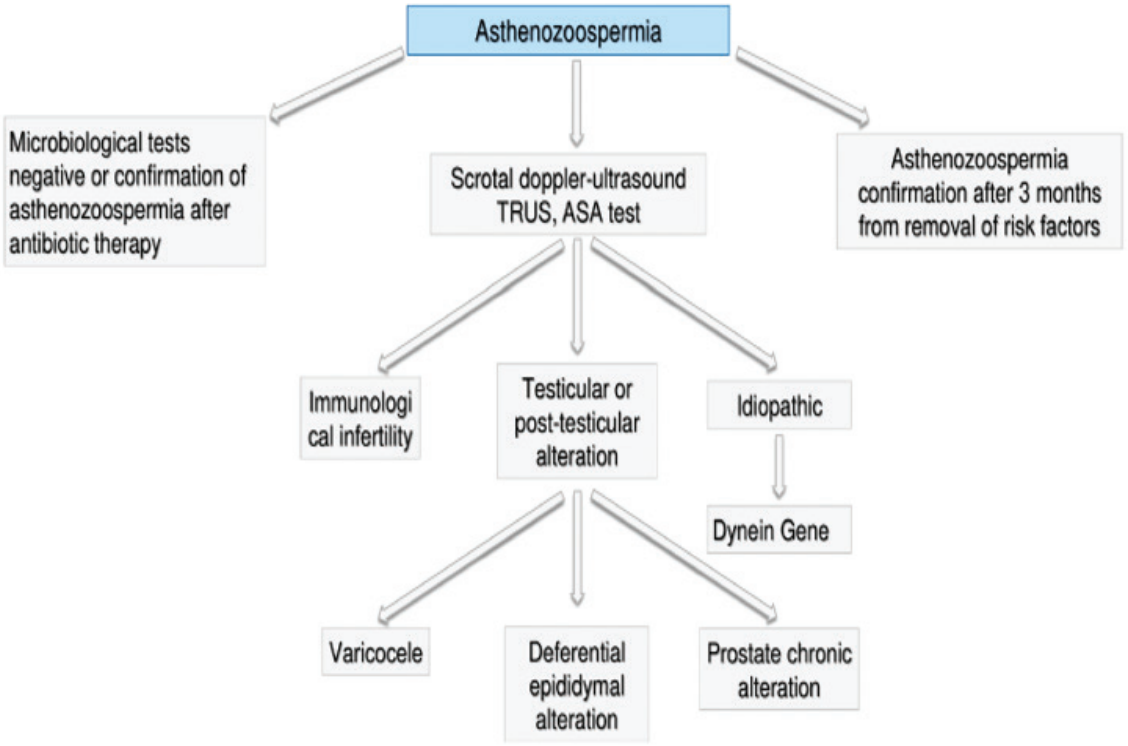


FIGURE 9 | Andrological specific flow chart: diagnostic investigation for man with asthenozoospermia.

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Box.

Common Questions About Infertility

What Can a Patient Do to Maximize Likelihood of Pregnancy?

There are several steps an individual can take to enhance his or her natural fertility, including maintaining a healthy weight (body mass index, 19–24) and abstaining from cigarette smoking. While data are limited regarding the effects on fertility, reducing alcohol consumption to <2 drinks per day and increasing intake of supplemental folic acid, fruits and vegetables with low pesticide residue, whole grains, seafood, dairy, and soy may be considered. Couples can maximize chances of conceiving by having sexual intercourse regularly during the most fertile part of the menstrual cycle (the 3-day interval ending on the day of ovulation). Timing ovulation with methods, such as monitoring of cervical mucus or use of ovulation predictor kits (available without a prescription), can help determine this timing.

Does Female Age Affect Fertility?

Frequently, infertility can be directly attributed to ovarian aging. With age, a drastic decline in the quantity of follicles and oocytes (the "ovarian reserve") occurs. Chromosomal segregation errors during meiotic divisions are increasingly common with age and lead to the production of oocytes with an incorrect number of chromosomes, causing deterioration of gamete quality and increasing the risk of birth defects and miscarriage. Moreover, with advancing age, women are also more likely to develop conditions such as uterine fibroids or endometriosis, which can impair fertility. This age-related decline in fertility occurs more rapidly after age 37 years. While less well-studied, data suggest that semen quality also declines with age.

When Should a Patient Be Evaluated for Infertility?

Women <35 years old should be evaluated after 1 year of attempting conception. Women >35 years should be evaluated after 6 months, and women ≥40 years should consider an immediate evaluation. However, women who may have difficulty getting pregnant, such as those with painful periods or endometriosis, irregular menstrual cycles, a history of pelvic inflammatory disease, or a partner with a low sperm count, should be evaluated sooner.

Do Insurance Plans Cover Infertility Treatment?

The degree of services covered depends on the state an individual resides in, as well as the insurance coverage available. Nineteen states have passed laws that require insurance companies to include fertility treatment in their plans. However, these laws vary greatly in their scope of what is and is not required to be covered. For more information about the specific laws for each of those states, an individual can contact his or her insurance carrier or state Insurance Commissioner's office.

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