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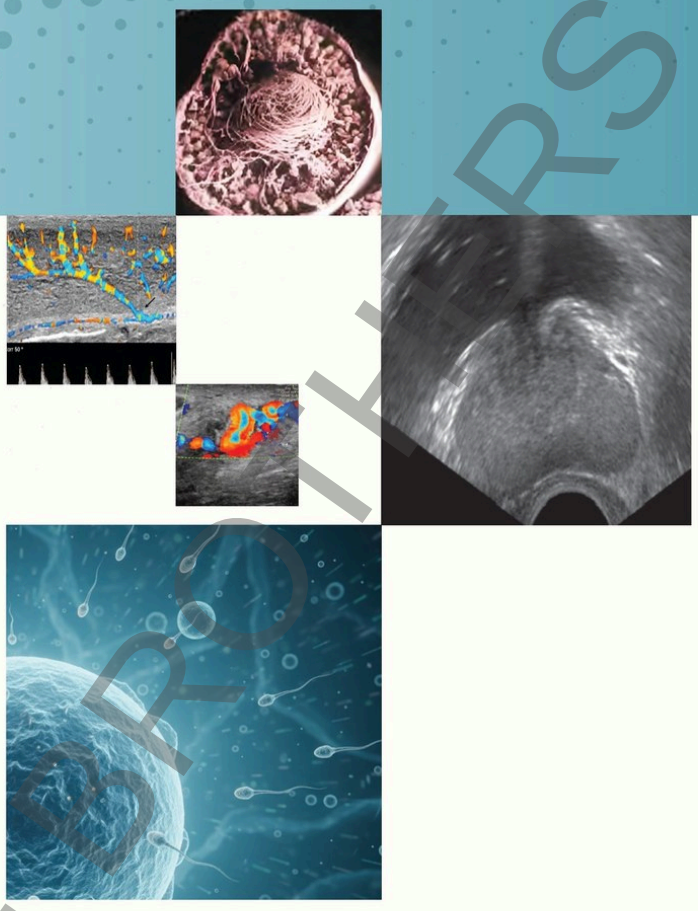

Practical Guide to Male Infertility

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JAYPEE BROTHERS

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2 CHAPTER

Semen Analysis

INTRODUCTION

Semen analysis is the gold standard for evaluation of male infertility. This is the only investigation in medicine that is done before history taking or examination. If semen analysis is normal and if patient does not volunteer any complaint, further investigations and urological assessment is not necessary.

Semen consists of spermatozoa and secretions of accessory glands such as seminal vesicles, prostate, and bulbourethral glands. Sperms are normally stored in epididymis.

REMEMBER

- Men with semen characteristics fall below the lower limits are not necessarily infertile and normal values do not guarantee fertility.
- Guidelines are not developed to predict success or failure of intrauterine insemination (IUI), in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), although these are used for this purpose.
- The World Health Organization (WHO) criteria for normal semen are revised from time to time **(Box 1 and Tables 1 and 2)**.
- The WHO criteria should be followed but it is not the blank cheque for fertility. It is used as a guideline for management.

AUA and ASRM report:

- Investigate of no pregnancy in one year.
- Earlier investigation if other factor exists.
- Only abnormal history or abnormal semen analysis, refer to Urologist.
- Further evaluation is required in unexplained infertility
- The male-female interaction in infertility is extremely important in outcome in relation to pregnancy and it cannot be incorporated into a semen analysis.

BOX 1: 2010[1] World Health Organization (WHO) criteria for normal semen.

- *Volume:* 1.5 mL
- *pH:* 7.2
- *Viscosity:* <3 (scale 0–4)
- *Sperm concentration:* 15 million/mL
- *Total sperm number:* 39 million/ejaculate
- *Percent motility:* 40% total and 32% progressive
- *Forward progression:* >2 (scale 0–4)
- *Vitality:* 58% sperms live/ejaculate
- *Normal morphology:* >4% normal
- *Round cells:* <5 million/mL
- *Sperm agglutination:* <2 (scale 0–3)

TABLE 1: Difference in the normal semen criteria according to the World Health Organization (WHO) criteria 1999[2] and 2010.[1]

Seminal parameter	*Semen 1999*	*Semen 2010*
Volume	2 mL	1.5 mL
Concentration	20×10^6/mL	15×10^6/mL
Progressive motility	50%	32%
Morphology	15%	4%
Millions of progressive motility	20	7.2 (12)

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TABLE 2: Difference in the normal semen criteria according to the World Health Organization (WHO) criteria 2010[1] and 2021.[3]

Parameters	*2010 (5th edition)*	*2021 (6th edition)*[4]
Semen volume (mL)	1.5 (1.4–1.7)	1.4 (1.3–1.5)
Total sperms (10^6 per ejaculate)	≥39 (33–46)	≥39 (35–40)
Sperm concentration (10^6 per mL)	≥15 (12–16)	≥16 (15–18)
Total motility (%)	≥40 (38–42)	≥42 (40–43)
Progressive motility (%)	≥32 (31–34)	≥30 (29–31)
Nonprogressive motility (%)	1	1
Immotile sperm (%)	22	20 (19–20)
Vitality (%)	≥58 (55–63)	≥54 (50–56)
Normal forms (%)	≥4 (3–4)	≥4 (3.9–4.0)

What is new in 6th edition of WHO manual for semen examination[4]:

- Revised basic methods for semen examination. Reintroduction of four category distinction of sperm motility
- Prognostic tool for ART for male general health.
- It guides for clinical characteristics of fertile and infertile male.
- Multiparameteric scoring and sperm morphology defects.
- Role of CASA
- But these can not be used for routine applications.

DNA fragmentation test is suggested by many studies as it increases miscarriage and decreases pregnancy rate and live birth rates. But whether it should be used widely is controversial as it is not standardized.

It may be age dependent or because of oxidative stress.

The treatment of SDF includes:

- FSH for 3 months
- Antioxidant has a doubtful role
- Varicocele ligation
- Use of testicular sperm
- Multiple fresh gametes
- Short abstinence
- Lifestyle changes
- Sperm selection for ICSI
- Various sperm preparation methods
- IMSI

AUA and ASRM advise SDF testing in

- Failed IUI/IVF/ICSI
- Recurrent pregnancy loss
- Advanced maternal age
- Paternal diabetes
- Inflammation in the lower urinary tract.

Younger the age, oocyte can repair SDF. So in older age female, male should be evaluated.[5]

We must diagnose and treat as the aim is to best predict health of future generation, who may otherwise carry mutation load to the future generation.[6]

The 6th edition of WHO manual for semen analysis has critical review and SWOT analysis.[7]

SWOT analysis includes strengthens, weakens, opportunities and threats.

Strengths:

- The extensive data on human semen in 6th Edition provide important insights into the global management of male infertility.
- Addresses the criticism of imbalanced geographical representation in the previous 5th edition by adding new data of fertile men from Southern Europe, Asia and Africa.
- Provides an updated laboratory technical guide on SA that includes comprehensive step by step procedures.

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- Provides detailed information on quality control and quality assurance that can help guide optimum laboratory performance. Introduces SDF and FISH as extended tests of semen that can be recommended in certain clinical indications. Acknowledges that the 5th percentile values of basic semen parameters alone are insufficient for accurate diagnosis of male infertility.

Weaknesses:

- Data on fertile men from some geographical areas such as south America and Sub-Saharan Africa, are still under-represented.
- Lacks reference thresholds or decision intervals to replace the 5th percentiles of basic sperm parameters.
- Lacks indications and criteria for interpretation of SDF testing.
- Lacks cut-off/threshold values for extended sperm analysis such as SDF tests.
- Considers seminal OS tests as specialized, mainly research based procedures despite extensive literature data suggesting their clinical use and implications.

Opportunities:

- Future research may help determine globally accepted reference ranges and thresholds that would be useful in the management of infertility.
- Future research may help in the development of updated guidelines on advanced sperm tests such as SDF and FISH.
- Future research may help incorporate epigenetic and seminal OS testing into clinical practice.

Threats:

- The abundance of technical details in the manual may diminish interest among clinicians in reading and adopting it.
- The lack of reference values for basic and extended semen parameters in the 6th edition may preclude the global utility of this new manual and instead increase the chances for continued use of the 5th edition reference values.

FATE OF THE SPERM

- Flow back
- Go to cervical crypts
- Loose motility in cervical mucous
- Few thousand sperms only swim up, 0.01% of 15 million/mL, i.e., 15,000 sperms
- Because of large surface area in the tube few reach the ovum
- Ratio of the sperm:ova may be as low as 1:1

SEMEN COLLECTION

- Abstinence is recommended between 2 and 7 days. But abstinence only adds the liquid content of the semen sample, not the spermatozoa. Sperms that come out in the semen on ejaculation are 84 days old and so abstinence has no significance. Ideally it should be according to the frequency of intercourse in a particular couple.
- First few drops are very rich in spermatozoa and so wide mouth jar is used for collection of semen sample. Water should not touch the inner wall of the jar in any case, otherwise it will decrease motility. Therefore hands should be washed only after the container lid is shut.
- The number of samples should be examined are three in all, i.e., 2 weeks and 2 months apart.
- Collection of the sample is done by masturbation either in the premises or at patient's residence. Sometimes sildenafil can be used or it can be collected in

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nonspermicidal condom. Coitus interruptus is not preferred because of infection and first portion may be lost.
- Proper documentation of sample is done.
- Collected sample should be put in the warmer, maintained at 37° for almost 30–60 minutes.

LIQUEFACTION

- Initially the semen ejaculated is coagulated lump. But after a few minutes, it starts liquefying and within 15–30 minutes it becomes homogenous and watery. In some patients, liquefaction may take 60 minutes. Before examination, gentle mixing of the sample is done with pipette.
- In case of delayed liquefaction, sample should be collected in media and then semen is processed.
- Media with buffer saline can be added or proteolytic enzyme bromelain can be added.
- It can be passed through 18 gauge needle repeatedly with syringe.

SEMEN VISCOSITY

Normal semen sample flows out from the pipette mouth drop by drop, but in a sample of increased viscosity, drop will form a long thread. It can be treated with trypsin and chymotrypsin. It is placed in incubator for 10–15 minutes.

Appearance: Liquefied sample has gray-opalescent appearance. Opacity depends on concentration of spermatozoa. It may differ if there is blood or infection or because of drug.

pH: Normal pH is 7.2. Seminal vesicle has alkaline secretion and prostatic secretion is acidic. Congenital absence of vas or ejaculatory duct has acidic pH, as the secretion from seminal vesicle is alkaline.

SEMEN VOLUME

Normal semen volume is 1.4–6 mL. Low volume is because of ejaculatory duct obstruction or absent vas deferens. Large volume may be because of long abstinence or production from accessory glands due to inflammation.

Aspermia means no semen secretion on ejaculation. Rule out retrograde ejaculations in these cases.

EXAMINATION

- Agglutination
- Motility
- Morphology
- Total count
- Sperm concentration
- Vitality

Agglutination of Spermatozoa

It should be differentiated from aggregation of sperms. It is attached to the debris or immotile sperms in mucous. Agglutination refers to motile spermatozoa. It may be head-head, tail-tail or tail, head or body agglutinations. But here motility or shaking movement is always present. It suggests presence of antisperm antibodies.

Sperm Motility

Sperm motility is directly related to pregnancy rate. According to the 2021 WHO 6th manual, 42% (40–43%) is total motility and progressive motility is 30% (29–31%). The immotile sperms are 20% (19–20%). Rapid progressive motility is directly related to pregnancy rate.

Role of Computerized-assisted Semen Analysis

Computerized-assisted semen analysis (CASA) is very useful for motility assessment. One can assess curvilinear velocity (VCL),

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average path velocity (VAP), straight line velocity (VSL), and amplitude of lateral head displacement (ALH) accurately.

But current testing has found that basic semen analysis has intra- and interlaboratory variables and these are the most significant limitations of semen analysis. CASA can overcome some of these problems. But it is expensive, labor intensive, and laboratory based. There is insufficient evidence for the routine use of CASA and also its efficacy against the expert manual examination. CASA is unable to obtain sperm count and motility. Secondly it cannot differentiate between sperm aggregation and sperm agglutination.[2] So, it can be added but it cannot replace manual examination.

Whenever motility is reduced, it may be due to accessory gland function. Rapid progressive motility is required for penetration in cervical mucus. When the infection is zero, patient is investigated for Kallmann disease or immotile ciliary syndrome.

Sperm Vitality

The normal vitality is ≥54% (50–56%) according to the 6th edition of the WHO manual 2021. It indicates the membrane integrity. This can be done by hypoosmolar swelling or dye exclusion. This is how we can differentiate dead sperm from live sperms. So immotile live sperms may have flagellar pathology while nonviable sperms indicate testicular or epididymal cause.

Microscopic Evaluation

- *Round cells:* These are immature germ cells and looks like leukocytes. This differentiation is necessary as otherwise patient may be given several different courses of antibiotics.
- *Leukocytospermia:* Presence of >1 × 10^6 white blood cells (WBCs)/mL of the sample is indicator of leukocytospermia. Doxycycline is the drug of choice. If there is prostate infection, quinolone group of drugs are used. Pyospermia is the term used when WBCs are 5 × 10^6/mL. It is essential to rule out acute or chronic infection which may be bacterial, fungal, or mycobacterial. Rule out chlamydia, gonorrhea, and trichomonas also.

Sperm Concentration

According to the 2021 WHO 6th edition, 16 million/mL is the reference value and the range is 15–18 million/mL. Total sperms per ejaculate should be >39 million/mL (35–40 million/mL). We usually take count/mL into consideration. But it is better to report total sperm per ejaculate rather than sperm concentration per mL as this is a reflection of average testicular sperm production and what is available at the site of fertilization in the female reproductive tract.

The count is calculated by Neubauer's heamatocytometer, Cell-VU, or Mackler's chamber. After centrifugation done twice, when no sperms are found only then it is reported as azoospermia. In cryptozoospermia, sperm up to 1,000/mL only are seen.

Sperm Morphology

According to the 6th edition of WHO manual 2021, 4% sperms should be normal morphologically. Kruger's classification strictly defines spermatozoa as normal only if these fall within the set of parameters of shape. Any spermatozoon that does not meet these criteria is considered abnormal.

Head: Smooth, oval, and well-defined acrosome that covers 40–70% of head, length 5–6 mm, and width 2.5–3.5 mm.

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Normal neck, midpiece, and tail: Tail is thinner than midpiece, uncoiled, and 45 mm.

Absence of fertilization can be due to absence of acrosomes. Sperms with poor morphology can give pregnancy as pregnancy occurs due to deoxyribonucleic acid (DNA).

SPERM FUNCTION TESTS

- *Fructose:* It is produced by seminal vesicles and it is released in the semen during ejaculation. So fructose will be absent when there is congenital absence of vas deferens or ejaculatory duct obstruction. So fructose estimation qualitatively will differentiate the obstruction and can be used to plan a surgical treatment.
- *Hypo-osmotic swelling:* This is especially used for sperm selection for ICSI to differentiate immotile sperms form dead sperms. This is a very useful test for "immotile ciliary syndrome". This test indicates functional integrity of membrane, which is required for fertilizing the ovum. In this test only the cells that have intact membrane will swell in hypotonic solution.

SPERM ANTIBODIES

Antisperm antibodies impair the motility of the sperm and fertilization process. Antibodies can be in seminal plasma or reproductive tract. Immunoglobulin G (IgG) antibodies can be diagnosed by direct sperm mixed antiglobulin reaction (MAR) test. Immunoglobulin A (IgA) is more important in male infertility. These are present only in genital tract and these are absent in serum. When IgA antibodies are there, IgG is mostly present. These are also detected by direct sperm MAR test. Immunobead test is more reliable than direct MAR test.

The treatment of choice is always IUI rather than steroids or azathioprine. If IUI does not succeed, assisted reproductive technique (ART) is done.

Sperm function tests are cumbersome, expensive, and impractical. Even in 2021 guideline, these are not included in routine testing of semen analysis. Same way DNA fragmentation test is not included as primary diagnostic test. It may be useful in some specific conditions.

REACTIVE OXYGEN SPECIES

Free oxygen radicles such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydrochlorite (OHCL), and hydroxyl radical (OH) are called reactive oxygen species (ROS). These have short half-life and are produced by WBCs or abnormal sperms. The details of ROS and its management have been discussed in the Chapter 6 of this book. This can be measured by ImmunoMeter.

BIOCHEMICAL TESTS

- *Zinc:* It is the specific marker of prostate function. Level of seminal zinc is 1.2–3.8 mmol/L or >2.4 mmol per ejaculate.
- *Citric acid:* It is indicator of prostatic gland function.
- *Neutral α-glucosidase:* It is the marker for epididymal function.
- *Fructose:* For seminal vesicle function it is quantitatively measured. The normal value is 150 ng/dL.

RECENT DEVELOPMENTS

Automated smartphone-based diagnostic assays have been developed recently. It has made remote and accurate semen quality testing available all around the world. So male partner may not require to visit the laboratory for the same. This may save time and can also get the test done in the comfort of their home. The home testing may offer the

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potential to improve the importance of male factor in infertility to the public.

There is negative dose response association between all semen parameters and all cause mortality. Some men with impaired semen quality may experience less healthy ageing than men with better semen quality. In future, biomarkers may help to diagnose diseases early and prevent these. So semen quality is a strong marker of mortality. Men with good semen quality live 2 years longer than the men with severely impaired quality.[8]

CARRY HOME MESSAGE

- Semen analysis is gold standard for treatment.
- WHO 6th edition manual 2021 should be followed.
- CASA cannot replace manual examination.
- Sperm function tests and biochemical tests are not of much practical use.
- Automated smartphone based diagnostic assays are the future.

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Practical Guide to

Male Infertility

Male factor infertility is not very commonly discussed in the literature on gynecology, in spite of the fact that male factor is completely or partially a cause of infertility in at least about 40% of the couples with infertility. Gynecologists may have avulsion from evaluating the male factor and treating it therefore. Dr Chaitanya Nagori has a very high success rate in treating couples with male factor infertility. "Practical Guide to Male Infertility" is a "to-the-point" book on diagnosis and male infertility. The book discusses chiefly the practical aspects of male factor infertility including the tips for diagnosis and management to facilitate couples to conceive with less-invasive technologies and also to improve the results significantly for invasive technologies such as ART. It has proved itself to be a very useful "under-the-desk" book for all gynecologists and infertility specialists.

Chaitanya Nagori MD DGO is the Director of Dr Nagori's Institute for Infertility and IVF, Ahmedabad, Gujarat, India. He is a successful infertility consultant for more than 32 years and is known for a very high success rate in his practice, especially so in cases with male factor infertility. He has a thorough knowledge of infertility and gynec-endocrinology. He is a core academician and a teacher of high repute. He is a synonym for to-the-point teaching, with crisp and clear concepts.

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