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Infertility Management

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Editor
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THIRD EDITION

Forewords
Firuza R Parikh
S Haimovich

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2

Initial Workup and Diagnosis

CHAPTER

Sushma Deshmukh

INTRODUCTION

Initial workup of an infertile couple should be very prompt and perfect. One should not delay the necessary investigations and tests. Investigations should be logical and cost effective. Special infertility file of each patient is to be maintained by the clinician.

DETAILED HISTORY AND PHYSICAL EXAMINATION OF THE COUPLE

Thorough history should be taken. Husband and wife should be examined completely.

Female

- *Professional history and age:* As the age advances, chances of pregnancy decreases. Career, hectic profession has a great impact on infertility.
- *Detailed menstrual history:* Age of menarche, cycle length, dysmenorrhea, oligomenorrhea, secondary amenorrhea, and gradual scanty bleeding in menstrual cycle can give certain clues like polycystic ovary syndrome (PCOS), endometriosis.
- *Duration of infertility:* Increased duration of years of infertility decrease the chances of conception and will require more evaluation.
- Coital frequency and timing and sexual history.

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- *History of sexually transmitted diseases (STDs):* Chlamydia and gonorrhea can cause infertility in both men and women.
- If secondary infertility, then history of abortions/ectopic pregnancy/delivery should be taken into account.
- *If patient has received previous treatment of infertility:* Use of oral CC/Lt, total number of intrauterine insemination (IUI). If in vitro fertilization (IVF), then number of attempts, protocols used, oocyte yield, quality of embryos, fresh/frozen cycles, source of sperms/oocytes, details of embryology, and difficulties in pick up/transfer.
- *Use of previous contraceptive methods:* History of using Cu-T can suggest pelvic inflammatory disease. Oral contraceptive pills can delay the pregnancy for first 2 months.
- Past history regarding surgery (route, site), tuberculosis or any medical illness like diabetes and thyroid are very important factors in treating infertility.
- *Medications and allergies:* Some drugs affect fertility, i.e., antivertigo drugs can affect cervical mucous.
- *Family history:*
  - Family history of diabetes, hypertension in her parents. If patient having irregular menstrual cycles with obesity, then history of same problems (particularly in PCOS patients) with paternal aunt or sisters. If patient having sister, then history of marital, fertile status of her sister. If patient presented with primary amenorrhea, then in such patients, family history of such problems matters.
  - History of consanguineous marriage especially in Indian setup.
- Then detailed examination starting from weight, height, blood pressure, clinical signs of PCOS (obesity, acne, hirsutism, acanthosis nigricans), breast examination to see evidence of galactorrhea, respiratory and cardiovascular

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system, abdomen, per speculum examination (to rule out genital infections, congenital malformations, cervical conditions—if needed Pap smear to be taken), and per vaginal examination.

All the important clinical findings of the patient should be noted in the separate record file.

Male

- Complete professional history/age.
- Frequency of coitus, history of tobacco chewing, smoking, alcoholism, STD.
- Any medical diseases in the past, trauma, surgery, exposure to gonadal toxins like anabolic steroids, childhood illness like mumps, developmental history (undescended testis) to be noted.
- General examination.
- Local examination to see, testis, scrotum, penis.

COUNSELING

- After examination, always try to counsel them together.
- If couple having previous tests, try to go through all investigations and if they are done recently then one can omit it while investigating.
- The couple is always in stress and strain. Many a times due to a long waiting period in reception, they can be irritable. Always use comfortable words. Clinician's real patience counts here only.
- Explain them everything regarding reproductive systems, fertile period by showing charts and, if possible, CD. Explain them the strategy of your treatment.
- Counseling has a very good impact on infertile couples.

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TRANSVAGINAL SONOGRAPHY

- It is user-friendly equipment and a real friend.
- Every clinician who wants to do infertility practice should have this important asset.
- Patient can be in any phase of menstrual cycle. Try to scan the patient in first visit only.
- Transvaginal sonography not only gives information regarding uterus, ovary but also can tell you the phase of the menstrual cycle according to endometrium. See for adnexal mass, small endometrial polyps, fibroid (submucous, intramural or subserous) or any congenital anomalies. Sometimes, hydrosalpinx also can be diagnosed.
- Polycystic ovaries can be diagnosed easily by evidence of multiple follicles and dense stroma.

LABORATORY INVESTIGATIONS

In any infertile couple, start with the basic investigations. Basic and specialized tests will give tons of information. In females, complete blood count (CBC), urine (R), blood group and Rh, venereal disease research laboratory (VDRL), blood sugar (fasting and postmeal), serum creatinine, human immunodeficiency virus (HIV), Australia antigen, Pap smear, any specific tests according to region, e.g., sickling (which is common in central India).

In males, semen analysis, CBC, urine (R), VDRL, blood group and Rh, blood sugar (fasting and postmeal), HIV, Australia antigen and Thyroid profile.

Then detailed evaluation of the female is planned as follows.

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Specific Hormonal Investigations

- For any infertile couple, it is better to have thyroid and prolactin profile of female. These simple investigations rule out two important causes of anovulatory infertility.
- *In PCOS patients:* According to international guidelines for the assessment and management of PCOS 2018, following investigations are suggested. (Refer to Chapter 9 also)
  - Free testosterone, free androgen index or calculated bioavailable testosterone to be done. Androstenedione and dehydroepiandrosterone sulfate (DHEAS) have limited role in PCOS diagnosis. High-quality assays needed for most accurate assessment.
  - In nonpregnant women with PCOS, glycemic status may be assessed by oral glucose tolerance test (OGTT), fasting plasma glucose (FPG) or hemoglobin A1c (HbA1c). OGTT has been reckoned gold standard test for diagnosing type 2 diabetes.
  - Fasting insulin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), LH/FSH (>2.5) in PCOS are not recommended. But in few patients showing clinically severe insulin resistance, e.g., acanthosis nigricans, it can be done to know gravity.
  - *Anti-müllerian hormone (AMH):* It is a product of granulosa cells of the preantral and small antral follicles of ovary. AMH regulates folliculogenesis and serves as a molecular biomarker for ovarian reserve. Data suggests a cut-off of AMH > 3.5 mg/mL suggests there are chances of hyperstimulation
  - *LH/FSH:* In PCOS, the LH/FSH ratio is increased. LH levels are higher.

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- *DHEAS:* Secreted by the adrenal gland. Hyperandrogenemia due to adrenal androgen excess can be due to genetic trait or due to hyperinsulinemia leading to increased production of DHEAS. DHEAS levels are high between 2,900 and 8,000 ng/dL. These patients are usually thin, hirsute with ovulatory dysfunction. DHEAS levels more than 9,000 ng/dL are diagnostic of adrenal or ovarian tumor.
- *17-hydroxy progesterone:* A level of 17-hydroxy progesterone more than 5 ng/mL is diagnostic of late onset congenital adrenal hyperplasia. In all patients, all the tests are not necessary. Judiciously, one can plan strategy of tests. Many a times, history and transvaginal sonography (TVS) help in minimizing the tests.

- In suspected patients of diminished ovarian reserve (DOR) and premature ovarian failure (POF) (discussed in Chapter 10).
  - AMH is an important marker along antral follicular count (AFC). If a patient is 30 years or above that, previous history of poor stimulation response, AFC by TVS is less than 5 then AMH must be done to know the ovarian reserve of that patient. AMH less than 1 mg/mL indicates poor response.
  - Day 2–3 LH and FSH. FSH 10 or more than that suggests DOR.

There are so many tests to know DOR and premature ovarian failure (POF).

- The indication of LH, FSH is only in a patient of secondary amenorrhea. If levels are raised, it indicates premature ovarian failure. If levels are normal or low, then probably we are dealing with hypogonadotropic hypogonadism

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provided other hormone profiles like thyroid, prolactin are normal.

- *Serum progesterone:* To evaluate luteal function progesterone estimations are suggested on day 21 of the menstrual cycle. Though exact value, at what day of menstrual cycle it is to be done is in dispute, it should be done. Many clinicians do it 1 week prior to onset of menstruation. Levels below 10–12 ng/mL are considered abnormal.
- If the patient having recurrent pregnancy loss the burden of tests again increased. Because in an infertility clinic, we do get secondary infertility patient with no live issue with repeated pregnancy loss. So antiphospholipid antibodies, karyotyping can be done. TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex) only with one pregnancy loss (though controversial) are some of the routinely recommended tests.

Hysterosalpingography

Hysterosalpingography (HSG) still considered as an important test to know the tubal status. Any gynecologist without any advanced infertility back-up, even in a small town can do this procedure.

- Though other better tests are available, HSG remains as important test.
- It is easy, does not require any anesthesia.
- It is done postmenstrually. It gives idea about uterine cavity and patency of tubes.
- Its reliability is better.

Other tests recommended to assess the tubal tests are sonosalpingography (SSG), HyCoSy (hysterosalpingo-contrast sonography involves the use of a sonography contrast media).

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Baseline Ovulation Study

One should plan first ovulation study of the patient without ovarian stimulation, i.e., baseline study.

With TVS, one can start it from 9th or 10th day of menstrual cycle.

- We can see normal ovulation pattern or anovulatory cycle.
- Endometrial response is also very important.
- Usually in a normal menstrual cycle, one dominant follicle grows and ruptures when it is 18–22 mm. Along with the follicle, the endometrium also grows. We have to observe the coordinated response of the follicle and endometrium.
- When we have come so far, take time to review all the reports. Analyze the history and investigations. See the previous reports, treatment, operative treatment (open or lap-hysteroscopy). Then come to a presumptive diagnosis.

For example, for a young couple with normal semen analysis, with normal hormonal investigations, with HSG normal, but anovulatory cycle, we can devote 3–4 months for ovulation study with clomiphene citrate or any other drug.

If patient having blocked tubes, immediately plan hysterolaparoscopy.

Laparoscopy and Hysteroscopy

It is the most reliable and definitive method to study the reproductive organs. Every gynecologist should be well-versed with this procedure.

- It is better to plan laparoscopy with hysteroscopy even though we are confident about normality of a uterine cavity.
  - In one sitting, we can assess surface as well as luminal pathology.

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- Undiagnosed small polyps are always located and treated by hysteroscopy in the same sitting.
- Cost effective for the patient, if hysterolaparoscopy is planned together.

- *For diagnosis of endometriosis:* Laparoscopy is the only method to confirm the suspected or undiagnosed cases of endometriosis.

  And, even in the same sitting, cauterization of endometriotic lesions with adhesiolysis is possible in undiagnosed case of endometriosis.
- Tubo-ovarian relationship is better judged.
- In resistant cases of PCOS, one can do laparoscopic ovarian drilling at the same time.

DIAGNOSIS AND MANAGEMENT

Divide the patients in different categories according to cause:

Anovulatory

Confirm whether they are PCOS or non-PCOS.

- *Non-PCOS:* TVS monitoring is mandatory
  - Ovulation induction with clomiphene citrate (CC)
  - Ovulation induction with letrozole (Lt)
  - Ovulation induction with CC/Lt + human chorionic gonadotropin (hCG)
  - Ovulation induction with CC/Lt + human menopausal gonadotropin (hMG)/FSH
  - Depending upon thyroid or hyperprolactinemia problem, addition of those drugs
  - If no response, then CC/Lt or CC/Lt/hMG or hMG with IUI

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- *In PCOS:* Treatment as above
  But, first drug of choice is letrozole and then CC
  - Obese, hyperandrogenic are best downregulated with metformin
  - Thin PCOS, nonresponsive to ovulation induction, then ovarian drilling.

Tubal

- Tubal pathology may be unilateral or bilateral.
- Unilateral tubal block/bilateral tubal block.
- Evidence of tuberculosis.
- Sometimes unilateral tubal agenesis.

Tubal Block

- In cornual tubal blocks, hysteroscopic cannulation can be possible.
- Fluoroscopic tubal recanalization (FTR) can be tried.
- Fimbrial tubal blocks better managed by laparoscopy.

Sometimes, we see severe degree of adhesions, plastered look, we may not even see ovaries. In such patients, assisted reproductive technology (ART) will be the treatment of choice.

Endometriosis

Treatment options are:

- Medical
- Surgical.

Mild to Minimal

- Medical treatment is not necessary.
- Even very small endometriotic lesion with good tubo-ovarian relationship is to be treated by laparoscopy. But, immediately after that ovulation induction with or without IUI is to be planned.

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- Couple should be well informed regarding endometriosis and treatment to be started as early as possible, once endometriosis is diagnosed.
- Fulguration of endometriotic lesion in all cases.

Moderate and Severe Endometriosis

- Treatment of choice is operative laparoscopy.
- Gonadotropin-releasing hormone (GnRH) analogs can be given only if postoperative ovarian reserve good and patient wants to wait. But, in infertile patients, medical therapy is not recommended. Thorough counseling is needed.
- ART will be a better solution.

Male Factor

Semen analysis: According to World Health Organization (WHO), at least 15 million/mL count, with motility 40% with forward progression 32% and 4% with normal morphology should be there.

Medical Management

- In case of oligospermia/oligoasthenospermia with normal hormonal values, treatment with CC, androgens, gonadotropins with multivitamins with vitamin E can be given.
- At least three times semen analysis of the patient is to be done with proper precautions before labeling him oligospermic or azoospermic.

Surgical

- In cases of varicocele, very large hydroceles surgical correction should be done.

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- In cryptorchidism, orchiopexy is to be done.
- In case of ductal obstruction, microsurgery is indicated.

ART Support

- IUI for oligospermia or asthenospermia. But count should be at least 5 million.
- IUI with donor for azoospermia.
- IVF with husband or donor.

Unexplained Infertility

- Proper counseling with supportive and conservative treatment for 3–6 cycles for young couples.
- For age group of 30–35 years, stimulation with CC/Lt or hMG/FSH with IUI for 3–6 cycles. If no response, ART can be considered.
- For age group >35 years, ART is to be always considered.

Luteal Phase Defect

- This condition though difficult to diagnose, evaluation of serum progesterone and TVS can help in evaluation.
- Treatment with CC/Lt, support with progesterone/hCG is required.

Assisted Reproductive Technology

This term is self-explanatory, i.e., assisted reproductive technology. When the couple is not getting pregnancy with natural course then the couples are assisted in overcoming the problem.

Indications

- Gross tubal damage
- Grade 3–4 endometriosis

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- Unexplained infertility
- Perimenopausal patients
- Male factor infertility
- Immunological causes of infertility
- Premature ovarian failure.

Techniques

There are a variety of techniques:

- *Intrauterine insemination:* Actually, it is not ideal form of ART as there is no extracorporeal handling of oocyte. IUI is the deposition of washed, concentrate spermatozoa in the uterine cavity around the time of ovulation. It is a safe, simple, cost-effective treatment.
- The most commonly used ART are:
  - In vitro fertilization-embryo transfer (IVF-ET).
  - Intracytoplasmic sperm injection (ICSI).

Others are:

- Intracytoplasmic morphologically selected sperm injection (IMSI).
- Gamete intrafallopian transfer (GIFT).
- Tubal intrafallopian transfer (TIFT).
- Peritoneal oocyte and sperm transfer (POST).
- Tubal embryo stage transfer (TEST).
- Zygote intrafallopian transfer (ZIFT).
- Subzonal insemination of sperm (SUZI).
- Microinsemination sperm transfer (MIST).
- Microinsemination microinjection into cytoplasm (MIMC).

Other variants are:

- Oocyte donation program:
  - For primary ovarian failure.
  - For perimenopausal/menopausal patients.

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- Donor embryo transfer program:
  - For elderly couples.
  - When husband is azoospermic and wife is also having ovarian failure.

CONCLUSION

- Proper history, thorough counseling and earlier approach to the diagnosis are very essential in treating the patient.
- All patients of infertility do not require exhaustive plan of treatment.
- TVS and specific hormonal tests are the backbone in the management of infertile couples.
- Laparoscopy–hysteroscopy is the mainstay while advancing toward investigations.
- IVF has revolutionized the treatment of infertility.
- Give all options to the couples.
- Never lose hope, there are alternatives always. Many a time in refractory cases also, we get sudden pleasant pregnancy results. So, be positive always.

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