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Textbook of

IUI & ART



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CHAPTER 2

Indications, Patient Selection and Work-up Before Intrauterine Insemination

Appropriate patient selection is the most important factor which determines the success of any treatment. With IUI, many a times the treatment is empirical, still it is possible to select a group of couples where the treatment will be significantly beneficial. The rationale behind the treatment is to deposit a good number of highly motile and morphologically normal sperms in the uterus near the fundus at the anticipated time of ovulation, bypassing factors which depend upon deposition of sperms in vagina and transport through the cervical mucus to the upper genital tract. There are several indications for IUI, which may be male factor infertility, female factor or combined factors.

A complete work-up is required before taking up the patient for IUI. Any contraindications to the procedure must be ruled out. Patients should be counseled about the procedure involved, success rates, other options and risks associated.

INDICATIONS OF INTRAUTERINE INSEMINATION

Male Factors

Impotence/Ejaculatory Dysfunction

This can be due to a number of causes.

- *Anatomical:* Hypospadias— Here deposition of semen occurs outside vagina or much away from the os. In such patients semen is collected by masturbation for IUI.

Neurological: This can be due to:

- Spinal cord injury
- Diabetes mellitus
- Multiple sclerosis
- Atherosclerosis
- Damaged hypogastric nerves during surgeries like abdominoperineal resection of rectum, retroperitoneal lymph node dissection and aortoiliac surgery.

In these conditions, the sperm quality especially its motility is hampered despite high sperm density. Furthermore debris, inflammatory cells and quite often bacteria abound in these samples. The success of treatment depends upon

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sperm quality. Good results are obtained with samples where the progressive motility is more than 20–30%.

Retrograde Ejaculation

In this condition, there is reflux of semen backwards from the posterior urethral valve into the bladder, at the time of ejaculation. The sperms lose their viability due to toxic effects and acidity of urine. It can be due to diabetes mellitus, multiple sclerosis, drugs like α-adrenergic blockers and phenothiazines and damage to innervation of bladder neck during surgeries like transurethral resection of prostate (TURP), and retropubic prostatectomy. In retrograde ejaculation, urine is centrifuged and then washed to isolate sperms and then IUI is performed.[1]

Treatment:

- Treat the cause
- *Intercavernosal injection:* Papaverine, phenoxybenzamine phentolamine,
- *Surgical methods:* Epididymal sperm aspiration, percutaneous vasal sperm aspiration
- Penile vibrator
- Electroejaculation.

Psychological conditions: Such patients need sex-psychotherapy. Drugs such as viagra or papaverine may be given to bring about a good erection. Some patients benefit with the use of mechanical vibrators. Very occasionally the patients may have to be subjected to general anesthesia and electroejaculation.

Drug induced: Drugs like sedatives, antidepressants, antihypertensive agents, cimetidine, etc. can cause ejaculatory dysfunction.

Subnormal Semen Parameters

This includes:

- Oligozoospermia
- Asthenozoospermia
- Teratozoospermia
- Hypospermia
- Highly viscous semen.

The cause of infertility in such conditions is decreased availability of normal motile sperms for fertilization. As defined by WHO, a normal semen sample has a sperm count of more than 20 million/mL, with 50% or more of them showing forward progression, and 30% or more having normal morphology.[2]

Ideally a total motile prewash count of more than 10 million or a postwash motile sperm count of five million is necessary to achieve a good pregnancy rate. Additionally percentage motility of more than 40% in the final semen preparation correlates well with favorable outcome.

Patients with severe male factor infertility should go directly for Intracytoplasmic Sperm Injection (ICSI) or the use of donor sperms for insemination (AID).

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Other Factors

Though the main treatment for obstructive azoospermia is percutaneous epididymal sperm aspiration (PESA) with ICSI, there is a recent report of achieving pregnancy after extracting sperms with PESA and performing IUI. Other conditions such as allergy to semen, vaginismus and other sexual dysfunctions may be treated with IUI.

HIV infection: Sperm washing can significantly reduce the viral load.[3] Recently insemination of HIV negative women with processed semen sample of HIV positive partner has been carried out to reduce the risk of transfer. However, prepared semen sample should be tested by polymerase chain reaction (PCR) before insemination.

Female Factors

Ovulatory Dysfunction

It contributes to 30–40% of the female factor. In these cases the first choice would be ovulation induction combined with timed intercourse or IUI. Many studies have shown that IUI gives better results as compared to timed intercourse.

Cervical Factor

The cervix plays an important role in achieving successful pregnancy. It performs the following functions:

- Control of sperm entry into the upper genital tract
- Protection of sperms from vaginal acidity
- Nutrition of sperms
- Selection of sperms based on motility
- Sperm reservoir function
- Initiation of capacitation.

The following are some common causes of cervical factor infertility:

- Insufficient mucus production, which may be due to previous cauterization, surgery or rarely cystic fibrosis.
- Altered quality of mucous
- *Abnormal cervix:* Stenosis, injury, malformation, infection, erosion
- Abnormal postcoital test (PCT) or hostile cervical mucous (the general consensus is that PCT has nonpredictive value in terms of pregnancy).

IUI helps bypass these hostile factors. It has been observed that only 0.1% of the sperms placed in vagina are present in the cervical canal one hour after insemination.[4] Direct deposition of motile sperms in the uterine cavity can reverse this situation, and increase the chance of pregnancy. The use of IUI in patients with cervical factor infertility, yields very good pregnancy rates with the success rate of 14–18%.

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Endometriosis

IUI with ovulation induction can be tried in cases of mild endometriosis. Patients with mild to moderate endometriosis have good pregnancy rates between 7–18%. However, as the pregnancy rates (3–5%) are very low with severe endometriosis, it is best to opt for in vitro fertilization (IVF)/ICSI.

Common Factors

Immunological

Antisperm antibodies can be found in both males and females. Causes in men are usually testicular trauma or obstruction to the male genital tract. In women, it can happen due to a break in the vaginal epithelium, peritoneal instillation, anal or oral intercourse. These antibodies prevent binding of sperm to zona pellucida and also impair the sperm movement. Various treatments like prolonged use of condoms, immunosuppression with steroids and laboratory procedures to wash sperm have been tried. However, all these have limited success.

Both IUI and IVF have shown to have high pregnancy rates in such patients. IUI helps to bypass these antibodies in cervical mucus.

Unexplained Infertility

This diagnosis is made when a couple fails to conceive despite there being no obvious cause, even after subjecting the patient to a complete work-up. The diagnostic protocol should include an assessment of ovulation, evaluation of tubal patency and a normal semen analysis. The average incidence of unexplained infertility is around 10–15%.

Defects in folliculogenesis, gamete development, fertilization, and embryo development may be the factors responsible. The rationale of empirical therapy is to bypass these causative factors. The managing principles are:

- Increasing availability of gametes by ovulation induction
- Improving gamete quality
- Bringing the gametes together by IUI or IVF.

The efficacy of various treatments in unexplained infertility is[5]:

Treatment	*Combined pregnancy rate per initiated cycle*
No treatment	1.3%
IUI	3.8%
CC	5.6%
CC with IUI	8.3%
HMG	7.7%
HMG with IUI	17.1%
IVF	20.7%

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Insemination with Husband's Frozen Semen

This is required in the following conditions:

- Absentee husband
- Antineoplastic treatment
- Vasectomy
- Poor semen parameters
- Drug therapy.

Insemination with Donor Sperms

It is now mandatory to use cryopreserved donor samples in order to minimize risk of HIV transmission. The indications for insemination with donor semen are:

- Azoospermia
- Severely subnormal semen parameters
- Hereditary disease in father
- Persistent IVF/ICSI failures
- Rhesus isoimmunization
- Patient unable to afford ICSI.

Patient Selection and Work-up

An appropriate patient selection is the key to success for any treatment. A complete work-up including a detailed history is required before taking a patient for IUI. Many infertile couples have more than one contributory factor which should be identified at the earliest. A scientific approach is warranted for a complete and efficient evaluation of female and male factors. More importantly, any contraindications to the procedure should be ruled out, as these can compromise the results. Apart from a detailed history and physical examination, and routine investigations certain specific tests for both the partners are required.

Contraindications

- Bilateral tubal block
- Very severe oligoasthenospermia
- Genital tract infection
- Pregnancy contraindicated in female partners
- Unexplained genital tract bleeding.

Relative Contraindications

- Tubal pathology
- Genetic abnormality
- Pelvic mass
- Older women
- Multiple infertility etiologies
- Pelvic surgery

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- Severe illness in one or both partners
- Recent chemotherapy or radiotherapy.

EVALUATION OF THE FEMALE PARTNER

Routine Investigations

complete blood count (CBC), erythrocyte sedimentation rate (ESR), sexually transmitted disease (VDRL, HBsAg, HIV) blood sugars, urine routine, bleeding and clotting time.

Anthropometric measurements such as body mass index (BMI) and waist to hip ratio (WHR) will help to identify patients with central adiposity. These patients may require further evaluation of hyperandrogenism and hyperinsulinemia that may cause aberration in ovulation and cause luteal phase deficiency despite medication.

Hormonal Investigations

Serum FSH, LH, Estradiol on Day 2/3 of Cycle

- FSH > 10 mIU/mL and E2 > 60 pg/mL indicates poor ovarian reserve
- LH/FSH > 2/1 indicates polycystic ovary syndrome (PCOS)
- Low LH, FSH, E2 indicates hypogonadotropic hypogonadism
- Follicle-stimulating hormone (FSH) more than 10 mIU/mL on day 10 after giving a clomiphene challenge indicates poor prognosis.

In case of patients suspected to be poor responders, one can do these additional tests:

- *Serum inhibin:* B test which is > 45 pg/mL in poor responders.
- *Clomiphene citrate challenge test:* CC 100 mg per day from day 5 to day 9 and FSH on day 10. A high FSH (>10 mIU/mL) indicates poor response and poor prognosis. This also points towards direct stimulation with gonadotropins instead of clomiphene citrate.
- Serum antimüllerian hormone (AMH)

Serum Prolactin and T3 /T4/ TSH

In case of patients with PCOS diagnosed by USG/symptomatology/clinical or biochemical features of hyperandrogenism, the following tests are indicated:

- Fasting serum insulin level (>10 mIU/mL is significant)
- Fasting and Postprandial blood sugars.
- Fasting blood glucose/fasting insulin ratio (>4.5 is normal)
- Dehydroepiandrosterone sulfate (DHEAS), androstenedione and testosterone
- In obese patients, a follicular phase 17-OHP (17-Hydroxyprogesterone) level (to rule out congenital adrenal hyperplasia) and dexamethasone suppression test (to rule out Cushing's syndrome) should be carried out.
- Rarely serum alanine transaminase level is done in patients who are intolerant to metformin treatment and who need to be placed on rosiglitazone.

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- In women with past history of renal disease on metformin treatment, serum creatinine and/or 24 h creatinine clearance may have to be done.

For screening and academic purposes a C-peptide assay may be performed to pick up latent diabetes.

Tests for Ovulation (Ovulatory or Anovulatory)

- Basal body temperature
- Serial vaginal ultrasound follicular scan in a spontaneous cycle
- Serum progesterone on day 21 of cycle >4 ng/ml indicates ovulation and >10 ng/mL indicates adequate luteal phase.
- Urinary LH surge testing.

Pelvic Sonography

This helps in evaluating uterus, uterine cavity and adnexae. Ovarian volume, antral follicle count and presence or absence of PCO pattern should be noted.

HSG: This is done just after the means and over. It helps in evaluation of uterine cavity and to check the tubal patency.

Diagnostic laparoscopy and hysteroscopy may be required in certain cases to establish the exact diagnosis (especially endometriosis).

Physical parameters	*Clinical parameters*	*Endocrinological*
Weight (kg)	USG – evaluation of uterus and cavity	Day 2/3 FSH, LH and E_2
Height (Meters)	Measurement of ovarian reserve	S. prolactin
Body mass index (kg/m^2)	Number of antral follicles	Fasting Insulin, SHBG and DHEAS
Waist to hip ratio	Diagnostic laparoscopy and hysteroscopy for evaluation of cervical, tubal, uterine and ovarian factors	Day 21 progesterone

Tests to Rule Out Tuberculosis

These are especially important in developing countries. These include:

- CBC with ESR
- Chest X-ray
- Mantoux test
- Endometrial biopsy
- TB ELISA IgG and IgM
- TB-PCR
- BACTEC.

EVALUATION OF MALE PARTNER

- Detailed history and examination
- Built

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- Hair distribution scoring
- Gynecomastia
- Examination of testis, vas, epididymis, volume of testis in case of azoospermia
- Semen analysis and culture

PREREQUISITES FOR IUI

- Age less than 40 years
- Patient capable of spontaneous or induced ovulation
- At least one patent Fallopian tube with good tubo-ovarian relationship
- Sperm count of more than 10 million/mL prewash or a postwash count of >3–5 million motile sperms with percentage motility of more than 40%
- Easy access to the uterine cavity via a negotiable cervical canal.

Case 1

30-year-old female, married for 5 years with primary infertility. She had regular cycles and has undergone many cycles of follicular monitoring which showed dominant follicle rupture on day 15 of cycle. Her hormonal profile was normal and hysterosalpingography (HSG) showed a normal uterine cavity with bilateral free spillage of dye. Husband semen analysis showed mild oligospermia with normal motility. The patient underwent ovulation induction with letrozole 5 mg from day 3 to day 7 with follicular monitoring and intrauterine insemination. She conceived in her 2nd cycle of treatment and delivered a healthy female child at term.

Case 2

28-year-old female, married for 3 years with irregular menses with primary infertility. USG showed evidence of polycystic ovaries. Hormonal profile revealed no abnormality. HSG showed a normal uterine cavity with bilateral free spillage of dye. Husband's semen analysis showed normal count and motility. The patient underwent ovulation induction with clomiphene citrate 100 mg from day 2 to day 6 of her periods. Transvaginal sonography on day 8 showed a single dominant follicle. This was followed by serial transvaginal scans. The ovulation was triggered when the dominant follicle reached 18 mm followed by IUI 36 hours later. A β-hCG 14 days later was 340 mIU/mL and sonography at 6 weeks showed a single intrauterine gestation sac.

It is preferable to have a dedicated and specialized counselor in every ART center for better guidance of patients. A practical approach, therefore, puts modern technology into perspective without forgetting the dreams of the couple. Care should be made in order to understand the psychological and financial stresses associated with infertility. Even the patient who has had a failure should feel that the best possible efforts were carried out for them.

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