

Indications, Patient Selection and Work-up Before Intrauterine Insemination

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ABSTRACT

Intrauterine insemination (IUI) is a common treatment for infertility. It involves the deposition of 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. This procedure is used for couples with unexplained infertility, minimal male factor infertility and women with cervical mucus problems. Despite its popularity, the effectiveness of IUI treatment is not consistent. Therefore, in spite of the fact that many a times the treatment is empirical, appropriate patient selection is very important and a complete work-up is required before taking up the patient for IUI. Patients should be counseled about the procedure involved, success rates, other options and risks associated.

Keywords: Intrauterine insemination, unexplained infertility, patient selection, work-up

Appropriate patient selection is the most important factor which determines success of any treatment. With intrauterine insemination (IUI), many a times the treatment is empirical, still it is possible to deduce a group of couples where the treatment will be actually 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 of IUI which may be due to male factor, 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.

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INDICATIONS OF IUI

Male Factors

Impotence/Ejaculatory dysfunction

This can be due to 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 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 and 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 the prostate (TURP) and retropubic prostatectomy. In retrograde ejaculation, urine is centrifuged and then washed to isolate sperms and IUI is then performed.¹

The treatment for various causes of male infertility is summarized in Table 1.

- **Psychological conditions:** Such patients need sex-psychotherapy. Drugs such as sildenafil 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 the World Health Organization (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

Table 1. Treatment for Various Causes of Male Infertility

Treatment

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

Mild male factor is defined as follows:

- Patient with only one abnormal male parameter
- Total motile sperm concentration of more than 5 million.

Ideally, a total motile pre-wash count of more than 10 million or a post-wash motile sperm count of 5 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 *in vitro* fertilization or intracytoplasmic sperm injection (IVF/ICSI) or the use of donor sperms for insemination (artificial insemination with donor sperm - AID).

Other factors

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

Human immunodeficiency virus (HIV) infection: Sperm washing can significantly reduce the viral load.³ Recently, insemination of HIV negative women with processed semen sample of HIV positive partners 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 factors. 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 mucus
- Abnormal cervix: Stenosis, injury, malformation, infection, erosion
- Abnormal post-coital test (PCT) or hostile cervical mucus (the general consensus is that PCT has non-predictive 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 1 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 of infertility yields very good pregnancy rates, in the range of 14-18%.

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% and 18%. However, as the pregnancy rates (3-5%) are very low with severe endometriosis, it is best to opt for IVF/ICSI.

Common Factors

Immunological

Antisperm antibody 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 shown in Table 2.⁵

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 only, to minimize risk of HIV transmission. The indications for insemination with donor semen are:

- Azoospermia
- Severely subnormal semen parameters

Table 2. Efficacy of Various Treatments in Unexplained Infertility

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

IUI = Intrauterine insemination; CC = Clomiphene citrate; HMG = Human menopausal gonadotropin; IVF = *In vitro* fertilization.

- Hereditary disease in father
- Persistent IVF/ICSI failures
- Rhesus isoimmunization
- Patient unable to afford IVF.

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 (Table 3). Apart from a detailed history and physical examination, and routine investigations, certain specific tests for both the partners are required.

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-hip ratio (WHR) help identify subjects 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.

Table 3. Contraindications of IUI

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

Hormonal investigations:

- Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) 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
 - FSH >17 mIU/mL on Day 10 after clomiphene citrate indicates poor prognosis.
- In case of patients who are 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: Clomiphene citrate 100 mg/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 AMH (anti-mullerian hormone).
- Serum prolactin and triiodothyronine/thyroxine/thyroid-stimulating hormone (T3/T4/TSH)
- In case of patients with PCOS diagnosed by ultrasonography (USG), or symptomatology or having feature of androgenization, one can do the following tests:
 - Fasting serum insulin level (>10 mIU/mL is significant).
 - Fasting and postprandial blood sugars.
 - Dehydroepiandrosterone sulfate (DHEAS), androstenedione and testosterone.
 - In obese patients, a follicle phase 17-OHP 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.
 - In women with past history of renal disease on metformin treatment, serum creatinine and/or 24 hours 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.

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.

Hysterosalpingography (HSG): This is done on Day 8 of periods. 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.

Pre-procedural work-up for IUI is summarized in Table 4.

Tests to rule out tuberculosis: These are especially important in developing countries (Table 5).

Table 4. Pre-procedure Work-up for IUI

Physical parameters	Clinical	Endocrinological
Anthropometry Weight (kg) Height	Transvaginal sonography Evaluation of uterus and cavity Measurement of ovarian volume No. of antral follicles, PCOS/non-PCOS	Day 2/3 hormones Serum LH, FSH, E2 TSH, prolactin, SHBG, F. insulin
Body mass index	HSG (to evaluate uterine cavity and tubal status)	
Waist-hip ratio	Diagnostic laparoscopy and hysteroscopy (if necessary): for evaluation of cervical, tubal, uterine and ovarian factors	Day 21 hormones: progesterone

PCOS = Polycystic ovary syndrome; LH = Luteinizing hormone; FSH = Follicle-stimulating hormone; E2 = Estradiol; TSH = Thyroid-stimulating hormone; SHBG = Sex hormone-binding globulin; HSG = Hysterosalpingography.

Evaluation of male partner

It involves evaluation of various clinical and laboratory parameters as shown in Table 6.

Pre-requisites for IUI

- Age less than 40 years.
- Patient capable of spontaneous or induced ovulation.
- At least 1 patent fallopian tube with good tubo-ovarian relationship.
- Sperm count of more than 10 million/mL pre-wash or a post-wash 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.

Table 5. Tests to Rule Out Tuberculosis

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

CBC = Complete blood count; ESR = Erythrocyte sedimentation rate; TB = Tuberculosis; ELISA = Enzyme-linked immunosorbent assay; Ig = Immunoglobulin; PCR = Polymerase chain reaction.

Table 6. Evaluation of the Male Partner

Clinical parameters	Laboratory parameters: Investigations
Detailed history and examination	Semen analysis and culture
Hair distribution scoring	Normospermia: No further investigations
Examination of testis, vas, epididymis	Astheno/necrospermia: Antisperm antibody
Volumes of testis in case of azoospermia	Teratospermia: Check for DM
	Moderate oligospermia: Sperm function test
	Severe oligospermia: Vasogram, color Doppler scrotum
	Azoospermia: Testicular biopsy/ FNA testis
	Endocrine evaluation: LH, FSH, Testosterone, PRL, TSH

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Make sure

DURING MEDICAL PRACTICE

SITUATION: A patient with hypertension on ACEI had nonresponding dry cough.



LESSON: Make sure to remember that the commonest cause of cough in a patient with high BP is the intake of ACEIs. A dry, persistent cough is a well-described class effect of the ACEI medications.

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