Guidelines for intra uterine insemination (Prepared by FOGSI Infertility Committee)

Sadhana Desai,
Vijay Mangoli, H.C. Bandhu, Partha Guharoy, G. Allahabadia

Introduction

Human fertilization is a complex process. Out of millions of sperms deposited in vagina during normal sexual intercourse only a few thousand sperms, actually reach the site of potential fertilization. This high loss is thought to be due to a variety of factors. Intrauterine insemination overcomes some of the barriers responsible for prevention of migration of sperms to the distal part of the fallopian tube.

IUI is the direct placement of processed highly motile, concentrated sperm, washed free of seminal plasma & other cells, into the uterus, adjacent to the medial ends of the fallopian tubes, as close to the ovulated oocytes as possible. This procedure greatly reduces the distance that the sperm must travel and increases the amount of spermatozoa available to the oocyte. The number of sperm that reach the fallopian tubes is increased as much as 25% with IUI.

Intrauterine insemination, both in spontaneous and perferably, in ovulation induction cycles, is recommended as the first choice option of assisted conception techniques, since the procedure is non invasive & also much more cost effective.

Section - Indications for Treatment

In male partner

1. Anatomic defects of penis (hypospdias)
2. Sexual or ejaculatory dysfunctions where semen is collected using vibrator or electro ejaculator
3. Retrograde ejaculation
4. Impotency
5. Immunological factor like auto antibodies and sperm agglutination
6. High and prolonged viscosity which results in a firm coagulum inhibiting transport of active sperms near the oocyte.
7. Oligoasthenoteratozoospermia which shows low profile seminogram as, low sperm count, less motility, poor grade motility & / or high percentage of abnormal sperms.
8. Donor sperm insemination

In Female partner

1. Anatomic defects of the reproductive tract where direct coitus is not possible.
2. Psycholoical & psychogenic sexual dysfunction eg. Vaginismus
3. Cervical factors
   Poor sperm - mucous interaction/failed post coital test cervical stenosis
   Destruction of endocervical glands as a result of conization, laser surgery or cryosurgery
4. Ovulatory dysfunctions responsive to clomiphene citrate.
5. Unexplained infertility where pregnancy is not achieved with other medical intervention
6. Minimal endometriosis
7. Antisperm anti bodies in the cervix

Women with altered tubal function or with blocked fallopian tubes (both) should not be taken for IUI treatment.

The initial workup

Before beginning IUI, couples should be informed of the expected course, the technique aspects of the procedures, the risks of complications & expected outcomes. The couple should be offered to speak with a psychotherapist/ social worker who specialized in infertility. Counselling must be adequate & realistic expectations for pregnancy rate should be explained.

The following minimal investigations are to be carried out

Husband :

1. Physical examination both systemic & local
2. Semen analysis
   - morphological, functional test
   - culture
   - antisperm antibody
3. Screening for infection including syphilis, Hepatitis B & HIV
4. If needed appropriate endocrinological investigations & therapy.

The investigations should be carried out within span of two months before collection of semen for IUI.

Wife :

1. History & physical examination both systemic & local
2. Detection & timing of ovulation by BBT, cervical mucus study, USG, monitoring of follicular growth.
3. Assessment of tubal patency - HSG / Laparoscopy, Hysterescopy
4. Premenstrual D & C and histopathological examination of endometrium
5. Screening for local factor including cervical mucus.
6. Screening for reproductive tract infections including syphilis, chlamydia, tuberculosis, Hepatitis B & HIV
7. Appropriate endocrinological investigation - FSH / day 3 of cycle
   LH / day 3 of cycle
   Progesterone / day 21
   TSH
   Prolactin
8. Antisperm antibody in both cervical mucus & Serum

Women with evidence of vaginitis or presence of pelvic inflammatory diseases should not be taken for IUI. In case it is present procedure should be postponed and condition be treated by appropriate local and systemic chemotherapeutic agents.

Stimulation Protocols and Monitoring of the cycle

IUI can be performed in natural or stimulated cycle. In natural cycle, ovulation is monitored carefully by either serial ultrasound examination of dominant ovarian follicle or by urinary, plasma or dipstic methods of LH assay. IUI is performed 24 hours after the onset of LH surge.

When in a woman who has ovulatory cycles but fails to become pregnant after 4-6 cycles of IUI, ovulation induction may provide an effective adjunct to therapy. In stimulated cycle, different protocols are used to activate ovary to produce more than one mature oocyte thus increasing the changes of fertilization & therapy pregnancy. The regimens may vary depending upon patients response to the drugs.

Different ovarian stimulation protocols used are :

1. Clomiphene citrate
2. C.C. + hCG
3. C.C. + FSH / HMG + hCG
4. FSH/HMG + hCG
5. GnRHa (long or short protocol) + FSH/HMG + hCG

Timing of IUI

A well timed IUI - is 'Must' and is a 'Critical Key' to success because spermatozoa survive for a limited period in the female reproductive tract and oocytes are fertilizable for only 12 to 16 hours. Timing of IUI becomes more important when indications include oligospermia. Good pregnancy rate depends on the correct identification of LH surges or on an ovulatory hCG injection given when follicle reach 18 to 22 mm with a single planned insemination 36 to 38 hours later.

Laboratory Setup

1. A room should be provided for the production and collection of semen. The room should be comfortable, large enough to accommodate two people, and furnished with any materials thought necessary to aid production of semen such as magazines and video films.
2. Trained laboratory personnel & basic equipment requirements should be fulfilled.
3. Outpatient clinic facilities & insemination room.

Equipments for the IUI unit.

1. Centrifuge capable of operating at 300 x g
2. Carbon Dioxide Incubator
3. Carbon Dioxide cylinders (medical grade)
4. light microscope
5. Laminar air flow hood
6. Class 2 cabinet
7. Makler sperm counting chamber / Neuber chamber
8. Pasteure pippets
9. Pipette controller
10. Refrigerator
11. Test-tube rack
12. Culture medium /Sperm washing kit/Percoll, Pure sperm or Isolate gradient
13. Sterile sperm semem specimen container
14. I ml insulin syringe (disposible)
15. Insemination catheter

Guidelines for Sperm Preparation

Male partner who has been physically examined & investigated for semen count, culture, antisperm antibodies, HIV, HBsAg & VDRL status, should have an abstinence of 3 to 4 days.

Collection of semen by masturbation in sterile container provided by the laboratory, after properly cleaning & drying the penis and hands. The aim of the sperm preparation is to remove cellular debris, abnormal & immotile spermatozoas, seminal fluid (containing prostaglandins) and WBCs from the ejaculate. And while doing sperm washing the spermatozoa gets capacitated (activated) to penerate the zona pellucida of the oocyte which has been released by the ovary.

Particular attention is to be given to the sample collection room which should be isolated, neat and clean, should include a urinal, a washbasin, a bed and a clean and disinfected platform to keep the bottles. Provision of vibrator and erotic - stimulating pictures, is of tremendous help to the tense male partner.

Containers in which sample is collected should be of non toxic material like polypropylene. If it is made up of glass, it should be borosilicates glass, should be tissue culture washed and heat sterilized.

Patient should collect sample by masturbation rather than direct coitus method, which encourages contamination.

Patient should be asked to collect sample by split ejaculation which separates prostatic fluid and sperm fraction from seminal plasma. This separation is helpful particularly in oligospermia and those with autoanitbodies.

Sperm need to be carefully washed before direct placement into the uterus. Semen is not sterile but does contain nonmotile, morphologically abnormal sperm and nonsperm cells in addition to the normal, motile sperm. Washing is necessary because sperm placed directly into the uterus bypasses the protective effects of the cervical mucus. During washing, sperm selection, hyperactivation, and partial capacitation occurs, events thought to normally occur in the mucus. Washing is important because the seminal plasma contains prostaglandins that can cause intrauterine contractions and therefore must be removed.

For IUI to be successful, adequate sperm must be present. The final washed sperm count should be preferably 3 to 5 million motile sperms. If there are fewer than 3 million total motile sperm present, the woman should be referred for IVF/ICSI.

Media - Although sperms are resistant to many adverse conditions and can survive even in normal saline, it is better to process semen sample in a biochemically defined medium to maintain sperm integrity and promote acrosome reaction and capacitation. Bicarbonate buffered media should be equilibriated with 5% Carbon dioxide, 5% oxygen and 90% nitrogen at 37*c, in atleast 95% humidity for 8 hours. A pH or 7.2 and osmolarity of 285 mili osmol./kg is recommended. 10% heat inactivated serum or HSA or synthetic serum can be added so the medium as protein supplement.

In cases where motility of sperms is adversely affected due to midpiece defects, methyxanthene derivatives like pentoxyphylline & caffine can be added to medium.

Catheters :-

Many types of catheters are available. Those used for IVF can be tissue culture washed, gas sterilized and

reused. Local catheters should be checked for toxicity. A simple method to check toxicity is to pass processed sample through the catheters and check its survival for 24 hours and 48 hours. If 80% sperms are surviving after 48 hours these catheters can be used. It is better to mark utero-cervical length on the catheter before insemination. The mark on the catheter should be 0.5 cm less than the actual utero cervical length to avoid touching the fundus, which may result in contraction of muscles and thus expulsion of inseminated fluid. The catheter should be rinsed with medium before loading processed sample.

Steps of semen preparation -

1. Let the semen sample liquify at room temperature for 15-30 minutes.
2. Use of labelled - Fresh, presterilized pippettes & conical tubes.
3. Semen analysis for count and motility is performed and recorded before and after the sperm washing procedure. This is an important part of quality assurance.
4. The medium to be used should be at 37* c or room temperature and equilibrated in carbon dioxide incubator before use.
5. Technique - Wash & swim up or Percoll, Puresperm or Isolate gradient.
6. Harvest semen analysis for sperm count motility & morphology should be atleast 3 million (ideal 3 to 5 million)

The principles that need to be adhered to during the washing and insemination process :-

1. Although the semen is not sterile, sterility should be maintained through the sperm washing procedure.
2. Protective eyewear and gloves should be used when handling the specimen.
3. The same pipette should not be used to enter more than one bottle.
4. A needle should never be used because it may damage the spermatozoa.
5. If many WBCs are present in the ejaculate, IUI should not be performed. The problem must be diagnosed and treated. Remember, immature sperm can look similar to WBCs.
6. The total volume of the nongravid uterus is 0.5 ml; therefore, no more than 0.5 ml should be injected or else the specimen may be displaced from the uterus.
7. Properly label all tubes and syringes containing the specimen.

Methods of Sperm Preparations

The following procedures are commonly used for semen preparation:

1. Sperm - Wash Procedure

The liquified sample is first diluated with a culture medium or with buffered physiological saline in the ratio of between 1:1 and 1:3 the suspension is then centrifuged for 10 min at 150-200 x g or for 3-5 min at 500 x g. The supernatant is discarded, and the resultant pellet is rediluted in a smaller volume of fresh medium. This wash procedure is repeated one to two times. The final Pellet is resuspended in 0.3-0.5 ml medium

2. Swim - up Technique

After washing and concentrating sperm, 0.3-0.5 ml of prepared medium is carefully layered over the final pellet and the sample is incubated for 30-60 min at 37^0C in 5% CO2. It is recommended that the tube be held at an angle of 30^0 so that a larger interface is created. The supernatant (swim-up specimen) is then collected with care, not disturbing the pellet at the bottom.

3. Percoll Density Gradient Separation

With the Percoll (PVP - coated colloidal silica particles) density gradient separtion method motile spermatozoa are isolated by layering liquified neat semen over an isotonic Percoll solution and centrifuging it for 10-20 min at about 200-600 x g. The supernatant is discarded, and after one to two wash runs pellet is resuspended for insemination in 0.3 - 0.4 ml medium.

No. of Inseminations and duration of treatment

It is recommended that only one or two insemination

should be performed per cycle depending upon clinical, USG monitoring & day / time of hCG administration.

No. of cycles : The clinician needs to discuss the number of expected cycles. Retrospective studies of a large number of women show a relatively constant probability of becoming pregnant after each IUI through four cycles after which the success rate reaches a plateau. Revaluation of the treatment strategy should be carried out after 4-6 cycles.

Treatment in a couple with cervical or male factor infertility and the woman who is anovlatory before treatment, should be continued longer than in the woman who is ovulatory or diagnosed with unexplained infertility. If no results are seen then the plan needs to be changed & alternative options discussed. Every time there is a move to a new technique the clinician must be careful not to give rise to any false hopes that the chances of pregnancy are substantially increased.

In a woman with documented ovulatory cycle who has failed to become pregnant after 4-6 cycles of IUI, ovulation induction may provide an effective adjunct to therapy. The combination is thought to increase the number of sperm & oocytes available, resulting in an increased chance of fertilization & pregnancy rates in stimulated cycles.

Methods of IUI

Steps of IUI -

1. Well lighted room with gynaec examination table.
2. Women to lie in dorsal lithotomy position after emptying the bladder (table may have slight degree of Trendelenberg)
3. Under strict aseptic conditions & precautions, the semen sample washed & prepared for insemination be loaded in IUI catheter.
4. Perform Bimanual examination to assess uterine size and position.
5. Insert speculum into vagina & visualise the cervix.
6. Clean the os if any discharge is present with dry sterile swab or swab dipped in normal saline.
7. Thread the preloaded catheter through the cervix. Do not use force.
8. A tenaculum does not usually need to be used, except with a marked degree of ante or retroflexion.
9. A stiffer catheter may be necessary in the presence of cervical stenosis.
10. Bring prepared specimen into the room in sterile wrapper. The name should be on the wrapper.
11. Slowly inject the specimen over 30 to 60 seconds to avoid flushing the uterus too fast and causing retrograde flow. Be careful the catheter does not act as an outflow wick. Injecting the solution too rapidly can force semen through the tubes into the peritoneum and cause considerable pain.
12. Remove the catheter with slight twist to avoid any spillage.
13. Inject 0.5 cc of air to clear the catheter of any remaining specimen; Be careful not to inject air into the uterus.
14. Leave the woman in a comfortable reclining position for 15 to 20 minutes.
15. Instruct the woman to call if any abdominal pain, cramps or fever develops; with the onset of menses, or if menses is 2 or 3 days late, she should call to arrange for a pregnancy test and further instructions.
16. If the catheter traumatises the lining of the uterus and bleeding occurs, the chance of fertilization is reduced because immunoglobulins may be secreted from the endometrium.

Risks of IUI

There are fortunately very few and rarely severe.

1. Uterine cramping (pain - 5%)
2. Spotting (1%)
3. Gastrointestinal upset (0.5%)
4. Infection (0.2%)
5. Risks of controlled ovarian stimulatin. Severe ovarian hyperstimulation syndrome (1%), Multiple gestation, Ectopic gestation

Conclusion

With a woman having 'Functional Patent Tubes' & male partner having 'Adequate Sperm Count', Intra Uterine Insemination is 'Reliable & cost effective treatment option'. In such couples IUI may 'maximise fertility' with 'minimum patient risk and less expense'.