

## IUI or IVF: In Resource Crunch Countries

Bindu Bajaj\*

Department of Obstetrics and Gynaecology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

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### INTRODUCTION

Infertile couples are usually advised to start their investigations after 12 months of trying to conceive or after 6 months if the female partner is more than 35 years old or immediately if there is an obvious reason to investigate.

Each couple undergoes thorough physical examination and a structured battery of investigations. In females this comprises performing hormonal profile, ovarian reserve evaluation, rule out tuberculosis, confirm tubal patency and assess uterine cavity, ovulation assessment and infectious screen in both partners to rule out HIV, Hepatitis B, and Hepatitis C. Similarly, in males after semen examination and repeat abnormal examination, he is further investigated with hormonal profile, scrotal ultrasound and FNAC of testes if needed. A diagnosis based on these investigations as to the cause of infertility is reached thereafter and treatment planned.

There is a tendency of these patients to change doctors once treatment does not seem to be bearing results and if they have had some previous assessment and treatment for their infertility, this data should be cautiously reviewed. Treatment options available will also depend on the duration of their infertility, which partner is affected, the age of the female partner and if any previous children conceived, the underlying pathological cause, and if the treatment will be covered by insurance or the cost involved. One of the most important achievements unarguably of the 20th century has been the birth of first baby by IVF in 1978. However, since its introduction in 1962, progress in IUI has remained static.

Counselling, ovarian stimulation and monitoring of follicles and semen preparation are steps common to IUI and IVF. First line treatment is an enigma for the treating doctor. IUI involves insemination of prepared semen in the uterine cavity and fertilization in the female genital tract whereas IVF involves fertilization in culture dish and transfer of embryo in the uterine cavity. IUI is less

intrusive, more patient friendly, less stressful, very safe procedure.

### Indications of IUI

- Ejaculatory failure
  - Anatomical (hypospadias)
  - Neurological (Spinal cord injury)
  - Retrograde ejaculation
  - Psychological (Impotence)
- Cervical Factor
  - Poor Cervical mucus
  - Cervical mucus hostility
- Male Factor
  - OAT (oligoasthenoteratozoospermia)
  - Oligospermia
  - Asthenozoospermia
  - Teratozoospermia
  - Azoospermia -AID
- Unexplained Infertility
- Endometriosis
- Immunological
  - Male antisperm antibodies
  - Female antiserum antibody (cervical, serum)
- Sero discordant couples

There is no dispute that where IVF can achieve pregnancy IUI may not, but it is precisely those indications where IUI stands a chance and IVF is resorted to that needs attention and is the contention of this review. For health facilities with availability for IVF, IUI may have long been abandoned considering its dismissal success rate (11% per cycle on the higher side). Cost is very important deciding factor in resource crunched

#### Corresponding Author:

Bindu Bajaj, Senior Specialist and Associate Professor, Department of Obstetrics and Gynaecology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India, E-mail: bindu\_bajaj@yahoo.com

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countries. In India, where government spends 2% of GDP on health care and IVF facilities mostly rest in private health care, getting IVF procedure is a distant dream for poor people, and getting it without adequate recourse to IUI is inexcusable.

As against IVF (ART) there has been lack of prospective randomized trials and large prospective cohort studies caused by the low budget linked to IUI when compared to the budget associated with other methods of assisted reproduction such as IVF and ICSI. Multiple births consequent to ovarian stimulation has been a single reason pitched against IUI. This prejudice is based on historical practices involving the irresponsible induction of high numbers of follicles during IUI procedures. Its effectiveness in terms of pregnancy rate is ~10–14% per cycle reaching cumulative values of 40% after 3 treatment cycles<sup>[1,2]</sup>. Monitoring of follicles has reduced the absolute rate of multiple pregnancies to 0.3% after mono follicular growth and 2.8% after multi follicular growth. Furthermore, IUI does not involve the cost required with embryo culture facilities and cryopreservation facilities<sup>[3]</sup>.

### Indications of IVF/ICSI (Dutch Society of Obstetrics and Gynecology)

- Tubal pathology-

If tubal surgery is not a realistic option

Following tubal surgery or non-occlusive tubal pathology, no success for 2 years.

- Unexplained infertility of 3 years duration or earlier if female >36years
- Male infertility

TMC<1 million, first treatment of choice is ICSI.

TMC>1 and<10 million, IVF can be performed if infertility is 2 years or more.

TMC > 10 million, treat as unexplained infertility.

- Endometriosis

In case of mild or moderate endometriosis, treat as unexplained infertility.

In case of severe endometriosis, treat as in tubal pathology.

- Cervical factor /immunological Infertility

After infertility duration of 2 years, IVF is indicated. This may be considered sooner if the woman is >36 years.

- Hormonal Disturbances – An ovulatory cycle are indicated for IVF if 12 cycles of treatment with ovulation induction have been unsuccessful.
- Fertility preservation
- Gestational Surrogacy
- Pre implantation genetic diagnosis and Screening.

### Indications for ICSI

1. TMC< 1 million
2. <4%normal morphology and TMC< 5 million
3. No or poor fertilization in two IVF cycle when TMC> 10 million
4. Epididymal or testicular spermatozoa

### Indications for oocyte donation

1. Premature ovarian failure
2. Gonadal Dysgenesis
3. Bilateral Oophorectomy
4. Ovarian failure following chemotherapy or radiotherapy
5. Certain cases of IVF treatment failure

There are clinical, economic, financial, and ethical realities which have been the basis for selecting one procedure over other. In countries where funding bodies dictate the treatment guidelines there have been disparities in treatment policies (NICE 2013). Excess embryos created through IVF procedures are frozen, possibly never used, and these monetary and emotional costs are not factored in when presenting the merits of IVF procedures.

Recent reports also highlight possible concerns from cancers to mothers who have undergone IVF and the need to be vigilant of risks. The potential increased risk of central nervous system (CNS) tumors in patients undergoing ART has been interpreted with caution, while long- term risk of ovarian and uterine cancers need careful follow-up<sup>[4,5]</sup>. The long-term health of children conceived after IVF also require careful studies<sup>[6]</sup>. Although most of the studies regarding safety of ART for mother and children conceived are reassuring yet the long-term effects associated with ART are yet to be determined<sup>[7]</sup>. Large international multi centre cohort studies are required to find whether there is risk associated with ART procedures<sup>[8]</sup>. There has been renewed interest in IUI due to the above reasons and the latest studies reinforce the place of IUI in certain indications which were dismissed by NICE 2013. (NICE 2013 recommended IVF directly after 2 years of expectant management for unexplained infertility).

### UNEXPLAINED INFERTILITY

An estimated 28% of all couples seeking reproductive assistance may have normal findings on their clinical evaluation, making the unexplained infertility a more common provisional diagnosis. IVF is widely accepted successful but invasive modality of treatment for unexplained infertility. It increases the number of oocytes available for fertilization and also helps in evaluating the embryo quality. IVF procedures may be associated with side effects like OHSS (Ovarian Hyper Stimulation

Syndrome), ectopic pregnancy, and increased perinatal morbidity and mortality. However few studies have shown the usefulness of IUI versus IVF cycles when matched equitably.

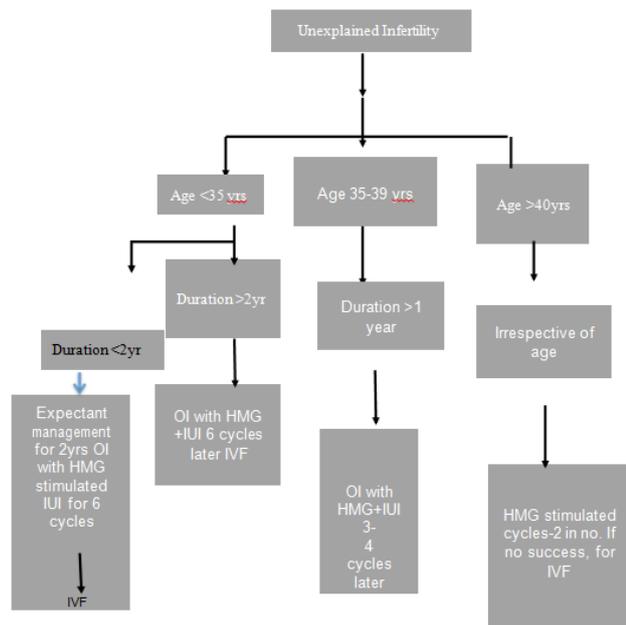


Figure 1: Flow chart showing Unexplained infertility according to age.

In one study on patients of unexplained infertility stimulated IUI, the pregnancy rate per couple was 28% when using FSH and 19% when using CC (OR 1.8; 95% CI 1.2 to 2.7) (as shown in Figure 1). The risk of multiple pregnancies was thwarted by strict cancellation criteria i.e. a cycle was to be cancelled when three or more dominant follicles developed<sup>9</sup>. In a RCT performed in the Netherlands in vitro fertilization with single embryo transfer and in vitro fertilization in a modified natural cycle were non-inferior to intrauterine insemination with controlled ovarian hyper stimulation in terms of the birth of a healthy child (52%, 43% and 47% respectively) and showed comparable, low multiple pregnancy rate. Without any significant difference in efficacy, the IVF procedure was significantly more expensive when compared with stimulated IUI<sup>10-13</sup>.

## ENDOMETRIOSIS

There is no role of medical therapy for infertility associated with endometriosis. On first laparoscopy itself aim should be to clear all the endometriosis lesions especially the peritoneal and cystectomy should be done in endometrium >3 cm. This increases the chances of spontaneous pregnancy. It is very important that ovarian reserve be assessed before surgery and after surgery and patient informed.

## In infertile women with AFS/ASRM Stage I/II endometriosis

Younger patients <35 yrs. expectant management or superovulation with or without IUI may be offered after laparoscopy. <sup>[14]</sup>In women >35 years superovulation with IUI may be done and if does not conceive in 4-6 cycles IVF offered, since pregnancy rates are similar to those achieved in unexplained infertility<sup>[14,15]</sup>.

## In infertile women with AFS/ASRM Stage III/IV endometriosis

IUI has no role.

Repeat surgery should be avoided as it depletes the ovarian reserve unless large endometrioma are likely to come in the way of follicular aspiration. SART (Society for Assisted Reproductive Technology) in a meta-analysis has shown that infertile women with endometriosis had substantially lower success with IVF compared with tubal factor infertility, including lower ovarian response, reduced implantation rate and pregnancy rate. In addition, a more advanced disease was related to increasingly inferior outcome. In two more recent meta-analyses on outcome of IVF in endometriosis, live birth rate was found to be similar in minimal/mild endometriosis and other indications for IVF, whereas in patients with moderate/ severe endometriosis, the results were inferior, including fewer oocytes retrieved, lower implantation rate, and lower birth rate. ASRM during the period 2010–2013, observed that women with endometriosis undergoing ART had a marginally higher cancellation rate and more embryos transferred compared with the tubal factor group, but achieved a comparable live birth rate per cycle. In a Cochrane review, the authors conclude that down-regulation for 3–6 months with a GnRH agonist in women with endometriosis increases the odds of clinical pregnancy by >4-fold in ART cycles<sup>[16]</sup>.

Infertility associated with adenomyosis - There is very limited data confined to case reports on this. Medical management includes GnRH for 3-6 months followed by spontaneous pregnancy. For a well-defined adenomyoma surgical removal may be undertaken after 3 months of GnRH analogues.

## MALE FACTOR INFERTILITY

Poor semen Quality is the single cause of infertility in 20% of infertile couples and is an important contributing factor in another 20-40%. Semen analysis is universally used to assess quality. In 2010, WHO (World Health Organization) defined new reference value for sperm parameters to differentiate between normal and abnormal. However, it does not have good prognostic value. TMSC (Total Motile Sperm Count) has been found to be of value to prognosticate couple undergoing IUI

and also in conventional IVF in predicting fertilization failure. It also has a good correlation with spontaneous ongoing pregnancy rate.

TMSC = Semen volume × concentration in millions/ml × percent progressive motile sperms ÷ 100.

TMSC can be calculated in either pre wash or post wash sample.

A pertinent explanation for this discrepancy is that TMSC considers absolute sperm parameter value simultaneously, while the WHO criteria treats sperm parameters discreetly. A validated classification is missing; the following groups are accepted according to the degree of male infertility:

Group 1 TMSC <1 × 10<sup>6</sup> spermatozoa,

Group 2 TMSC 1–5 × 10<sup>6</sup>

Group 3 TMSC 5–10 × 10<sup>6</sup>

Group 4 TMSC 10–20 × 10<sup>6</sup>

A TMSC of >20 × 10<sup>6</sup> is considered normal.

A guideline as to the management in case male infertility is the only cause is-

TMSC 10-20 million - 6 months of expectant treatment, if no pregnancy, 6 cycles of IUI with ovarian stimulation.

TMSC 5-10 million - 6 cycles of IUI with ovarian stimulation followed by IVF.

TMSC 1-5 million - these patients are directly offered IVF.

TMSC <1 million - these patients are directly offered ICSI.

For mild to moderate male factor infertility, stimulated IUI is cost-effective. The average IUI success rates of around 13% per cycle typically translate to around 20–25% of the cohort for most clinics. Best results with IUI are achieved when the total motile sperm count in the insemination specimen exceeds 10 million and 14% or more of sperm have normal morphology. It is also surprising that spontaneous pregnancies occur even in the presence of extremely poor sperm quality<sup>[16]</sup>.

## TUBAL INFERTILITY

The role of IUI in tubal factor infertility is not adequately covered in western literature. However, it is relevant for developing countries and a few studies that have been performed have shown that there is place for IUI in unilateral tubal block. Since there are not many studies, to appreciate the success rate in such cases is not clear although even one pregnancy without an IVF is an achievement in such cases<sup>[17,18]</sup>.

Overall chance of a live birth following IVF treatment decreases with rising female age, as the number of

unsuccessful cycles increase, and it increases if there has been a previous pregnancy. Results of ART are also decreased if female consumes ≥ 1 unit of alcohol per day, smokes and with caffeine consumption.

## CONCLUSION

With the given evidence couples especially <35 years should be counselled that in mild endometriosis, mild to moderate male factor infertility, unexplained infertility, and one patent tube, ovarian stimulation along with IUI stands equal chance as IVF and hence a uniform policy of 6 IUI cycles followed by 3 cycles of IVF needs to be adopted. In case of blocked tubes, severe endometriosis, severe male factor infertility, poor ovarian reserve, where oocyte donation or surrogacy is indicated IVF/ICSI is the only option. These are broad guidelines and treatment for each patient needs to be individualized. This is especially important for a country like ours where there is resource crunch and also strong economic reasons to delay IVF.

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