Intrauterine inseminations (IUI) have been performed since the beginning of the past century for the treatment of infertility. Despite its widespread use, the overall success rate of IUI remains controversial. In general, the most common indications for IUI are unexplained infertility, mild to moderate male-factor infertility, and other cases of infertility in which the woman has an unobstructed genital tract and some ovarian function and the man has motile sperm (1). Other indications that may apply to male factor infertility include; immunological infertility, coital and ejaculatory problems due to different sexual dysfunctions and anatomical defects (2). With the advent of more sophisticated assisted reproductive techniques (ART), offering IUI for infertile couple become a matter of debate. The reported pregnancy rate after IUI showed profound variations in the literature ranging from 0 to over 50% (3). However, many confrontations are challenging the use of IUI on the ground of evidence-based medicine.

The rationale for IUI in the treatment of male subfertility is to increase the density of normal motile spermatozoa at the site of fertilization. Removal of nonmotile spermatozoa, leucocytes and immature germ cells, might contribute to an enhanced sperm quality by a decreased release of lymphokines, cytokines, and free oxygen radicals that may have a negative effect on the fertilizing ability of spermatozoa. On the other hand, the reservoir effect of the cervical mucus and the natural selection of normal fertile spermatozoa are compromised thus decreasing the window of opportunity for sperm oocyte interaction and fertilization. Before insemination, semen has to be processed using one of the established sperm preparation techniques to select a sperm population with best quality. The techniques used for sperm processing vary across the centers worldwide. The most commonly used are the simple wash using various culture media, swim-up, and discontinuous gradient centrifugation (DGC). However, other less commonly used methods such as; glass bead column, swim-down, and sperm select system have been used in several studies. Despite the diversity in sperm processing techniques, few randomized controlled trials (RCT) could demonstrate a borderline advantage for DGC, while others failed to demonstrate such advantage (4). Large high quality randomized controlled trials, comparing the effectiveness of a gradient and/or a swim-up and/or wash and centrifugation techniques on clinical outcome are lacking. Concerning the frequency of insemination some studies favored double insemination (2). On the other hand, double intrauterine insemination showed no significant benefit over single intrauterine insemination (5).

In male factor infertility due to impaired semen parameters the results are contradictory. Ideally evidence should be gained from large multi-center well-designed randomized studies in clearly defined populations of subfertile males. Despite
the presence of many randomized trials, most of them are single-center, small, and lacking some essential data. Comparing these studies is difficult because of the presence of many variables including the etiology of infertility, variability of semen parameters, female age, duration of infertility, method of ovarian stimulation and monitoring, timing and number of insemination, number of treatment cycles, method of sperm processing and technique of IUI. However, systematic reviews and meta-analysis of randomized controlled studies showed that, Intrauterine insemination offers couples with male subfertility some benefit over timed intercourse, intracervical insemination and natural intercourse (2,4,5,6,7). Comparing IUI alone with IUI combined with controlled ovarian hyperstimulation (COH) revealed some contradictory data. In mild and moderate male factor, COH seemed to improve the results of IUI in some studies but not in others. Human menopausal gonadotropin (HMG) stimulation seems to be superior to clomiphene citrate stimulationas evident by few randomized trials (2,5,7). It should be emphasized that the pregnancy rate per cycle after IUI in male subfertility is relatively low. In most studies it ranged from 0- 30% compared to 0-15% in the control cycles. In other words, IUI will slightly improve the chances of pregnancy compared to no treatment. Conversely, higher pregnancy rate can be achieved for other indications such as cervical factor and unexplained infertility (8). The best results are achieved in male factor infertility related to failure of deposition of semen inside the vagina since any success rate will be compared to zero chance. Apparently other assisted reproductive techniques such as IVF-ET and ICSI offers better results in male factor infertility. Other studies demonstrated that three cycles of IUI offer the same cumulative pregnancy rate as IVF, whilst being more cost-effective (9). ICSI remains the main option when other measures fail and for the most severe forms of male infertility when no specific treatment can be offered. However studies comparing the cumulative results of ICSI and IUI in patients with milder forms of subfertility are lacking.

In male immunologic infertility, large-dose long-term steroid therapy may reduce antibody titres but carries a high risk of complications that overweighs its benefit. Only few prospective randomized trials support a beneficial effect using long low dose, cyclic steroid therapy, IUI alone or IVF alone (10). However, it has been shown that IUI was significantly better than timed intercourse in male patients receiving low dose cyclic steroid (11).

It has previously been demonstrated that the success of IUI may be influenced by different semen parameters particularly the motility before sperm preparation. A threshold value of 40-50% was shown to offer better results. Total motile sperm count ranging from 1 to 5 million after processing was shown to be good determinant for successful outcome (2). Other studies related the success of the procedure to the percentage of sperm with normal morphology using strict criteria. In one study, sperm morphology was a useful predictive tool in a subgroup of patients with a motile sperm count of <1 million (12). Since the impact of sperm morphology on IUI outcome is relatively small and the majority of the studies are retrospective, prospective well-designed studies are needed to establish the role of sperm morphology in predicting IUI outcome.

The prognostic value of several other semen parameters that can measure the sperm fertilizing ability were initially promising. Sperm functional assays such as zona penetration assay, acrosin activity and acrosome reaction assays, nuclear maturity, and sperm chromatin decondensation may prove to be good prognostic tests (2). However, the current sperm function tests are not quite reproducible. Since the introduction of ICSI the interest in sperm function tests have waned.

When we look to value of IUI in male subfertility we should consider the risks. Multiple pregnancies impose a less favorable obstetric outcome. COH has been associated with increased rates of multiple pregnancies and ovarian hyperstimulation syndrome. Generally IUI itself is relatively a simple safe procedure but there are reports of rare complications such as hypersensitivity and pelvic infection (13). When evaluating the advantages of IUI/COH these risks should not be ignored.

In conclusion, the efficacy of IUI in male factor infertility has not been consistently documented in
the literature. Much work is needed in order to standardize the technique and to improve the outcome in various forms of male infertility among different clinics offering this treatment modality. Since this technique is much easier to perform and less expensive than other methods of assisted reproduction, and seems to be reasonably effective, it should be considered in mild to moderate forms of male factor infertility when no specific treatment can be offered. Better results are expected in patients with initial motility above 40-50% or when the total motile sperm count after processing is above 1-5 million/ml. COH using hMG improves the results in couples undergoing IUI for male factor.

REFERENCES


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The place of intrauterine insemination (IUI), especially in relation to in vitro fertilization (IVF) remains controversial. There are wide variations in indications, protocols of ovarian stimulation, semen preparation, timing, number & technique of insemination. There are divergent opinions regarding the benefits obtained from IUI. Indications of IUI include unexplained infertility, male factor infertility, endometriosis, cervical factor infertility & male immunological infertility.

Unexplained infertility

Both stimulated & un-stimulated IUI are more effective than no treatment. Stimulated IUI is an