Intrauterine insemination (IUI) with or without ovulation induction is a common treatment modality of assisted reproduction and most often offered to couples with at least one patent uterine tube. Main accepted indications for IUI are mild-moderate male infertility, infertility due to ovulation disorders, unexplained infertility and endometriosis. However it is still being a debate that these indications, especially for moderate male and unexplained infertility, are also similar to those for in-vitro fertilization (IVF) and indeed for intracytoplasmic sperm injection (ICSI). Subsequently this debate is arising some other controversial questions those recently indicated in a review of randomized studies on IUI (1); Is the patient referred specifically for IUI or other further treatments such as IVF? Do all practitioners and clinics have equal access to each technique? What influences the decision to have a particular cut-off for the one or the other, say for male factor?

Another controversial point is the right timing of IUI in order to obtain a maximum chance for conception. The randomized trials studied on the timing of IUI after administration of human chorionic gonadotropin (hCG) or after spontaneous LH surge reveal also a great heterogeneity in both timing and ovulation induction protocols. It is commonly known that ovulation varies considerably and might also depend on the used ovulation induction protocols. Analysis of natural cycles by World Health Organization shown that ovulation mainly occurs within a mean time of 32 hours after the onset of LH surge ranging between 24-56 hours (2). However in stimulated cycles ovulation usually occurs within 36-38 hours and sequential over several hours from this interval after hCG administration (3). Besides spermatozoa survive and be able to fertilize only for a limited period in the female reproductive tract, and also oocytes are being fertilizable for only 12-18 hours beginning 6 hours after ovulation. From this physiological point it can be considered as IUI success rates should decrease when it is not done in this specific interval. However apart from these data some oocytes can be fertilized as early as 12 hours after hCG administration with Clomiphene Citrate (CC) induction. Thus there are several articles in the literature indicated various timing for IUI leading the best clinical results ranging between 12-60 hours. Moreover this interval is also varies according to detection of a spontaneous or a premature LH surge (which can occur in about 20%-25% of patients), resulting in ovulation within an average of 12-16 hours, therefore IUI timing will need to be adjusted.

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Therefore some different intervals have been reported for IUI leading the best chance for conception varies from 32-34 to 38-40 hours. A recent study poses that IUI either done in a short (32-34-hour) or long (38-40-hour) interval after hCG injection yields same pregnancy rates (PRs) (4). Furthermore timing of IUI and of ovulation with ultrasonic monitoring of folliculogenesis along with hCG induction, a relatively expensive and time-consuming method, does not appear to produce an increased PR compared to monitoring of ovulation by urinary LH (5). In addition Arici et al. defined an increase in PR by triggering ovulation with hCG administration than cycles in which ovulation was monitored with urinary LH levels, however they compare CC stimulated versus non stimulated (6). A retrospective study of Awonuga et al., which compared the results of IUI after 40 hours from hCG administration and IUI after 24-30 hours from detecting spontaneous LH surge with or without additional hCG administration in natural cycles and stimulated cycles, showed no statistical differences between three groups (7). They concluded that there is no additional benefit obtained from waiting spontaneous LH surge for timing of IUI in stimulated cycles. Thus hCG administration yields same PRs and also provides to planning the timing of IUI. More recently in a retrospective study Mitwally et al. also reported that hCG administration is associated with favorable outcome in ovulation induction (8). However, today the right time interval of IUI, the method of ovulation monitoring or triggering of ovulation with administration of hCG or not are still controversial.

One can assume that this timing problem due to various intervals can be defeated by usage of double IUI performed in different time intervals in one cycle. Principal in this approach is to provide sufficient motile spermatozoa for in vivo fertilization regardless from ovulation time. However studies compared double and single IUI are also conflicts. An increase in the probability of achieving pregnancy with double IUI approach was noted in two previous studies (9,10). On contrary there are some recent reports failed to show any benefits of double IUI (11-13). In these studies most commonly double IUI performed at 12-18 and 34-42 hours assuming that first IUI provides a sufficient number of motile spermatozoa close to the first ovulated oocyte(s). The release of sperm from cervical mucus after the first IUI preceding to additional sperm provided by second IUI (34 hours) to fertilize the oocytes ovulated subsequently is the main principal for filling the complete ovulation window. A recent Cochrane review comparing double versus single IUI emphasized the necessity of high-quality randomized trials regarding heterogeneity of double IUI timing, various sperm preparation methods and different ovulation induction regimes with different drugs (13). The reviewers with available data indicated that there is no difference observed between double IUI and single IUI in clinical PRs (per couple or per cycle). However double IUI is also reported to increase PRs in some studies (9,10) and increase slightly the cost (10,11). Thus, it is still a common debate whether double IUI is efficient and also cost-effective or not? Another point is the double IUI role in moderate male infertility. One can assume that the second sperm sample, may be the most crucial one, could be of inferior quality and might not provide any benefit of double IUI in moderate male infertility. However the majority of the trials and the cochrane meta-analysis comparing double versus single IUI did not separately presented the results or the comparisons according to male factor. Except from these comparisons only Alborzi et al. (12) were mentioned the PRs in double IUI and single IUI as 4.7% versus 7.8% per cycle, and 22.2% versus 16% per couple in cases with male infertility. Thus one can speculate that double IUI performed in male infertility is reducing PRs however it was not found statistically different from single IUI results. Furthermore there is a major necessity of the studies on double IUI especially in male infertility cases.

Besides there are also no certain accepted cut off values for the sperm counts and number of IUI cycles that should be performed mainly in male infertility particularly in unexplained infertility for single IUI. Therefore two main debates should also be considered. First, should there be new cut off values required for sperm counts when cost-effectiveness is taken in consideration in male infertility cases?, and second, what should be the
number of IUI cycles prior to IVF or further techniques in unexplained and male infertility cases again when cost-effectiveness is assumed?

In order to answer the first and the second questions the prognostic values of sperm count values and diagnosis in IUI cycles should be kept in mind. It was reported that mean PRs for cycles 1-4 were significantly lower for patients with the following characteristics: age ≥43 years, poor semen quality, single preovulatory follicles, and diagnoses other than ovulatory dysfunction in CC induction (15). Therefore it was indicated in the same study that two additional cycles of CC-IUI after 3-4 cycles should be considered to compensate low PRs in cases with advanced partner age, poor semen quality and poor response but not for unexplained infertility. It was also reported that cumulative PRs reached to 43% after four CC-IUI cycles and to 57% after six CC-IUI cycles in male infertility with semen parameters below the WHO standards but met IUI threshold levels of ≥ 5 million total motile count and ≥ 30% progressive motility (15). However cumulative PRs are plateau at 10% after three CC-IUI cycles and no further pregnancies have been reported for the sperm quality lesser than mentioned IUI threshold levels (15). Oembelet (16) reported that patients with sub-threshold sperm values has a PR of 3.2 % per cycle and it seems logical to perform IUI in male infertility cases with inseminated motile sperm (IMSC) count of 1x106-5x106 and with normal morphology of 4-14 %. However in patients with IUI threshold values (<5x106) other prognostic risk factors such as duration of infertility (less than 3 years), partners age (<35) and other additional infertility diagnoses should be taken in consideration (17). In our opinion the patients with poor sperm quality under IUI threshold levels, but with good prognostic factors such as young partner age and short infertility duration (<3 years) have chance to try six cycles due to compensation of PRs by two additional IUI cycle. On contrary it has been also reported that when the average total motile sperm count is under 10x106/ml, IVF with ICSI was more cost-effective than IUI suggesting an average total motile sperm count (TMSC) of 10x106/ml might be a useful threshold value for decisions about treating a couple with IUI or IVF (18). On contrary a total motile sperm count of 10x106/ml, and even lesser 5x106/ml have been reported to yield considerable PRs with a upper value of 12 % in a previous study (19). Therefore the exact cut-off values of sperm count especially for moderate male factor varies to define the technique in literature. Nevertheless threshold values of 5 or 10x106 TMSC in the ejaculate (19,20) and of 1x106 or 1.5x106 IMSC in the inseminate (16,21) have been reported in recent studies. Consequently we believe that the values of 1,5x106 or 5x106 IMSC according to other prognostic factors mentioned above should be taken as a threshold for IVF or further techniques.

The second debate mentioned above is related with the efficacy of IUI and the maximum number of IUI cycles that should be performed in unexplained infertility. It has been concluded in a meta-analysis of Hughes et al.(22) that both IUI and stimulation of insemination cycles with follicle-stimulating hormone significantly improve fecundity independently in unexplained subfertility. In addition an ESHRE multicentre trial comparing the efficacy of other treatments versus IUI and IVF in idiopathic subfertility, indicated that IUI and IVF have increased chances of pregnancy compared with superovulation alone (23). Nevertheless neither IVF nor IUI was found to be superior to the other (23). However the common risk factors should be kept in mind such as the duration of infertility and the female partner age in patient selection to these treatments. Besides IUI along with controlled ovulation induction has been shown to be more cost-effective than IVF and associated with significantly lower costs per pregnancy resulting in at least one livebirth in unexplained and male infertility (24). A recent Cochrane meta-analysis indicated that until more evidence is available IVF may not be the preferred first line of treatment for these couples and it might be appropriate to continue with the less invasive options. Furthermore Aboulghar et al. (25) reported that patients should be offered IVF or ICSI who fail to conceive after three trials of COH (controlled ovarian hyperstimulation) and IUI the cycle fecundity in the first three trials of COH and IUI was higher statistically significant than in cycles 4-6. Consequently it has been clearly accepted that not for initial treatment but after 3
COH and IUI cycles IVF should be performed in respect of other data.

Conclusively we are in the beginning to define even the current role of IUI as well many technical innovations in assisted reproduction. Today many debates are ongoing to detect the right role of IUI especially on timing of IUI, triggering by hCG or waiting spontaneous LH surge, sperm IUI thresholds in male infertility, and the current role of IUI in unexplained infertility. Moreover to define the right role of IUI in assisted reproduction or to draw a firm conclusion we should have wealthier and clearer data.

REFERENCES

Approximately 10 to 15% of women will receive infertility treatment during their lifetime and of all subfertile couples, only 1-2% will undergo treatment with assisted reproductive technologies (ART). Artificial insemination with husband's semen (AIH) has been used in clinical medicine for more than 200 years in the treatment of infertile couples. The first documented application of AIH was done in London in the 1770s by John Hunter. A patient with severe hypospadias was advised to collect the semen (which escaped during coitus) in a warmed syringe and inject the sample into the vagina. J.M. Sims reported his findings of postcoital tests and 55 inseminations in the mid 1800s but only after the introduction of sperm donation artificial insemination became very popular. For many years homologous artificial inseminations were only indicated in cases of physiologic and psychologic dysfunction, such as retrograde ejaculation, vaginismus, hypospadias and impotence. With the routine use of post-coital tests other indications were added such as hostile cervical mucus and immunologic causes with the presence of antispermatozoal antibodies in the cervical mucus.

The term AIH covers a wide range of different techniques. Washed or unwashed semen can be used and inseminated at various levels in the female reproductive tract. The insemination can be done intravaginally, intracervically, pericervically using a cap, intrauterine, intratubal or directly intraperitoneal. Most studies refer to intrauterine inseminations (IUI) which seems to be an easy and better way of treatment. The rationale for the therapy of artificial insemination is the increase of gamete density at the site of fertilization. The theoretic advantage of IUI over intravaginal techniques may be due to the increasing number of sperm arriving at the fertilization site, even when sperm or cervical mucus abnormalities are present. The increasing use of AIH in idiopathic and male infertility is mainly the result of the refinement of techniques for the preparation of washed motile spermatozoa as they were used in IVF procedures, finally resulting in a post-wash fraction containing a high number of motile spermatozoa with a better sperm morphology.

For ART, success in subfertility treatment is generally described as pregnancy rate per treatment cycle (IVF, ICSI, IUI). On the other hand, it is important to be aware of the complex weave of secondary issues to consider such as neonatal outcome, short and long term infant morbidity and maternal complications, all of them closely linked to the higher incidence of multiple pregnancies after treatment with assisted reproductive techniques. Consequently, ART (especially IVF and ICSI) accounts for 0.4-0.8% of the total health care costs in the USA compared to 0.08 - 0.16% in Scandinavian countries. This can only be explained by the lower incidence of multiples in Scandinavian countries.

When male subfertility is found in couples with longstanding infertility, IVF and ICSI are not the only treatment options. From a theoretic point of view, increasing the number of motile spermatozoa at the site of fertilization with intrauterine insemination, especially when sperm quality is suboptimal, should increase the probability of conception. In two meta-analyses, Cohlen et al (1)