

To inseminate or not, that is the question. A reflection of existing evidence

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Abstract

A short review stating levels of evidence is given regarding the indications for IUI and the cost-effectiveness of (stimulated) IUI compared with that of IVF. It is concluded that IUI in natural cycles should be applied in couples with cervical hostility, might be applied in couples with a moderate semen factor and should not be applied in couples with unexplained subfertility. Intrauterine insemination in cycles with MOH should be applied in couples with unexplained subfertility and might be applied in couples with a mild semen factor. Furthermore there still seems to be a place for IUI in natural and stimulated cycles comparing cost-effectiveness with IVF. However, cumulative pregnancy rates after mild IVF combined with single transfer of frozen and thawed embryos is increasing and therefore future RCTs are mandatory comparing modern IVF with IUI.

Key words: IUI, IVF, cost-effectiveness, indications.

Introduction

When eye-balling the recent literature there seems to be a discord between those who still believe in the cost-effectiveness of intrauterine insemination (IUI) and those who do not (ESHRE Capri workshop Group, 2009). On the one hand there is existing evidence that IUI should not be started too soon (Steures *et al.*, 2006a) and on the other hand the success rates of IVF and ICSI seem rising. However, IUI is safe, simple, non-invasive and relatively inexpensive. In developing countries IUI seems to gain popularity whereas in developed countries it is still one of the most frequently applied treatment options to enhance the probability of conception for several indications. What is nowadays the place of IUI in the wide range of treatment options?

Indications for IUI

The three classical indications for IUI are: (1) Cervical Hostility, (2) Male Subfertility and (3) Unexplained subfertility including mild endometriosis. In couples with anovulation, ovulation induction

without IUI seems to be the treatment option of first choice while in couples with sexual dysfunction high intravaginal or intracervical insemination with unprepared semen could be applied.

In many (older) trials IUI has been compared with so-called timed intercourse. Discussion has been raised that timed intercourse might impair the probability of conception compared with unrestricted intercourse. A direct trial comparing both options does not exist. Gathering indirect evidence and performing a meta-analysis Snick and colleagues showed no significant difference between timed intercourse or expectant management as a control group in RCTs dealing with IUI (level of evidence (LOE) 1a) (Snick *et al.*, 2008). It would have been rather surprising when the authors would have detected a significant difference between these two control options: all couples defined as subfertile have probably performed unrestricted intercourse for several years before entering a trial of IUI.

In case of a cervical factor IUI in natural cycles has been proven effective (LOE 1b) (Steures *et al.*, 2007). The publication by Steures *et al.* showed that IUI significantly increased ongoing pregnancy rates

compared with unrestricted intercourse with a number needed to treat of 6 (Steures *et al.*, 2007). However, cervical hostility is a rare diagnosis. When the postcoital test is timed and performed adequately, and a male factor is excluded, only few couples will suffer from cervical hostility. This is one of the reasons why many clinics stopped performing postcoital testing. On the other hand, the postcoital test has a strong prognostic value in predicting treatment-independent conception and should therefore remain part of the fertility work-up (Hunault *et al.*, 2002).

In case of a male factor most of the evidence from RCTs is somewhat older and the characteristics of these trials do not fulfill the strict criteria of the Cochrane Collaboration. For years IUI seemed to be the treatment of first choice in case of a moderate to mild male factor based upon several RCTs (Cohlen *et al.*, 1995). However, the latest Cochrane review clearly states that there is insufficient data for robust conclusions (LOE 1) (Bensdorp *et al.*, 2007). For daily practice IUI in natural cycles is recommended when at least 0.8 – 5.0 million motile sperm can be inseminated after sperm processing (LOE 1) (van Weert *et al.*, 2004). In case of a mild semen defect (average total motile sperm count above 10 million before sperm processing) IUI in cycles with mild ovarian hyperstimulation is recommended (LOE 1b) (Cohlen *et al.*, 1998).

In couples with unexplained subfertility IUI in natural cycles should not be applied. Compared with intercourse IUI does not increase the probability of conception (Bhattacharya *et al.*, 2008; Verhulst *et al.*, 2006). This seems very plausible because without a cervical factor nor impaired sperm or tubal function sufficient motile sperm reach the site of fertilization every month. The combination of IUI with mild ovarian hyperstimulation (MOH) does improve live birth rates and it is therefore advised to apply this combination as first-line treatment option in couples with unexplained subfertility (LOE 1) (Verhulst *et al.*, 2006). The thin line between enhancing the probability of conception by increasing the number of available oocytes and minimizing the risk for achieving a multiple pregnancy should be walked with great care. Adjusting the individual dosage of FSH to strive after two oocytes seems to be the optimal strategy (LOE 1) (van Rumste *et al.*, 2008). Close ultrasound monitoring of all follicles larger than 10 mm in combination with strict cancellation criteria has been proven in daily practice to minimize the risks for twin pregnancies below 10% and triplets below 1-2% (Steures *et al.*, 2006b).

In conclusion IUI in natural cycles should be applied in couples with cervical hostility, might be applied in couples with a moderate semen factor and should not be applied in couples with unexplained

subfertility. Intrauterine insemination in cycles with MOH should be applied in couples with unexplained subfertility and might be applied in couples with a mild semen factor.

IUI compared with IVF

Should we compare the cost-effectiveness of (MOH) IUI with that of IVF? In many countries there is not a question of choice because both treatment modalities are reimbursed or IVF is much too expensive to be applied at all. When reimbursed, the optimal strategy in couples with mild male subfertility or unexplained subfertility seems to be a number of 3 to 9 cycles of MOH/IUI followed by IVF in those couples that did not conceive. Cumulative ongoing pregnancy rates after MOH/IUI in these couples varies among clinics but might be as high as 40% (LOE 2b) (Custers *et al.*, 2008).

When resources are limited or couples pay for their own treatment the question of the most cost-effective treatment option arises. A systematic search of the literature reveals limited evidence only. This might be explained by the fact that cost-effectiveness is an issue of recent growing interest. The perfect multicenter, adequately powered, randomized trial that compares the cost-effectiveness of MOH/IUI with IVF including direct and indirect costs, obstetrical and neonatal costs but also benefits for society has to be performed yet (a nice example of the complexity of such a study is described by Fiddeler *et al.* (2009)).

In 1997 and 2001 van Voorhis and colleagues performed two retrospective cohort studies in which they compared the cost effectiveness of (stimulated) IUI with IVF or IVF-ICSI (LOE 2b) (Van Voorhis *et al.*, 2001; Van Voorhis *et al.*, 1997). In couples with unexplained or mild male subfertility they concluded MOH/IUI to be more cost-effective than IVF and they recommended that IUI should be applied before starting IVF. The direct costs per delivery after (stimulated) IUI varied between \$ 7,800 and \$ 10,300 whereas after IVF is was \$ 37,000. In couples with an average total motile sperm count below 10 million IVF/ICSI seemed more cost-effective than IUI. By modeling several treatment pathways Philips and coworkers concluded that in case of unexplained or moderate male subfertility MOH/IUI is the most cost-effective treatment option in the UK (LOE 2b) (Philips *et al.*, 2000). In 1999 Karande *et al.* published the first randomized trial to compare the cost-effectiveness of two treatment strategies: either couples received IVF or a standard infertility treatment algorithm (Karande *et al.*, 1999). Again it was advised not to start IVF immediately although indirect costs nor obstetrical or neonatal cost were

included (LOE 1b). In 2000 Goverde *et al.* published one of the first RCTs comparing the cost-effectiveness of (MOH) IUI with IVF in couples with mild male or unexplained subfertility (Goverde *et al.*, 2000). Their conclusion was clear: IUI was a more cost-effective treatment than IVF (costs per pregnancy resulting in at least one live birth: \$ 4,511-5,710 for IUI vs \$ 14,679 for IVF) (LOE 1b). Critics stated that the drop-out rate in the IVF group was rather high (42%) and pregnancy rates per IVF attempt were too low (12,2%). Recently Reindollar *et al.* compared two treatment strategies in a randomized trial: CC/IUI followed by FSH/IUI and IVF compared with CC/IUI followed by IVF directly (Reindollar *et al.*, 2009). They concluded that the accelerated track was the most cost-effective although confidence intervals were wide and crossed the zero (average charges per delivery were \$ 9,800 lower 95% CI, \$ 25,100 lower to \$ 3,900 higher) (LOE 1b). Furthermore, even after three failed attempts of CC/IUI pregnancy rates per treatment cycle after FSH/IUI were non-significantly higher compared with CC/IUI (9.8% versus 7.6%). This underlines the conclusion by Cantineau *et al.* that in IUI cycles gonadotropins are more effective compared with CC (LOE 1) (Cantineau *et al.*, 2007).

While the success rates of IVF seem to have increased over the last decades, pregnancy rates after (stimulated) IUI remain more or less the same (Nyboe *et al.*, 2009). The ESHRE 2005 report stated a pregnancy rate per IVF aspiration of 26.9% and a pregnancy rate per IUI attempt of 12.6%. Multiple pregnancy rates still differ largely between both treatments: 21,8% after IVF and 12,1% after IUI. With these general results in mind and the fact that 1 IVF/ICSI cycle is approximately three times as expensive as 1 MOH/IUI cycle regarding direct costs, there still seems to be a place for (MOH) IUI in Europe. But will we still embrace this opinion in 10 years from now?

With an European tendency towards single embryo transfer in combination with increasing number of transfer cycles of frozen and thawed embryos, a mild IVF stimulation protocol aiming at lesser follicles (Verberg *et al.*, 2009) or even IVF in natural cycles (Pelinck *et al.*, 2002) new RCTs are mandatory to compare cumulative live birth rates between these modern IVF protocols and (stimulated) IUI. These RCTs should be adequately powered, multi-centered, performed in well defined populations of subfertile couples with a moderate to poor prognosis regarding spontaneous chance of conception. Furthermore, these trials should focus on live birth rates as primary outcome but also on side-effects, multiple pregnancies, patients discomfort and drop-out rate, direct and indirect costs (including

obstetrical and neonatal costs) in relation to the number of healthy infants born. At this moment such a large RCT is performed in the Netherlands (Bensdorp *et al.*, 2009).

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