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-ball 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 save, 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 exists. 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 reason why many clinics stopped performing postcoital testing. On the other hand, the postcoital test has an 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 UII 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 UII 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) UII in cycles with mild ovarian hyperstimulation is recommended (LOE 1b) (Cohlen et al., 1998).

In couples with unexplained subfertility UII in natural cycles should not be applied. Compared with intercourse UII 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 UII with mild ovarian hyperstimulation (MOH) does improves 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 UII 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.

**UII compared with IVF**

Should we compare the cost-effectiveness of (MOH) UII 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/UII followed by IVF in those couples that did not conceive. Cumulative ongoing pregnancy rates after MOH/UII 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/UII 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 Fiddelers 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) UII 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/UII to be more cost-effective than IVF and they recommended that UII should be applied before starting IVF. The direct costs per delivery after (stimulated) UII 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 UII. By modeling several treatment pathways Philips and coworkers concluded that in case of unexplained or moderate male subfertility MOH/UII 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) IUl with IVF in couples with mild male or unexplained subfertility (Goverde et al., 2000). Their conclusion was clear: IUl was a more cost-effective treatment than IVF (costs per pregnancy resulting in at least one live birth: $4,511-5,710 for IUl 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/IUl followed by FSH/IUl and IVF compared with CC/IUl 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/IUl pregnancy rates per treatment cycle after FSH/IUl were non-significantly higher compared with CC/IUl (9.8% versus 7.6%). This underlines the conclusion by Cantineau et al. that in IUl 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) IUl 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 IUl attempt of 12.6%. Multiple pregnancy rates still differ largely between both treatments: 21.8% after IVF and 12.1% after IUl. With these general results in mind and the fact that 1 IVF/ICSI cycle is approximately three times as expensive as 1 MOH/IUl cycle regarding direct costs, there still seems to be a place for (MOH) IUl 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 (Pelinc et al., 2002) new RCTs are mandatory to compare cumulative live birth rates between these modern IVF protocols and (stimulated) IUl. 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).

References
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