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Intrauterine insemination

The ESHRE Capri Workshop Group[1]

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BACKGROUND: Intrauterine insemination (IUI) with or without ovarian stimulation is a common treatment for infertility. Despite its popularity, the effectiveness of IUI treatment is not consistent, and the role of IUI and *in vitro* fertilization (IVF) treatment in practice protocols has not been clarified.

METHODS: Medline searches were done by individual topics (utilization, procedures, effectiveness of partner but not donor IUI and related endocrine issues). Effectiveness of IUI was evaluated in relevant randomized controlled trials, using meta-analysis and meta-regression where necessary.

RESULTS: Stimulated IUI is ineffective in male infertility and the effect on other diagnoses is small. With clomiphene citrate and IUI, the most common IUI protocol, pregnancy rates average 7% per cycle. FSH ovarian stimulation and IUI treatment is only modestly better than observation only with pregnancy rate 12% per cycle but multiple birth rates averaging 13%. Mildly stimulated (1–2 follicles) cycles might reduce the cost and multiple birth rates but may require more cycles of treatment. Prevention of premature luteinizing hormone surges and luteal phase support do not appear to be major requirements in IUI cycles.

CONCLUSIONS: IUI treatment requires ovarian stimulation to achieve modest results, but the high multiple pregnancy rates mean that it is no more than a poor substitute for IVF treatment. More trials are needed on IUI treatment with mild stimulation and on the order of IUI and other treatments.

Key words: intrauterine insemination / unexplained infertility / male subfertility / multiple pregnancy / mild ovarian stimulation

Introduction

The first paper entitled intrauterine insemination (IUI) was published in 1962 (Cohen, 1962). Since then IUI has evolved through innovations such as sperm preparation, monitoring for pre-ovulatory timing and induction of ovulation with human chorionic gonadotrophin (hCG). IUI also has been combined with ovarian stimulation using clomiphene citrate (CC) or gonadotrophins. Despite the fact that it has not been classified as an assisted reproductive technique (ART) (Zegers-Hochschild *et al*., 2006a,b), it is widely used, often as an empirical treatment, for a broad range of profertility indications. The European IVF Monitoring Programme in 2004 reported 98 388 IUI

cycles from 19 countries leading to 12 081 births (12.3% per cycle), of which 87% were singleton and 13% were multiple births (Andersen *et al*., 2008).

Although widely utilized, there is little evidence of the effectiveness in male infertility (Bensdorp *et al*., 2007), and one large trial found that stimulated IUI was not effective in the treatment of unexplained infertility (Steures *et al*., 2006). Thus, it is timely to assess the evidence on the effectiveness of IUI across the range of methods and indications. The clinical context for the evidence on the effectiveness of IUI includes the extent of IUI utilization, the indications for IUI, the optimal procedures for sperm preparation, insemination methods and timing, and the need, if any, to prevent premature luteinizing hormone (LH) surges and luteal deficiency in stimulated IUI cycles. Also, because IUI is often a stop-gap treatment while waiting for, or instead of *in vitro* fertilization (IVF), a consideration of the evidence on IUI and IVF in treatment protocols is relevant to clinical practice.

Methods

Searches were done in Medline and other databases by individual subjects (utilization, procedures, effectiveness and related endocrine considerations). The highest quality articles most relevant to clinical practice were selected. For the effectiveness questions, trials were truly randomized, with parallel trial designs unless pre-crossover results are reported, and with placebo or untreated control groups because active control treatments may be unproven. The effectiveness of IUI is limited to the use of IUI with partner's sperm. Trials are limited to those in which co-interventions other than ovarian stimulation were the same in the IUI and control groups. Meta-analyses, where necessary, were fixed effect models, weighted by the inverse of the variance. If heterogeneity could not be ruled out at the 10% level of significance, random effect models were used (DerSimonian and Laird, 1986). Meta-regression was done where necessary to explain heterogeneity. Each subject summary was presented to the Workshop Group, where omissions and disagreements were resolved by discussion.

Utilization of IUI

Although IUI utilization has not generally been included in ART registries, the European IVF Monitoring Programme has included data on IUI cycles using husband or donor sperm since the report on 2001 activity (Andersen *et al*., 2005). Data for pregnancy and birth rates were drawn from the countries that provided this information (Table I).

Where direct comparison was possible in the 17 countries that reported the number of cycles for each of the partner IUI, IVF and ICSI in 2004, there were 97 180 IUI cycles, 52 866 IVF cycles and 93 845 ICSI cycles (Andersen *et al*., 2008). The ratio of registered IUI cycles to the total of registered IVF and ICSI cycles in these countries is ~0.66. Uptake of IUI was greater than uptake of IVF in the Netherlands, however, which was not included in the above summary. There were an estimated 28 500 cycles of IUI in the Netherlands in 2003 compared with 9761 cycles of IVF (Steures *et al*., 2006).

The pregnancy rates per cycle are close to the pregnancy rates of 12% in the gonadotrophin-stimulated arm of an RCT (Guzick *et al*., 1999). Thus, although the European report does not specify stimulation, many of the IUI cycles may be stimulated. Also, the multiple pregnancy rates are consistent with those of stimulated cycles. The average pregnancy rates with donor insemination are ~4% higher than those with partner insemination, and the multiple pregnancy rates suggest that in the donor IUI cycles, ovarian stimulation also is common.

Indications for IUI treatment

Rationale

The rationale of IUI treatment is to increase the rate of conception in the couple by increasing the chance that maximum number of healthy sperm reaches the site of fertilization. In couples with abnormal mucus, the rationale might be to bypass a possible cervical factor. The post-coital test is not, however, a recommended routine in most countries (The Practice Committee of the American Society for Reproductive Medicine, 2006).

Contraindications

IUI is contraindicated in women with cervical atresia, cervicitis, endometritis or bilateral tubal obstruction and in most cases of amenorrhea or severe oligospermia.

Table I IUI cycles performed in Europe using partner's or donor's semen (Andersen *et al*., 2005, 2006, 2007, 2008)

	2001	2002	2003	2004
IUI partner				
Countries	15	16	18	19
Cycles	52 939	78 505	82 834	98 388
Pregnancies (%)	6696 (12.6)	8961 (11.4)	9995 (12.1)	12 216 (12.4)
Singleton births (%)	5826 (88.8)	6553 (88.7)	3880 (86.9)	10 499 (86.9)
Multiple births (%)	732 (11.2)	831 (11.3)	585 (13.1)	1582 (13.1)
IUI donor				
Countries	15	17	16	15
Cycles	14 185	14 779	16 743	17 592
Pregnancies (%)	2307 (16.3)	2327 (15.7)	2620 (15.6)	3108 (17.7)
Singleton births (%)	1980 (89.6)	1928 (90.0)	2283 (88.6)	2686 (88.2)
Multiple births (%)	230 (10.4)	215 (10.0)	294 (11.4)	360 (11.8)

Table II Categories of unexplained infertility (ESHRE Capri Workshop Group, 2004)

- 20% of couples after the initial work-up
- Couples with mild male subfertility (20–40%)
- 50% of those in whom conventional treatments have failed

Indications

IUI with or without ovarian stimulation is considered to be indicated for a broad range of diagnostic conditions. The most obvious diagnosis is male infertility, especially where donor sperm is required (Bensdorp *et al*., 2007). IUI is indicated for all categories of unexplained infertility (Table II) and for couples with minimal and mild endometriosis. IUI in stimulated cycles may be considered while waiting for IVF, or when in women with patent tubes IVF is not affordable. In most of these indications, IUI or stimulated ovary/IUI is an empiric treatment since it is likely that the majority of infertility involves factors that are untreatable or unknown.

Potential unknown defects

Many defects are still unknown, making unexplained infertility a frequent condition. No test is available to investigate oocyte quality, whereas structural defects in oocyte chromosomes are frequently reported that may cause a 75% post-fertilization failure rate (Mastenbroek *et al*., 2007; Swain and Pool, 2008). Unknown defects in fertilization also may occur, although failed fertilization *in vitro* occurs in <5% of IVF cycles (Liu *et al*., 1995; Moomjy *et al*., 1998). Total fertilization failure does not seem to be a dominant feature in patients who undergo IUI for unexplained infertility (Tanahatoe *et al*., 2009). An important defect would be a failure of uterine receptivity and implantation. Implantation involves four stages: apposition, adhesion, attachment and invasion. Successful completion of each stage depends on numerous enzymatic processes (Fazleabas, 2007; Mardon *et al*., 2007; Tapia *et al*., 2008). Given that each enzyme is a gene product, failure of implantation may arise from *de novo* or inherited genetic defects.

Thus, IUI is prescribed in a wide variety of presumed diagnoses even if, in some of them, the rational for its use would be debatable.

IUI procedures and insemination methods

Semen preparation

Prior to IUI, it is necessary to remove seminal plasma to avoid prostaglandin-induced uterine contractions. Insemination with unprocessed semen is also associated with pelvic infection (Boomsma *et al*., 2007). Removal of the seminal plasma can be achieved by relatively simple procedures. The most frequently used methods involve centrifuging spermatozoa through culture medium or density gradients followed by re-suspension in suitable culture media. A systematic review of sperm preparation techniques concluded that there were insufficient randomized studies to choose the best method (Boomsma *et al*., 2007). For normal semen samples, it is still unclear whether there is any advantage in isolating the most motile spermatozoa prior to insemination or whether similar results can be obtained using the whole population of spermatozoa in the sample.

Quality of the specimen

There is no consensus on a lower limit of semen quality at which one would advocate ICSI rather than IUI. Authors define their lower limits differently, as sperm concentration per millilitre or as the total number of motile spermatozoa in the semen sample or as total number of motile spermatozoa in the sample for insemination. It has been reported that pregnancy rates are lower if the semen sample contains <10 million sperm in total (Van Voorhis *et al*., 2001). Concerning the insemination sample, the recommended lower limit ranges from 3 million motile sperm (Strandell *et al*., 2003), to 5 million (Khalil *et al*., 2001b) to 10 million (Kahn *et al*., 1992a, b; Van Voorhis *et al*., 2001).

Mode of insemination

The sperm suspension can be deposited in the cervix, the uterus, the peritoneum or the Fallopian tube. IUI is by far the most common method. It is performed by introducing a 0.2–0.5 ml sperm suspension into the uterus with a small catheter, usually without imaging guidance. With Fallopian tube sperm perfusion (FSP), the inseminate is 4 ml, so that with this large volume of fluid the inseminate may fill not only the uterine cavity and Fallopian tubes, but also some of the volume may even end up inside the peritoneal cavity (Kahn *et al*., 1992a). For frozen semen, IUI is better than intracervical insemination (ICI): the likelihood of live birth after six insemination cycles is 2-fold higher (OR: 1.98; 95% CI: 1.02–3.86) (Besselink *et al*., 2008). In two trials among patients with unexplained infertility, results with FSP were better than with IUI (Kahn *et al*., 1993; Cantineau *et al*., 2003). For other indications, there is not sufficient data to suggest that FSP is any better than IUI.

Timing of insemination

Insemination can be done at various time points around ovulation and can be done once or several times. In the majority of the published studies, the insemination is done 32–36 h following hCG administration.

It is assumed that the timing of insemination relative to ovulation is critical for an optimal success rate, so it is rather surprising that few studies were designed to find the optimal time for insemination (Ragni *et al*., 2004). A systematic review found no difference in the pregnancy rate per couple with two inseminations compared with one (Cantineau *et al*., 2003).

Critical evaluation of the method's effectiveness

Timed intercourse (TI) is not a natural spontaneous human sexual activity, although well-informed couples seeking pregnancy usually focus their sexual activity around midcycle. Also, some indications exist that the frequency of intercourse increases around ovulation, probably due to biological influences (Wilcox *et al*., 2004). Since TI involves interfering with natural coital habits by asking couples to refrain from intercourse until some marker shows that ovulation is

imminent, it may theoretically reduce the likelihood of pregnancy and therefore would not be an appropriate comparison treatment for IUI. Indeed several studies suggest that while timing intercourse according to the LH surge is appropriate for IUI, such timing might allow the optimal period for spontaneous conception to pass (Nulsen *et al*., 1987; Wilcox *et al*., 1995).

Since there are no trials comparing TI with expectant management or ordinary intercourse (OI), it is necessary to compare IUI treatment effects in trials where TI is the alternative and in trials where OI is the alternative. When this was done, there were 11 relevant trials allowing 13 comparisons of IUI and TI or OI among 1329 couples with subfertility (Snick *et al*., 2008). The average difference in pregnancy rate between IUI and controls was 6.1% in TI trials and 3.9% in OI trials. The adjusted indirect estimate of the difference between the types of control groups was 2.8%. The difference between trials with TI and OI controls was not significant, neither in the 11 most relevant trials ($P = 0.82$) nor in a broader group of 19 trials and 2512 patients ($P = 0.20$). The additional benefit accruing to IUI from using TI as the control is not significant, but it is consistent with the possibility that pregnancy may be less likely in TI controls than expectant management controls (Snick *et al*., 2008).

This is in agreement with previous work by Nulsen *et al*. (1987) who found a rapid decline of cervical mucus quality in the 24 h following the LH surge. Although a rapid increase in cervical hostility may not constitute a major problem in case of normospermia, it may become of concern in couples with sperm defects or unexplained subfertility. In the latter, the fertile window may be shortened (Keulers *et al*., 2007), and it may close before ovulation, especially in ovulation induction patients who are at risk of premature luteinization, reflected in premature poor mucus quality. The latter may be overcome by IUI, but it may turn into a barrier to conception in spontaneous or—especially—TI. In this regard, it is noteworthy that the two most recent large IUI trials (Steures *et al*., 2007; Bhattacharya *et al*., 2008) applied OI instead of TI in their controls. TI is an artificial—and possibly even deleterious—alternative to OI.

Outcome of IUI cycles

IUI in natural cycles

Unexplained infertility

In four relevant trials involving 990 women with a duration of infertility ranging from 1.7 to 6.5 years (Martinez *et al*., 1990; Guzick *et al*., 1999; Steures *et al*., 2007; Bhattacharya *et al*., 2008), the average difference in pregnancy rates between IUI and control groups was 7% (95% CI: 4, 12) per couple (four trials) and 3% (95% CI: 1, 24) per cycle (three trials). Although the effect of IUI alone per cycle is small and only marginally significant, a protocol that includes an average of three IUI cycles led to a statistically significant effect. The magnitude of the benefit, however, is modest: one additional pregnancy in 14 IUI couples (95% CI: 8, 23) compared with control couples.

Male infertility

In a systematic review only one trial reported on IUI versus timed intercourse in natural cycles (Kerin *et al*., 1984). IUI was not superior to TI (OR: 5.3; 95% CI: 0.42, 67) but the small sample size does not permit firm conclusions (Bensdorp *et al*., 2007).

Other diagnoses

No RCTs involving other diagnoses met the inclusion criteria listed in the methods section.

IUI in cycles stimulated with clomiphene

Unexplained infertility

Two trials compared CC and IUI with CC (Karlstrom *et al*., 1993; Agarwal and Mittal, 2004). In both trials, the pregnancy rate was better with CC/TI than with CC/IUI. One trial involving 26 patients which compared CC/IUI with natural cycle IUI found no significant difference (OR: 3.8; 95% CI: 0.3, 48) (Arici *et al*., 1994). Only one trial met the inclusion criterion of an untreated control group, with a comparison between CC/IUI and TI in a total of 51 patients (Deaton *et al*., 1990). Eight patients (11%) conceived in 73 CC/IUI cycles and four patients (4%) conceived in 103 TI cycles before crossover. The 7% difference in pregnancy rates was not significant (95% CI: −1, 15). Another trial compared a sequence of CC/IUI, gonadotrophin-stimulated IUI and IVF with CC/IUI and IVF only (Reindollar *et al*., 2007). In both arms, the pregnancy rate per cycle with CC/IUI was ∼7%. Although only one trial using untreated controls was found, CC/IUI treatment is widely used. Interestingly, in a retrospective study, the pregnancy rates per cycle averaged ∼5% even in the seventh to ninth cycles of treatment (Custers *et al*., 2008). The sequential management trial (Reindollar *et al*., 2007) indicates that pregnancy rates per cycle are high enough to merit CC/IUI treatment for unexplained infertility in lieu of more costly and complex FSH/IUI treatment, with the attendant risks of multiple pregnancy.

Male infertility and other diagnoses

No trials evaluating CC/IUI in male infertility and other diagnoses met the inclusion criteria.

IUI in FSH-stimulated cycles

Classical dose

IUI combined with FSH ovarian stimulation (FSH) aimed in the past to develop multiple dominant follicles, leading to the availability of multiple oocytes for fertilization. The overall likelihood of conception is increased but the added value of ovarian stimulation is limited, and multiple gestation occurs more frequently (Fauser *et al*., 2005). Three questions are relevant: (i) is FSH/IUI superior to no treatment? (ii) is FSH/IUI more effective than CC? and (iii) is FSH/IUI superior to IUI alone? Two recent Cochrane meta-analyses addressed questions 2 and 3.

Is FSH/IUI superior to no treatment?

Among four trials that compared FSH/IUI treatment with untreated controls, two lacked pre-crossover results (Zikopoulos *et al*., 1993; Gregoriou *et al*., 1995). Two remaining multicenter trials involved couples with unexplained infertility and compared FSH/IUI with ICI (Guzick *et al*., 1999) or expectant management (Steures *et al*., 2006). The average female ages were similar (32 and 33 years, respectively), but the average duration of infertility was 3.5 years in one trial (Guzick *et al*., 1999) and 2 years in the other (Steures *et al*., 2006). In the trial with longer duration of infertility, the pregnancy rates per cycle were 12% with FSH/IUI and 3% with ICI. The 9% rate difference was significant (95% CI: 6, 12). In the trial with

shorter duration of fertility, there was no difference in pregnancy rates with FSH/IUI (4.3%) and no treatment (4.6%). It appears that, at least among patients with unexplained infertility, FSH/IUI is no better than expectant management when the prognosis is good, but has a modest effect with more than 3 years duration of infertility. There would be one additional pregnancy for every 11 cycles of FSH/IUI (95% CI: 8–16) compared with control cycles.

Is FSH/IUI more effective with gonadotrophins than with CC?

This question was addressed in one section of a Cochrane review (Cantineau *et al*., 2007). In seven trials involving 556 couples with unexplained infertility, mild male factor and mild endometriosis, pregnancy rates were higher with gonadotrophins than with anti-estrogens (OR: 1.8; 95% CI: 1.2–2.7). One study, however, used donor sperm, which is not within the scope of the present review (Matorras *et al*., 2002). In a meta-analysis of the remaining six trials involving 456 couples, the 5.7% difference in pregnancy rates was not significant (95% CI: −1.0, 12.5) (Fig. 1).

Is FSH/IUI superior to IUI alone?

A meta-analysis reported that live birth was significantly more likely with IUI and ovarian stimulation than with IUI in the natural cycle in four trials among patients with unexplained infertility (OR: 2.1; 95% CI: 1.2, 3.5) (Verhulst *et al*., 2006). One trial, however, involved CC treatment (Arici *et al*., 1994). In the three gonadotrophin trials among 370 women, the average difference in the live birth rate was 8.9% (95% CI: 1.4, 16.4) (Fig. 2). The effect is modest: there would be one additional pregnancy with 12 IUI cycles (95% CI: 7, 72) with gonadotrophin stimulation compared with no stimulation.

In each comparison, the overall likelihood of conception was increased but the added value of FSH was limited and multiple gestation occurred frequently. The multiple pregnancy rate was 29% in one trial (Goverde *et al*., 2000). In another trial, 465 women treated with ovarian stimulation had 3 sets of quadruplets, 4 sets of triplets and 17 sets of twins; six women were hospitalized with ovarian stimulation syndrome (Guzick *et al*., 1999). Multiple pregnancy rates including higher-order multiples up to 40% have been reported in large retrospective studies (Gleicher *et al*., 2000; Tur *et al*., 2001; Fauser *et al*., 2005).

Low dose

Although reducing the dosage of gonadotrophins (mild ovarian stimulation) would prevent multiple pregnancies in FSH/IUI cycles, it remains a matter of debate whether mild stimulation can maintain overall pregnancy rates (Tur *et al*., 2005; Ragni *et al*., 2006). That better results in women with increased ovarian responsiveness would be directly linked to the higher number of released oocytes is intuitive and logical. The higher the number of released oocytes, the higher is the chance for at least one embryo to implant, but there is an alternative explanation for the increased pregnancy rate in women with multifollicular growth. The high responsiveness to ovarian stimulation may reflect a better ovarian reserve and thus the

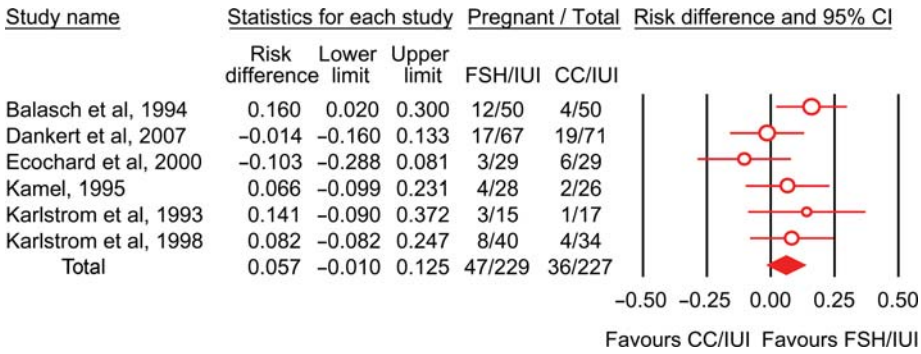

Figure 1 Pregnancy rates following IUI combined with ovarian stimulation using either anti-estrogens or FSH. Live birth rates could not be assessed (Cantineau *et al*., 2007).

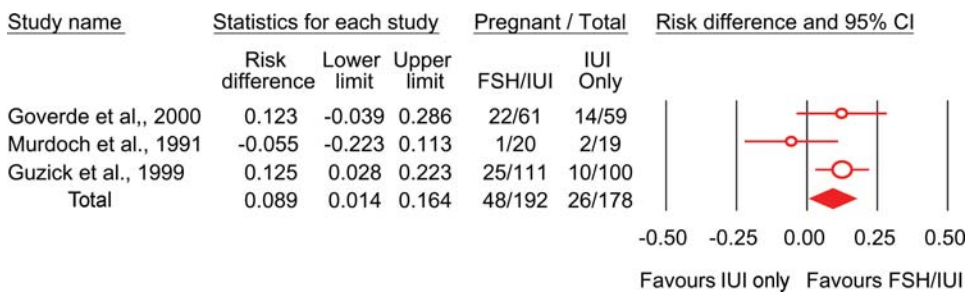

Figure 2 Live birth rate per couple following IUI with or without FSH ovarian stimulation (Verhulst *et al*., 2006).

release of oocytes of higher quality. Thus, women developing more follicles would naturally have a better prognosis. Evidence from IVF cycles supports this hypothesis: mild ovarian stimulation success rates are similar to conventional regimens (Baart *et al*., 2007; Heijnen *et al*., 2007). Also consistent are the data from a multicenter Italian survey which compared IVF success prior to and after the legislation that banned the use of more than three oocytes per cycle. The pregnancy rate correlated with the number of oocytes retrieved regardless of the number of oocytes used (Ragni *et al*., 2005).

In line with this concept, the effect of the number of follicles on the success rate has been found to be modest in large observational studies (Gulumser *et al*., 2008; van Rumste *et al*., 2008).

If multifollicular responses reflect oocyte quality more than gonadotrophin dosage, then future strategies for ovarian stimulation should aim to achieve optimal monofollicular growth and the rate of multiple birth would be minimized without impairing the pregnancy rate.

Unfortunately, the available literature does not disentangle the issue and a large RCT comparing different dosages of gonadotrophins in IUI cycles is warranted to shed light on the debate and more importantly, on the related clinical implications.

Conditions affecting the prognosis

Success rates with FSH/IUI depend on age of the female partner, duration of subfertility, sperm quality and tubal patency (Steures *et al*., 2004). The quality of the ovarian response is a less certain predictor: a significant proportion (around 30%) of stimulated cycles remain mono-ovulatory (Goverde *et al*., 2005; van Rumste *et al*., 2006), whereas up to 15% over-respond despite careful monitoring (Gleicher *et al*., 2000; Dickey *et al*., 2005). An association between the number of large follicles in the late follicular phase and pregnancy rates has been reported in some (Khalil *et al*., 2001a,b; Dickey *et al*., 2002; Ibérico *et al*., 2004; Ghesquiere *et al*., 2007), but not other studies (Goverde *et al*., 2005; Gulumser *et al*., 2008; van Rumste *et al*., 2008).

In contrast, a relationship between follicle number and multiple gestation has been confirmed in all studies. The higher-order multiple pregnancy rate was over 50% when nine or more follicles beyond 10 mm in diameter were present (Dickey *et al*., 2005). A cycle involving the development of many follicles carries the risk of higher-order multiple pregnancy and OHSS and should be cancelled.

Treatment decisions should also be considered against the likelihood of pregnancy without treatment in a given couple, which is usually underestimated (Steures *et al*., 2006). The treatment decision hinges on whether the modestly increased chance of pregnancy with IUI in stimulated cycles justifies the cost of medication, the need for monitoring and the patient discomfort together with the chance of complications such as multiple pregnancy and OHSS (van Weert *et al*., 2007; Haagen *et al*., 2008). If confirmed, the effectiveness of IUI in mono or bifollicular cycles would change future treatment choices, but at the moment for safety reasons many Northern European clinics have stopped using gonadotrophin ovarian stimulation and the recent NICE guidelines also advised against the combined use of ovarian stimulation and IUI (National Institute for Clinical Excellence, 2004) (Table III).

Table III Factors involved in balancing pregnancy rates versus side effects, complications, patient discomfort and cost resulting from IUI combined with ovarian stimulation

• The chance of pregnancy without treatment in couples with younger female partners and shorter duration of subfertility)
• The aim of ovarian stimulation (the development of one, two, or more than two Graafian follicles)
• The compounds and doses used for ovarian stimulation (gonadotrophins, anti-estrogens, aromatase inhibitors, GnRH analogue co-treatment or combinations)
• The intensity of ovarian response monitoring
• The willingness to cancel the cycle if there are more than two large dominant follicles (Under those conditions the puncture of supernumerary follicles or 'escape IVF' may also be considered.)
• Whether treatment success is defined as pregnancy rates or live birth rates per cycle, cumulative rates per started treatment/multiple cycles or per given period of time (It may be considered to take singleton (term) live birth as the desired primary end-point in future studies.)
• Complications such as multiple gestation or OHSS
• Whether the indication for treatment is unexplained infertility, mild male factor or endometriosis
• Everyday use is quite different from reported efficacy trials in homogeneous and carefully selected patient populations

The premature LH surge in IUI cycles

The midcycle LH surge in the reproductive cycle is an intriguing endocrinological phenomenon. The exact details of the mechanism in many species including human are still not known while it is known that central signalling by hypothalamic GnRH is permissive (Knobil, 1992). Complete blockade of the GnRH receptor terminates the periovulatory LH surge, although alterations in the magnitude of GnRH secretion are not crucial for timing and size of the LH surge (Dubourdieu *et al*., 1994).

The LH surge is an absolute requirement for luteinization, final maturation of the oocyte and follicle rupture. It is obvious, too, that the organ containing the mature, ready to ovulate, follicle(s) should send out the crucial signals. Indeed, most data indicate that the timing of the occurrence of the LH surge is governed by signals from the ovaries (Knobil, 1992). The main signal is presumably the progressive rise in estradiol secretion from the dominant follicle. The positive feedback of estradiol comes from progressive pituitary sensitization to GnRH in combination with a progressive and time-dependent increase in estradiol levels. Several mechanisms underlie this phenomenon: first, estrogen enhances pituitary sensitivity to GnRH; second, non-esteroidal ovarian compounds such as activin increase in concentration, whereas gonadotrophin surge inhibiting factor decreases (de Koning *et al*., 2001); and third, subtle rises in progesterone concentration may augment LH secretory sensitivity to GnRH (Batista *et al*., 1994).

A premature LH surge can be defined as a premature rise of LH (>10 IU/l) accompanied by a concomitant rise in progesterone (>1 μg/l−3.2 nM/l) (Lambalk *et al*., 2006). Premature LH surge in

the natural cycle seems very rare (de Koning *et al*., 2008), but may be more frequent in older women since their maximum follicle diameter at the time of ovulation is substantially smaller (Klein *et al*., 2002; de Koning *et al*., 2008).

Premature LH surges also occur in 25–30% of stimulated IUI cycles (Lambalk *et al*., 2006; Cantineau *et al*., 2007) and theoretically may interfere with timing of the IUI or result in cancellation and more treatment failures. Administration of a GnRH antagonist almost completely abolishes premature luteinization but does not substantially improve the pregnancy rate. Probably premature luteinization is not the cause but one of the consequences of the poor quality of the growing follicle (Fig. 3) (Lambalk *et al*., 2006). In seven RCTs, the average ongoing pregnancy rate was only 5.3% greater with GnRH antagonist treatment (95% CI: 1.5, 9.2). This means that it would take 20 cycles of GnRH antagonist administration to have one pregnancy more than without GnRH antagonist treatment (Fig. 4).

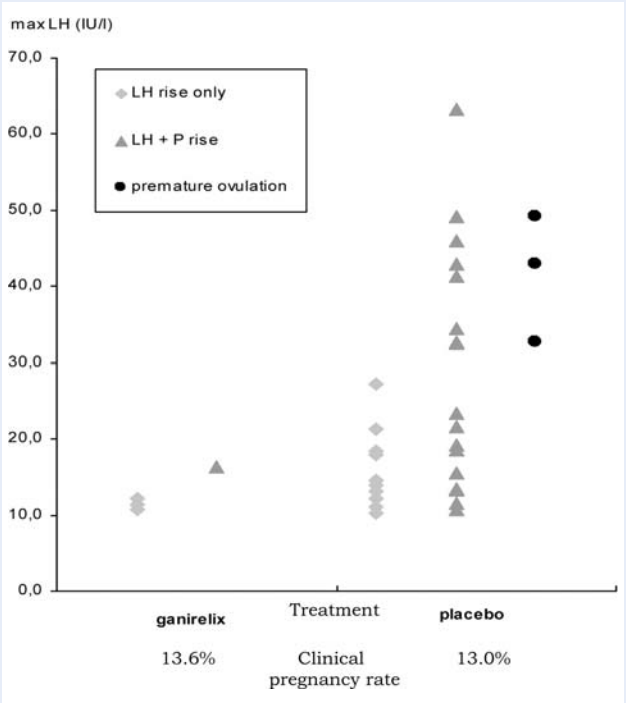

Figure 3 Premature LH surge during mild FSH stimulation with and without antagonist (203 cycles) (Lambalk *et al*., 2006). Max LH (IU/l) is shown in subjects treated with either ganirelix or placebo and having premature LH rises only, premature LH and progesterone and premature ovulation.

Luteal support: is it really necessary in stimulated IUI cycles?

Progesterone is absolutely essential for the establishment and maintenance of pregnancy (Csapo and Pulkkinen, 1978). In its absence or if its action is blocked by a progesterone antagonist such as mifepristone, the endometrium remains hostile to implantation and pregnancy cannot occur (Baird, 2000).

The minimum amount of progesterone essential for maintenance of pregnancy is unknown. Successful pregnancies have been reported when the concentration of progesterone was never above 15 nmol/l for the first 14 days (Csapo and Pulkkinen, 1978).

Luteal phase after ovarian stimulation

If the objective of the ovarian stimulation in IUI cycles is to stimulate the development of multiple follicles, the treatment overrides the physiological feedback mechanisms which normally ensure that only one or two large follicles reach ovulation. As a result, multiple follicles and corpora lutea secrete large amounts of estradiol and progesterone. The luteal phase of these cycles is characterized by high levels of one or both hormones which together with inhibin A suppress the levels of LH and FSH to very low levels (DiLuigi and Nulsen, 2007).

It has been suggested that the low levels of LH may result in lack of luteotrophic support manifested by low levels of progesterone and/or short luteal phase (Abu-Heija *et al*., 1995). While the latter has been documented to occur in some FSH-stimulated cycles, the existence of the former is more controversial. It remains uncertain to be due solely to high levels of steroids. Low levels of steroids would lead by negative feedback to a rise in the secretion of LH by the anterior pituitary. It may be that the high levels of estradiol present within the corpus luteum play some role in its premature demise.

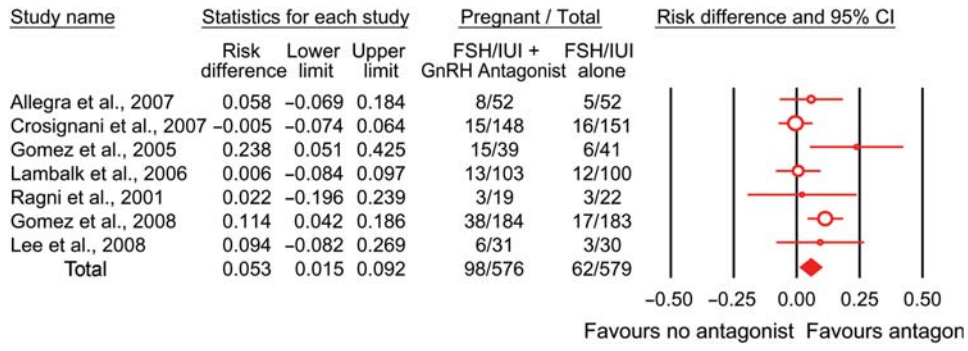

Figure 4 Ongoing pregnancy rate per couple with one cycle of FSH/IUI with and without GnRH antagonist treatment.

However, in women who have been co-treated with GnRH agonist it seems more plausible that there is insufficient luteotrophic support. Low levels of LH in analogue treated (agonist or antagonist) cycles have been associated in some studies with poor implantation and pregnancy rates (Beckers *et al.*, 2003; Tarlatzis *et al.*, 2006).

Whether this poor outcome is due to a direct effect of these compounds on the corpus luteum and/or endometrium or due to suppression of luteal function is not clear. A more popular theory is that the abnormally high levels of estradiol lead to inappropriate hormonal priming of the endometrium (Macklon and Fauser, 2000). Some studies have shown advanced maturation of the endometrium and histological differences in biopsies obtained from FSH-stimulated cycles when compared with spontaneous cycles (Albano *et al.*, 1998; Kolibianakis *et al.*, 2003). But whether these changes compromise the chance of implantation is debatable.

In summary, if IUI is used in spontaneous or in mildly stimulated (1–2 follicles) cycles there is no biological or empirical evidence that treatment with hCG or progesterone in the luteal phase is necessary or improves the pregnancy rate (Ragni *et al.*, 2001). Nevertheless the addition of progesterone, hCG and/or other substances became established clinical practice even in the absence of any robust evidence of effectiveness. Experience from induction of ovulation with gonadotrophins in hypophysectomized women had demonstrated that it was necessary to provide continued support in the form of hCG at least until the mid-late luteal phase (Lunenfeld, 2004). But women undergoing ovarian stimulation during IUI cycles are not totally hypogonadotrophic, even those cotreated with potent GnRH antagonists. Moreover, the half life of hCG is relatively long so that if at least 5000 IU are used for ovulation induction, biologically significant amounts persist for at least 10 days by which time the embryo is secreting hCG.

Clinical decisions about IUI and IVF

The majority of infertile couples do not conceive after initial specific treatment and together with couples who have the original form of unexplained infertility they become eligible for empiric treatment in the form of IUI or IVF. These couples have to make many decisions: when to start treatment? What order of treatments is most sensible? When should the couple shift to more sophisticated and costly treatment? The decision-making process should not depart from the evidence, but infertility management decisions should be under the control of the couple. The best evidence reviewed in the manuscript is summarized in the following statements:

- unstimulated IUI: does not significantly increase pregnancy rates;
- CC/IUI: 5–7% pregnancy rate per cycle even after 7 cycles (Custers *et al.*, 2008);
- IUI/ovarian stimulation: modest effect and risks of multiple pregnancy and OHSS;
- IUI/mild ovarian stimulation: the efficacy needs to be confirmed by large studies;
- IVF: 7-fold higher likelihood of pregnancy (ESHRE Capri Workshop Group, 2007);
- ICSI: is better that IVF only in couples with severe male infertility (ESHRE Capri Workshop Group, 2007);

The background prognosis

Before deciding on a treatment, couples need to consider their chances of conceiving spontaneously. With a shorter duration of infertility, the chance of conception is greater without treatment, thus reducing any advantage from treatment. The association between duration of infertility and rate ratios (equivalent to the relative risks) is shown for all of the trials in this review which had an untreated control arm (Fig. 5). The trial results are clinically heterogeneous, of course, because the treatments are different. The trials are also statistically heterogeneous, with $Q = 30.8$, df 7, $P < 0.001$ and $I^2 = 77\%$. Since the rate ratio appears to be associated with the mean duration of infertility in Fig. 5, a meta-regression is indicated. That analysis shows that the slope is highly significant and that mean duration of infertility accounts for 78% of the heterogeneity in the rate ratios. After accounting for this relationship, the residual heterogeneity among the studies is no longer significant ($P = 0.34$).

Even though the RCTs involve different treatments, the variation in their effect on pregnancy depends more on the duration of infertility than on the type of treatment. Perhaps, the lack of heterogeneity among the treatments after accounting for duration of infertility reflects the fact that all of the treatments are empiric in nature.

Treatment plan

Despite the extensive literature on the subject, controversy remains about the order of treatment and the effectiveness of stimulated IUI cycles in relation to IVF and ICSI. Management trials are needed to address these questions. Such trials should evaluate not only success rate but also other important outcomes such as availability of the methods, adverse effects, satisfaction, likelihood of resolution and cost, together with an analysis of the invasiveness of the techniques and likelihood of couple compliance. Four infertility management RCTs compared IVF treatment and standard management including IUI with ovarian stimulation, with inconsistent results because of differences in patients and the definitions of the control intervention

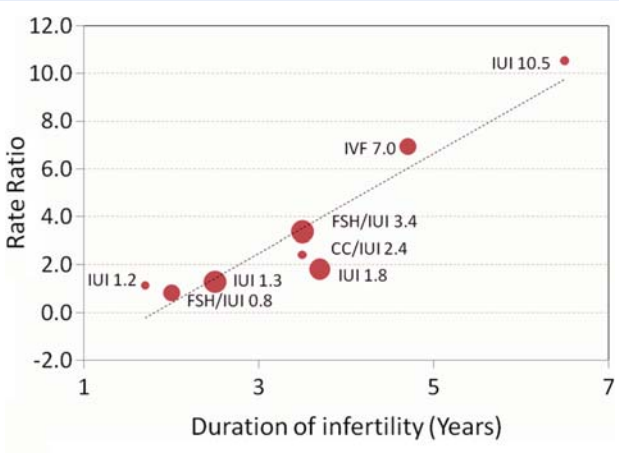

Figure 5 Rate ratio (relative risk) for pregnancy according to the duration of infertility in randomized controlled trials with untreated control groups involving various treatments. Each symbol represents one study. Symbol size is proportional to weight.

Table IV Pregnancy rate per cycle and number needed to treat (NNT) per cycle

Treatment	Pregnancy rate per cycle	NNT	95% CI	Source of results
IUI	5	32	(12, −46)	Guzick *et al.* (1999), Martinez *et al.* (1990) and Steures *et al.* (2007)
CC/IUI*	7	14	(7, −100)	Deaton *et al.* (1990)
FSH/IUI	4	−25	(15, −7)	Steures *et al.* (2006)
FSH/IUI	12	11	(9, 16)	Guzick *et al.* (1999)
IVF	31	4	(3, 7)	Hughes *et al.* (2004)

*Pregnancy rate per cycle is from Reindollar *et al.* (2007). NNT is from Deaton *et al.* (1990) before crossover.

(Crosignani *et al.*, 1991; Soliman *et al.*, 1993; Karande *et al.*, 1999; Goverde *et al.*, 2000). The results of these trials are no longer relevant to practice because IVF success rates are much higher than they were before 2000, while success rates with stimulated IUI have not changed.

One management trial, reported so far only in abstract form, addresses the comparison of IVF and IUI in stimulated cycles (Reindollar *et al.*, 2007). The trial involved couples with unexplained infertility who had had no previous treatment. The standard protocol was three cycles of CC/IUI, three cycles of IUI with FSH stimulation and up to six cycles of IVF; the alternate protocol was accelerated with three cycles of CC/IUI, no FSH/IUI and up to six cycles of IVF. In the accelerated arm, 167 (65%) of 256 couples had a clinical pregnancy compared with 157 (64%) of 247 in the standard arm. The median time to pregnancy was shorter in the accelerated arm. The numbers in the abstract imply that the average number of IVF cycles was 1.1 and 1.4 in the standard and accelerated arms, respectively. These results indicate that where IVF is affordable, IUI is unnecessary. Otherwise potentially IVF may be a premature choice in women aged <35 with an unexplained infertility <3 years duration.

Counselling couples

Information for couples should include the beneficial effects of a good prognosis. In the Steures *et al.* (2006) trial, for example, the enrolled couples were selected to have a good prognosis without treatment. In these couples, IUI with ovarian stimulation did not improve the pregnancy rate compared with no treatment. Couples also need information about the order of treatment. The recent management trial suggests that CC/IUI and IVF may be the optimal treatment order, but not all couples have access to assisted reproduction (ART).

If ART is not an option, the trial results summarized in Table IV can help with decisions. The results pertain to unexplained infertility, mild categories of male infertility and endometriosis as well as persistent infertility after treatment for other diagnoses and therefore they are broadly relevant. For severe male infertility, however, neither unstimulated nor stimulated IUI (or any other non-ART treatment) is effective (ESHRE Capri Workshop Group, 2007).

Prevention of multiple pregnancy

The high multiple pregnancy rate is still a major problem with IUI in cycles stimulated with classical doses of FSH. Multiple pregnancy rates range from 10 to 40% and have not changed in more recent reports (Nan *et al.*, 1994; Guzick *et al.*, 1999; Gleicher *et al.*, 2000; Goverde *et al.*, 2000; Tur *et al.*, 2001; Fauser *et al.*, 2005; van Rumste *et al.*, 2006). With this kind of ovarian stimulation, multiple pregnancy cannot be avoided. In IVF and ICSI cycles, one- or even two-embryo transfers are safer than IUI in superstimulated cycles with its greater risk of higher-order multiple births.

Cost-effectiveness

Local conditions are the most practical source of cost information on IUI and IVF. Studies on the cost-effectiveness of infertility treatment mainly involve IVF treatment (Ombelet, 2005). Although there are no recent patient-based studies, starting treatment with IUI rather than IVF was either cheaper or more cost-effective in unexplained and persistent infertility (Van Voorhis *et al.*, 1998; Karande *et al.*, 1999; Goverde *et al.*, 2000).

In the absence of patient-based cost data, mathematical modelling can compare cost-effectiveness. In one model, the cost-effectiveness ratios for IVF alone, unstimulated IUI followed by IVF and stimulated IUI followed by IVF were £12 600, £13 100 and £15 100 per live birth, respectively. The authors concluded that for couples with unexplained infertility and mild male factor, a primary offer of an IVF cycle was both cheaper and more cost-effective than starting with IUI or stimulated IUI followed by IVF (Pashayan *et al.*, 2006).

European IUI guidelines

Due to the constantly increasing body of relevant literature, the development and publication of IUI guidelines by appropriate regulating authorities could substantially aid clinicians in helping patients choose the right treatment strategy. A systematic review evaluated the quantity and quality of the IUI guidelines issued in the European countries (Haagen *et al.*, 2006). Only four (Denmark, England and Wales, France and the Netherlands) out of 25 European countries have issued IUI guidelines. The four available guidelines were considered of sufficient quality for use in clinical practice. One guideline recommends that for unexplained infertility ovarian stimulation should not be offered, even though it is associated with higher pregnancy rates than unstimulated IUI, because it carries a risk of multiple pregnancy (National Institute for Clinical Excellence, 2004).

Conclusions

- In good prognosis couples, the live birth rate is better without treatment.

- IUI is widely used with infertility diagnoses other than bilateral tubal obstruction, severe male infertility and severe ovulation defects.
- Differences in sperm preparation and IUI methodology do not have profound effects on the success rate.
- Prior to using IVF, IUI with clomiphene ovarian stimulation is relatively cheap and many couples will conceive and not require IVF.
- There is a need for more placebo-controlled trials of CC/IUI, including trials to determine the optimal length of treatment.
- IUI in stimulated cycles was effective only in patients with more than 3 years duration of infertility but is associated with a significant rate of higher-order multiple births.
- The good success rate recently associated with mild stimulated IUI cycles must be confirmed by large trials.
- Prevention of premature LH surges and luteal phase support do not appear major requirements in IUI cycles.
- Although IUI treatment is cheaper and less demanding on the patient, IVF is the most effective treatment for infertility.
- There is a need for management trials to evaluate the order of treatment and overall effectiveness of treatment strategies in more clinical and cost settings.

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Appendix

A meeting was organized by ESHRE to discuss the above subjects. The speakers included: M. Aboulghar (Obstetrics and Gynecology, Cairo University, Clinical Director, The Egyptian IVF-ET Center, Cairo, Egypt), D.T. Baird (Centre for Reproductive Biology, University of Edinburgh, UK), J. Collins (McMaster University, Hamilton, Canada), J.L.H. Evers (Department of Obstetrics and Gynecology, Academic Hospital Maastricht, The Netherlands), B.C.J.M. Fauser (Department of Reproductive Medicine and Gynecology, University Medical Center, Utrecht, The Netherlands), C.B. Lambalk (Division of Reproductive Medicine, Department of Obstetrics and Gynaecology, Vrije Universiteit Medical Centre (VUmc), Amsterdam, The Netherlands), E. Somigliana (Infertility Unit, Fondazione Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milano, Italy), A. Sunde (Department of Obstetrics and Gynecology, University of Trondheim, Norway), B. Tarlatzis (Infertility and IVF Center, Thessaloniki, Greece). The discussants included: P.G. Crosignani (Fondazione Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milano, Italy), P. Devroey (Centre for Reproductive Medicine, Universitair Ziekenhuis Vrije Universiteit Brussel, Belgium), E. Diczfalusy (Karolinska Institutet, Stockholm, Sweden), K. Diedrich (Klinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Germany), L. Fraser (Reproduction and Rhythms Group, School of Biomedical and Health Sciences, Kings College London, UK), J.P.M. Geraedts (Head Department of Genetics and Cell Biology, University Maastricht, The Netherlands), L. Gianaroli (S.I.S.Me.R., Bologna, Italy), A. Glasier (Family Planning and WW Services, Edinburgh, UK), A. Van Steirteghem (Centre for Reproductive Medicine, Universitair Ziekenhuis Vrije Universiteit Brussel, Belgium). The report was prepared by J. Collins (Hamilton) and P.G. Crosignani (Milano).

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