Intrauterine insemination, what do we really know? A critical appraisal of the literature

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Abstract

Intrauterine insemination (IUI) is the first line treatment in couples with unexplained subfertility, cervical factor subfertility and male subfertility. To appraise the effectiveness of IUI for these three indications, we performed a systematic review and a comprehensive series of meta-analyses. We included Cochrane reviews and searched the literature for additional studies. Outcomes were live birth, ongoing pregnancy, clinical pregnancy and multiple pregnancy.

We were able to include 14 studies reporting on IUI for unexplained subfertility, two studies reporting on IUI for cervical factor subfertility and nine studies reporting on IUI in male subfertility.

In couples with unexplained subfertility, IUI without controlled ovarian hyperstimulation (COH) was associated with higher ongoing pregnancy rates than expectant management (relative risk (RR) 1.3, [95% CI 0.84 to 1.9]), whereas IUI with COH was more effective than IUI without COH (RR 1.8, [95% CI 1.2 to 2.7]). However, in couples with relatively good prospects for spontaneous pregnancy, there was no benefit from IUI with COH over expectant management. In couples with a cervical factor, IUI without COH was associated with higher pregnancy rates compared to expectant management (RR 1.6, [95% CI 0.87 to 3.1]), but addition of COH did not further improve the pregnancy rates (RR 1.0, [95% CI 0.59 to 1.8]). In couples with male subfertility, IUI was more effective than expectant management, although the limited power of the included studies hampers strong conclusions. In these couples, addition of COH also had no extra benefit (RR 0.92, [95% CI 0.46 to 1.8]). Studies comparing IUI and IVF were rare, limiting assessment of the strategy of IVF as first line treatment.

Despite the fact that IUI is one of the most frequently used treatments in reproductive medicine, our review shows that the number of studies assessing it's effectiveness is limited and that most of these studies had small sample sizes. This results in imprecise effect estimates, as demonstrated by the non significant effects and large confidence intervals. Also, many studies did not adhere to present quality standards for design, conduct and report of clinical trials.

Therefore, there is an urgent need for more RCTs in which IUI is compared to expectant management or IVF.

Key words: cervical factor, effectiveness/intrauterine insemination, male subfertility, subfertility, unexplained subfertility.

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Introduction

Subfertility, defined as one year of unprotected intercourse without conception, affects 10 to 15% of the couples who are trying to conceive. In 5% of subfertile couples a cervical factor is diagnosed, in 35% mild male subfertility, in 5% severe male subfertility and in 35% of the couples there is another cause for their subfertility. In 20% of the couples an explanation for their subfertility cannot be found (Collins and van Steirteghem, 2004; Dutch Society Guideline 2004).

In couples with unexplained subfertility, cervical factor subfertility and male subfertility intrauterine insemination (IUI) is often the first step in the treatment cascade. In an IUI cycle, semen of the partner is processed in the laboratory and thereafter inseminated in the uterine cavity at the time of ovulation. Treatment with IUI was first performed two centuries ago and has gained great popularity since (Schellen, 1960). IUI is easy to perform, inexpensive, and a minor burden to the couples. For these reasons it is probably the most frequently performed treatment in daily fertility practice.

But what do we really know? Recently, some authors have recommended the abolition of IUI with COH, because of its limited effectiveness and high multiple pregnancy rates (Fauser *et al.,* 2005). They argued that pregnancy rates after in-vitro-fertilisation (IVF) have steadily increased, and that the problem of multiple pregnancies after IVF can be controlled with elective single embryo transfer (Gerris *et al.,* 1999; Martikainen *et al.,* 2001; Gardner *et al.,* 2004; Thurin *et al.,* 2004; Lukassen *et al.,* 2005; van Montfoort *et al.,* 2005).

Decision-making on the place of IUI in reproductive medicine should be based on valid and precise effect estimates of IUI relative to expectant management and to other treatment modalities. Meta-analysis after systematic review of the available literature is the best method to obtain such estimates. So far, separate reviews on the effectiveness of IUI have been published in the Cochrane library for the indications unexplained subfertility, cervical factor subfertility and male subfertility (Helmerhorst *et al.,* 2006; Verhulst *et al.,* 2006; Bensdorp *et al.,* 2007). Here, we perform a comprehensive review of the literature, including the most recently published trials, to critically evaluate the effectiveness of IUI for all indications.

Methods

Search strategy

We summarized the Cochrane reviews on IUI for unexplained subfertility, cervical factor subfertility and male subfertility. To find additional studies on IUI for these indications, we searched the Cochrane Menstrual Disorders & Subfertility Group trials register, the Cochrane Central Register of Controlled Trials (both searched February 2007), MEDLINE (January 1966 to February 2007) and the website for the registration of controlled trials (controlled-trials.com). All electronic databases were searched using the following keywords: unexplained subfertility, cervical factor or male subfertility and intrauterine insemination or in-vitro fertilisation. We also searched the reference lists of selected trials. No restrictions were made concerning publication year or language.

Study inclusion criteria and data extraction

Studies were included if they reported on couples with unexplained subfertility, cervical factor subfertility and/or male subfertility. Subfertility was defined as trying to conceive for at least one year without establishing a pregnancy. Unexplained subfertility was defined as subfertility without any demonstrable cause after the basic fertility work-up. Cervical factor subfertility was defined as the absence of progressive motile spermatozoa in cervical mucus of good quality and normal semen parameters (Dutch Society Guideline 2000). Male subfertility was defined by semen quality below the standards of the World Health Organization (WHO), i.e. sperm concentration $< 20 \times 10^6$ per ml, and/or total motility $< 50\%$ and/or normal morphology $< 15\%$ and/or $> 50\%$ anti-sperm antibodies (WHO, 1999).

We included randomised trials that compared the effectiveness of IUI with or without COH to expectant management or IVF. We also included trials that assessed the additional value of COH in IUI by comparing IUI with COH to IUI without COH.

Outcomes were live birth, ongoing pregnancy, clinical pregnancy and multiple pregnancy. Live birth was defined as the delivery of at least one living child beyond 20 weeks. Ongoing pregnancy was defined as the presence of fetal cardiac activity at ultrasound at a gestational age of $\geq$ 12 weeks. Clinical pregnancy was defined as a pregnancy confirmed by a gestational sac on ultrasound. Studies only reporting on other types of pregnancy, such as biochemical pregnancies, were not included in the analysis.

For each trial, information on the quality of the trial was extracted based on a number of items: adequate randomisation, concealment of allocation, parallel design, exclusions after randomisation, and the intention-to-treat principle in the analysis. If a trial did not adhere to these standards, its validity

was deemed to be compromised, and the randomised trial was not included in the analysis.

Statistical analysis

Trial specific characteristics of all studies were tabulated. We extracted the data on an intention to treat basis. From crossover trials we only used data from the first phase, prior to crossover. Relative risks (RR) with 95% confidence intervals were calculated for all studies. Statistical homogeneity was assessed using forest plots, I^2 and c^2 test statistics. Clinical homogeneity was assessed by reviewing differences across trials in characteristics of randomised couples. In case homogeneity could not be rejected, pooled relative risks were calculated using fixed effects models for live birth rates, ongoing pregnancy rates, clinical pregnancy rates and multiple pregnancy rates where possible (Mantel and Haenszel, 1959). We did so, because the majority of studies reported only ongoing or clinical pregnancies. If statistical homogeneity was rejected, we performed a sensitivity analysis by pooling using a 'random effects'-method (Dersimonian, 1986). Review Manager-software (RevMan 4.2.7, Cochrane Collaboration, Oxford, United Kingdom) was used for the statistical analysis.

Results

Unexplained subfertility

We identified 14 trials, of which 11 had been included in the Cochrane review (Deaton *et al.,* 1990; Crosignani *et al.,* 1991; Murdoch *et al.,* 1991; Karlstrom *et al.,* 1993; Arici *et al.,* 1994; Chung *et al.,* 1995; Melis *et al.,* 1995; Arcaini *et al.,* 1996; Janko *et al.,* 1998; Guzick *et al.,* 1999; Goverde *et al.,* 2000; Agarwal and Mittal, 2004; Bhattacharya *et al.,* 2006; Steures *et al.,* 2006). The quality features of these 14 trials and their main characteristics are presented in Table I. The outcomes of the comparisons are summarized in Figure 1.

IUI without COH was associated with higher ongoing pregnancy rates than expectant management and timed intercourse with COH, but these effects were not statistically significant, with RRs of 1.3 [95% CI 0.84 to 1.9] and 1.5 [95% CI 0.95 to 2.3], respectively.

IUI with COH offered no benefit over expectant management (RR 1.0, [95% CI 0.67 to 1.5]). In line with the comparison IUI with COH versus expectant management, IUI with COH had also no beneficial effect over timed intercourse with COH (RR for clinical pregnancies: 1.1, [95% CI 0.90 to 1.5]).

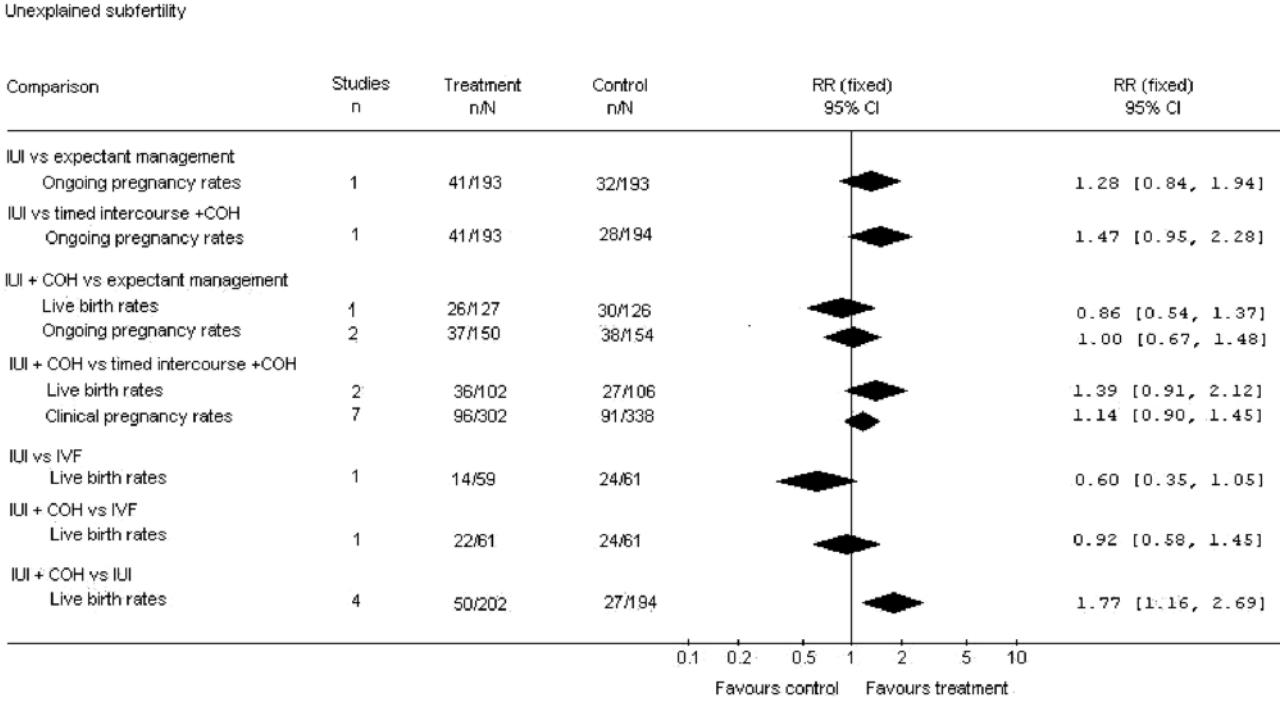

Fig. 1. — Summary of pregnancy results per couple for unexplained subfertility

Table I — Characteristics of randomised trials on the effectiveness of IUI in unexplained subfertility

Trial n = number of randomised couples w = number of withdrawn couples	**Participants**	**Intervention**	**Comparison**	**Main Outcomes**	**Quality features**
Agarwal 2004 n = 70 versus 70w = 26 versus 1	Unexplained subfertility Age: 29.5 versus 28.8 Duration subfertility: 4.9 versus 4.9 Basic fertility work up normal, semen normal, no previous treatment	IUI with COH 50-150 mg CC/day, day 3-7 Ovulation: 10000 IU hCG, ≤ 4 follicles of > 16 mm Timing 36-40 hr after hCG Duration 6 cycles max	TI + COH 50-150 mg CC/day, day 3-7 Ovulation: 10000 IU hCG, ≤ 4 follicles of > 16 mm Timing 36-40 hr after hCG Duration 6 cycles max	PR per couple and per cycle Pregnancy: US showing gestational sac	Randomisation with random number table, sealed envelopes Trial design: Parallel Single centre ITT- analysis: possible
Arcaini 1996 n = 36 versus 32 w = 14	Unexplained subfertility Age: 34.6 versus 33.4 Duration subfertility: 4.2 versus 3.9 Basic fertility work up normal, semen normal, previous treatment not stated	IUI + COH 100 mg CC/day, day 3-7 and 1-3 ampule hMG/day Ovulation: 10000 IU hCG, 2-6 follicles > 17 mm Timing 24 and 48 hr after hCG Duration 5 cycles max	TI+COH 100 mg CC/day, day 3-7 and 1-3 ampule hMG/day Ovulation: 10000 IU hCG, 2-6 follicles > 17 mm Timing 24 and 48 hr after hCG Duration 5 cycles max	PR per couple Multiple pregnancies Pregnancy: confirm by US	Randomisation unclear Trial design: Parallel Single centre ITT- analysis: yes
Arici 1994 n = 26 w = unclear	Unexplained and male subfertility Age: 33 (range 24-41) Duration subfertility: 3.5 (range 1-15) Unexplained: Basic fertility work up normal, semen normal, no previous treatment	IUI +COH 50 mg CC/day, day 5-9 Ovulation: 10000 IUI hCG, at least 1 follicle 18 mm Timing: 32 hr after hCG Cancel: unclear Duration 4 cycles max	IUI without COH - - Timing: On day of LH-surge and next day - Duration 4 cycles max	Live birth and PR per couple PR per 1 st cycle Multiple pregnancies Pregnancy: US showing gestational sac	Randomisation with random number table by computer in locked files Trial design: crossover (after 1 cycle) Single centre ITT- analysis: yes
Bhattacharya 2006 n = 193 versus 193 w = unclear	Unexplained subfertility Age: mean 31.7 Duration subfertility: median 30 months Unexplained Basic fertility work up normal, semen normal, previous treatment not stated	IUI without COH Ovulation: not stated Timing not stated Duration 6 months	Expectant management Duration 6 months	Ongoing pregnancy rate per couple Miscarriage rates per couple Multiple pregnancies	Randomisation and concealment not stated Trial design: parallel Multicentre: 5 centres ITT- analysis: yes
Bhattacharya 2006 n = 193 versus 194 w = unclear	Unexplained subfertility Age: mean 31.7 Duration subfertility: median 30 months Unexplained Basic fertility work up normal, semen normal, previous treatment not stated	IUI without COH Ovulation: not stated Timing not stated Duration 6 months	Timed intercourse with COH 50 mg CC/day, day 2-6 Ovulation not stated Timing not stated Duration 6 months	Ongoing pregnancy rate per couple Miscarriage rates per couple Multiple pregnancies	Randomisation and concealment not stated Trial design: parallel Multicentre: 5 centres ITT- analysis: yes

Chung 1995 n = 50 versus 50 w = 12	Unexplained subfertility Age: 31.8 versus 32.1 Duration subfertility: 4.7 versus 5.3 Basic fertility work up normal, semen 15 million motile per ejaculate, previous treatment not stated	IUI + COH 150 IU/day FSH and GnRH nasal spray from day 21 on Ovulation: 5000 IU hCG, < 4 follicles > 16 mm Timing: 36-48 hr after hCG Duration 3 cycles max	TI + COH 150 IU/day FSH and GnRH nasal spray from day 21 on Ovulation: 5000 IU hCG, < 4 follicles > 16 mm Timing: 24+ 48 hr after hCG Duration 3 cycles max	PR per couples and per cycle Total delivered Multiple pregnancies	Randomisation blocked randomisation scheme in sealed envelopes Trial design: Parallel Single centre ITT- analysis: possible
Crosignani 1991 n = unclear w = unclear Analysed= 90	Unexplained subfertility Age: < 38 years Duration subfertility: > 3 years Basic fertility work up normal, semen normal, previous treatment not stated	IUI + COH Stimulation not stated Ovulation: not described Timing: not described Duration 2 cycles max	TI + COH Stimulation not stated Ovulation: not described Timing: not described Duration 2 cycles max	PR per 1 st cycle and per cycle	Randomisation not clear Trial design: Crossover after 1 cycle Multi centre, 4 centres ITT- analysis: not possible
Deaton 1990 n = 67 w = 4 Analysed 51, of which 24 were unexplained	Unexplained subfertility & surgically treatment of endometriosis Age: 33 years Duration subfertility: 3.5 years Basic fertility work up normal, semen normal, previous treatment not stated	IUI + COH 50 mg CC/ day, day 5-9 Ovulation: 10000 IU hCGat least 1 follicle 18 mm Timing: 36 hr after hCG Cancel: unclear Duration 8 cycles max	TI without COH - - Timing: Based on urinary LH-surge or BBT Duration 8 cycles max	Ongoing PR Multiple pregnancies	Randomisation not clear Trial design: Crossover after 4 cycles Single centre ITT- analysis: not possible
Goverde 2000 n = 120 w = unclear Analysed 93	Unexplained and male subfertility Age: 31.7 versus 31.6 Duration subfertility: 4.2 versus 3.9 Basic fertility work up normal, semen > 20 million in ejaculate, previous treatment not stated	IUI + COH 75 IU/day FSH (starting dose) Ovulation: 10000 IU hCG, 1-3 follicles of 18 mm Timing: 40-42 hr after hCG Cancel > 3 follicles of 8 mm or > 6 follicles of 14 mm Duration 6 cycles max	IUI without COH - - Timing: 20-30 hr after LH surge Duration 6 cycles max	Live birth per couple	Randomisation computer generated randomisation schedule in sealed envelopes Trial design: Parallel Single centre ITT- analysis: yes
Goverde 2000 n = 120 w = unclear Analysed 77	Unexplained and male subfertility Age: 31.6 versus 32.1 Duration subfertility: 3.9 versus 4.5 Basic fertility work up normal, semen > 20 million in ejaculate, previous treatment not stated	IUI without COH - - Timing: 20-30 hr after LH surge Duration 6 cycles max	IVF 150-225 IU/day FSH with GnRH agonist Ovulation:10000 hCG, at least 1 follicle 18 mm, and minimum 3 follicle 16 mm Aspiration: 35 hr after hCG ET: 48-72 hr after retrievel, 2-3 embryo's Luteal phase: progesterone	Live birth per couple	Randomisation computer generated randomisation schedule in sealed envelopes Trial design: Parallel Single centre ITT- analysis: yes

Table I — Continuation

Trial n = number of randomised couples w = number of withdrawn couples	**Participants**	**Intervention**	**Comparison**	**Main Outcomes**	**Quality features**
Goverde 2000 n = 122 w = unclear Analysed 84	Unexplained and male subfertility Age: 31.7 versus 32.1 Duration subfertility: 4.2 versus 4.5 Basic fertility work up normal, semen > 20 million in ejaculate, previous treatment not stated	IUI + COH 75 IU/day FSH (starting dose) Ovulation: 1000 IU hCG, 1-3 follicles of 18 mm Timing: 40-42 hr after hCG Cancel > 3 follicles of 8 mm or > 6 follicles of 14 mm Duration 6 cycles max	IVF 150-225 IU/day FSH with GnRH agonist Ovulation:10000 hCG, at least 1 follicle 18 mm, and minimum 3 follicle 16 mm Aspiration: 35 hr after hCG ET: 48-72 hr after retrievel, 2-3 embryo's Luteal phase: progesterone	Live birth per couple	Randomisation computer generated randomisation schedule in sealed envelopes Trial design: Parallel Single centre ITT- analysis: yes
Guzick 1999 n = 932, of which 465 treated with IUI w = 72 Unexplained: 211	Unexplained subfertility & couples with stage I or II treated endometriosis or male subfertility Age: 32 versus 32 Duration subfertility: 3.5 versus 3.8 Basic fertility work up normal, semen normal, no previous treatment	IUI + COH 150 IU FSH/day, day 3-7 Ovulation: 10000 IU hCG, 2 follicles > 18 mm Timing: 36-40 hr after hCG Cancel: E2 > 3000pg/ml Duration 4 cycles max	IUI without COH - - Timing: Day after urinary LH-surge Duration 4 cycles max	Live birth and PR per couple Multiple pregnancies Pregnancy: two positive hCG tests. Confirmed by live birh	Randomisation computer generated permuted block in locked files Trial design: Parallel Multi centre, 10 clinics ITT- analysis: not possible
Janko 1998 n = 72 w = not stated	Unexplained subfertility Age: not stated Duration subfertility: > 3 years Basic fertility work up normal, semen normal not specified, previous treatment not stated	IUI + COH hMG (10 ampul per cycle) Ovulation: 10000 IU hCG Timing: not specified Cancel: not given Duration 3 cycles max	TI + COH hMG (10 ampul per cycle) Ovulation: 10000 IU hCG Timing: not specified Cancel: not given Duration 3 cycles max	PR per cycle	Randomisation not clear Trial design: Parallel Single centre ITT- analysis: possible

Karlstrom 1993 n = not clear w = not clear Analysed 79	Unexplained subfertility & minimal or mild endometriosis Age: 32 (range 21-38) Duration subfertility: 5 (range 2-14) Basic fertility work up normal, semen normal, no previous treatment	IUI + COH 1ste method: 150 IU hMG/ day Ovulation: 10000 IU hCG, at least 1 follicle 17 mm or LH-surge Timing: 36-41 hr after hCG or 24 hr after LH-surge 2nd method: 100 mg CC/day for 5 days Timing: 20-28 hr after LH-surge Cancel: according to serum E2 Duration 1 cycle max	TI + COH 1ste method: 150 IU hMG/ day Ovulation: 10000 IU hCG, at least 1 follicle 17 mm or LH-surge Timing: the two following nights after hCG injection 2nd method: 100 mg CC/day for 5 days Timing: day of LH-surge and day after Cancel: according to serum E2 Duration 1 cycle max	PR per cycle	Randomisation not clear Trial design: Parallel Single centre ITT- analysis: not possible
Melis 1995 n = 108 w = 5 Analysed 103	Unexplained subfertility & mild male subfertility Age: 33.1 years Duration subfertility: 4.3 years Basic fertility work up normal, semen normal, previous treatment in all couples	IUI + COH 3 amp FSH/ day Ovulation: 10000 IU hCG, at least 2 follicles 16 mm Timing: 30-36 hr after hCG Cancel: E2 > 1500pg/ml Duration 3 cycles max	TI + COH 3 amp FSH/ day Ovulation: 10000 IU hCG,at least 2 follicles 16 mm Timing: 12 hr after hCG Cancel: E2 > 1500pg/ml Duration 3 cycles max	Live birth and PR per couple Multiple pregnancies Pregnancy: fetal heart activity on US	Randomisation computer generated random number list, sealed envelopes Trial design: Parallel Single centre ITT- analysis: possible
Murdoch 1991 n = 20 versus 19 w = 5	Unexplained subfertility Age: 33.1 versus 30.5 Duration subfertility: 5.1 versus 5.7 Basic fertility work up normal, semen normal, no previous treatment	IUI + COH 75 IU hMG/ day and 200 µg buserelin 4/day intranasal Ovulation: 5000 IU hCG, < 4 follicles of > 16 mm Timing: 30-36 hr after hCG Cancel: > 4 dominant follicles Duration 3 cycles max	IUI without COH - - Timing: IUI on alternate days until ovulation confirmed on US Duration 3 cycles max	Live birth and PR per couple PR per cycle Multiple pregnancies Pregnancy: fetal heart activity on US	Randomisation: random number sequence, sealed envelopes Trial design: Parallel Single centre ITT- analysis: yes
Steures 2006 n= 127 versus 126	Unexplained subfertility Age: 33 versus 33 Duration subfertility: 2.0 versus 1.9 Basic fertility work up normal, one sided tubal pathology was allowed, semen normal, no previous treatment	IUI + COH Mean 75 IU FSH/ day (range 37-150), minority used 50-150 CC/day for 5 days Ovulation: 5000 or 10000 IU hCG, at least 1 follicle 16 mm Timing: 36-40 hr after hCG Cancel: 3 follicles at least 16 mm, or 5 follicles at least 12 mm Duration 6 months, mean 4 cycles	Coitus without COH - - Timing: - Duration 6 months	Live birth and ongoing PR per couple Multiple pregnancies Ongoing pregnancy: fetal heart activity on US at gestation of 12 weeks	Randomisation computer generated in balanced blocks, sealed envelopes Trial design: Parallel Multi centre, 26 centres ITT- analysis: yes

One study compared IUI versus IVF. It did not show a significant beneficial effect with a RR for IUI without COH compared to IVF: 0.60, [95% CI 0.35 to 1.1] and a RR for IUI with COH compared to IVF: 0.92, [95% CI 0.58 to 1.5].

The comparison IUI with COH versus IUI without COH was made in four studies and showed that IUI with COH was significantly more effective than IUI without COH (RR: 1.8, [95% CI 1.2 to 2.7]).

Nine of these 14 studies reported on multiple pregnancies. The multiple pregnancy rate varied between 3% and 30%, with wide confidence intervals of the effect. The RR for the comparison IUI with COH versus expectant management was 1.3 [95% CI 0.25 to 6.7] and for the comparison IUI with COH versus timed intercourse with COH 1.1 [95% CI 0.44 to 2.7]. In the comparison of IUI with COH versus IUI without COH only one out of the three pregnancies in the group allocated to IUI with COH was a multiple pregnancy.

Cervical factor subfertility

In the Cochrane review, five RCTs were reported (Glazener *et al.,* 1987; Martinez *et al.,* 1990; Kirby *et al.,* 1991; Check *et al.,* 1995; Goverde *et al.,* 2000). These five studies compared IUI without COH with timed intercourse. The quality of these five trials was rather poor as none of these studies used an appropriate method of randomisation or had adequate concealment of allocation. All five trials had a crossover design, and only one study reported separately on the pre-crossover data. Since we included studies with parallel design or pre-crossover data in the meta-analysis, we could only evaluate this study. In this study 80% of the cycles were stimulated despite the aim to investigate the effectiveness of IUI without COH versus timed intercourse without COH. Separate data on the stimulated and none stimulated cycles were not available and therefore we had to exclude this study from the analysis.

Since the publication of the Cochane review two new studies have been published (Steures *et al.,* 2007a; 2007b). The quality of these trials and their main characteristics are presented in Table II. The outcomes of these studies are summarized in Figure 2.

The first study compared IUI with expectant management and included couples with an isolated cervical factor. In this study, treatment with IUI for 6 months was compared to expectant management for 6 months. Treatment with IUI started with three attempts of IUI without COH, followed by IUI with COH if these attempts failed. IUI was associated with higher pregnancy rates, albeit not statistically significant (RR live birth: 1.6, [95% CI 0.87 to 3.1], and RR ongoing pregnancy: 1.6, [95% CI 0.91 to 2.8]).

The second study compared IUI with COH to IUI without COH in couples with an abnormal PCT, due to a cervical factor or a male factor. In the couples with a cervical factor additional COH had no beneficial effect (RR: 1.0, [95% CI 0.59 to 1.8]). Two multiple pregnancies occurred in the IUI with COH group and one in the IUI without COH group.

Male subfertility

We were able to identify 18 trials, of which 17 had been included in the Cochrane review (Kerin *et al.,* 1984; Kerin *et al.,* 1987; Ho *et al.,* 1989; te Velde *et al.,* 1989; Martinez *et al.,* 1990; Kirby *et al.,* 1991; Ho *et al.,* 1992; Crosignani and Walters, 1994; Nan *et al.,* 1994; Aribarg and Sukcharoen, 1995; Arici *et al.,* 1995; Melis *et al.,* 1995; Gregoriou *et al.,* 1996; Cohlen *et al.,* 1998; Jaroudi *et al.,* 1998; Guzick *et*

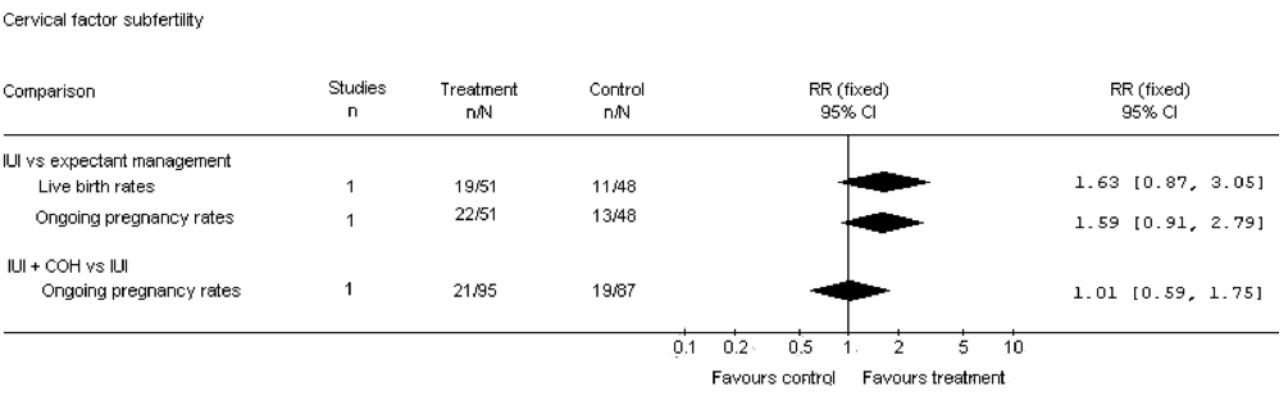

Fig. 2. — Summary of pregnancy results per couple for cervical factor subfertility

Table II. — Characteristics of randomised trials on the effectiveness of IUI in cervical factor subfertility

Trial n = number of randomised couples w = number of withdrawn couples	**Participants**	**Intervention**	**Comparison**	**Main Outcomes**	**Quality features**
Steures 2007 n = 52 versus 49 w = 1 versus 1 Analysed= 51 versus 48	Isolated cervical factor taking the prognosis into account Negative PCT: a well-timed non-progressive PCT, i.e. absence of spermatozoa moving in a straight direction and at a functional speed Age: 30 years Duration of subfertility: 1.7 years Basic fertility work up normal, semen normal, no previous treatment, in each group two women with one-sided tubal occlusion	IUI without COH Timing: 20-30 hr after LH-surge or 36-40 hr after hCG hCG when follicle at least 16 mm Duration: 6 months, mean 4 cycles After 3 failed cycles IUI with COH was given Mean 75 IU FSH/ day (range 37-150) Ovulation: 5000 or 10000 IU hCG, at least 1 follicle 16 mm Timing: 36-40 hr after hCG Cancel: 3 follicles at least 16 mm, or 5 follicles at least 12 mm	Coitus without COH - - Timing: - Duration 6 months	Live birth and ongoing PR per couple Multiple pregnancies Ongoing pregnancy: fetal heart activity on US at gestation of 12 weeks	Randomisation computer generated in balanced blocks, sealed envelopes Trial design: Parallel Multi centre, 17 centres ITT- analysis: yes
Steures 2007 n = 136 versus 136 w = 4 versus 3 Analysed = 132 versus 133, of which 95 versus 87 had TMC > 10 million	Abnormal PCT due to cervical factor or male factor, taking the prognosis into account Negative PCT: a well-timed non-progressive PCT, i.e. absence of spermatozoa moving in a straight direction and at a functional speed Age: 33 versus 33 years Duration of subfertility: 2.5 versus 2.7 years Basic fertility work up normal, prognosis of a spontaneous pregnancy < 30%, no previous treatment, with one-sided tubal occlusion 8 versus 9 women	IUI with COH Mean 75 IU FSH/ day (range 37-150), minority used 50-150 CC/day for 5 days Ovulation: 5000 or 10000 IU hCG, at least 1 follicle 16 mm Timing: 36-40 hr after hCG Cancel: 3 follicles at least 16 mm, or 5 follicles at least 12 mm Duration: max 3 cycles	IUI without COH Timing: 20-30 hr after LH-surge or 36-40 hr after hCG hCG when follicle at least 16 mm Duration: max 3 cycles	Live birth and ongoing PR per couple Multiple pregnancies Ongoing pregnancy: fetal heart activity on US at gestation of 12 weeks	Randomisation computer generated in balanced blocks, sealed envelopes Trial design: Parallel Multi centre, 24 centres ITT- analysis: yes

al., 1999; Goverde *et al.,* 2000). Nine of these studies had no parallel design or pre-crossover data. We could therefore only evaluate nine of the 18 studies in the current review. The quality of these nine trials and their main characteristics are presented in Table 3. The outcomes of the comparisons are summarized in Figure 3.

The effectiveness of IUI without COH was only investigated in one study in which IUI without COH was almost five times more effective than timed intercourse. However, due to the small numbers the confidence interval is very wide (RR 4.5, 95% CI 0.52 to 39).

One study found IUI with COH equally effective as timed intercourse with COH in terms of live birth (RR: 0.91, [95% CI 0.39 to 2.1]). For the outcome clinical pregnancies two more studies could be included. The summary estimate indicated a beneficial effect of IUI with COH but this was not statistically significant (RR: 1.4, [95% CI 0.79 to 2.4]).

Only one randomised trial compared IUI with or without COH with IVF, which was already discussed in the section on unexplained subfertility. We found no significant beneficial effect of any of the treatment modalities (RR for IUI without COH compared to IVF: 1.2, [95% CI 0.59 to 2.4] and RR for IUI with COH compared to IVF: 1.1, [95% CI 0.52 to 2.3]). Most trials about IUI in male subfertility compared IUI with COH to IUI without COH. COH had no additional effect in these couples (RR live birth: 0.92, [95% CI 0.46 to 1.8], RR ongoing pregnancies 1.2, [95% CI 0.88 to 1.8]). Effects on multiple pregnancies could not been extracted from the study reports.

Discussion

Treatment of subfertile couples with IUI has been applied for over 60 years. In many countries, IUI is the first line treatment in couples with unexplained subfertility, cervical factor subfertility and male subfertility. Our comprehensive systematic review showed that the number of randomised trials assessing the effectiveness of IUI is limited and that most of these studies had small sample sizes. Overall, this results in imprecise effect estimates, as demonstrated by relatively large confidence intervals. Also, many studies did not adhere to present quality standards for designing, conducting and reporting randomised clinical trials. Only one comparison was significant in this meta-analysis: IUI with COH improved pregnancy rates compared to IUI without COH in unexplained subfertility. However, this data is of limited clinical value as we do not know whether IUI without COH is of any benefit compared to expectant management.

An explanation for the limited evidence of the effectiveness of IUI could be that IUI was already widely performed before evidence based medicine was introduced. The term "evidence based" appeared in the medical literature for the first time in 1993 (Guyatt and Nishikawa). The Cochrane Collaboration, developing systematic reviews of the effectiveness of interventions in health care, was founded in 1993. It may be possible that the appealing rationale of IUI (bringing the gametes closer together) and the lack of competition from alternative treatment options limited the challenge posed by the principle of evidence-based medicine to existing beliefs in the effectiveness of IUI.

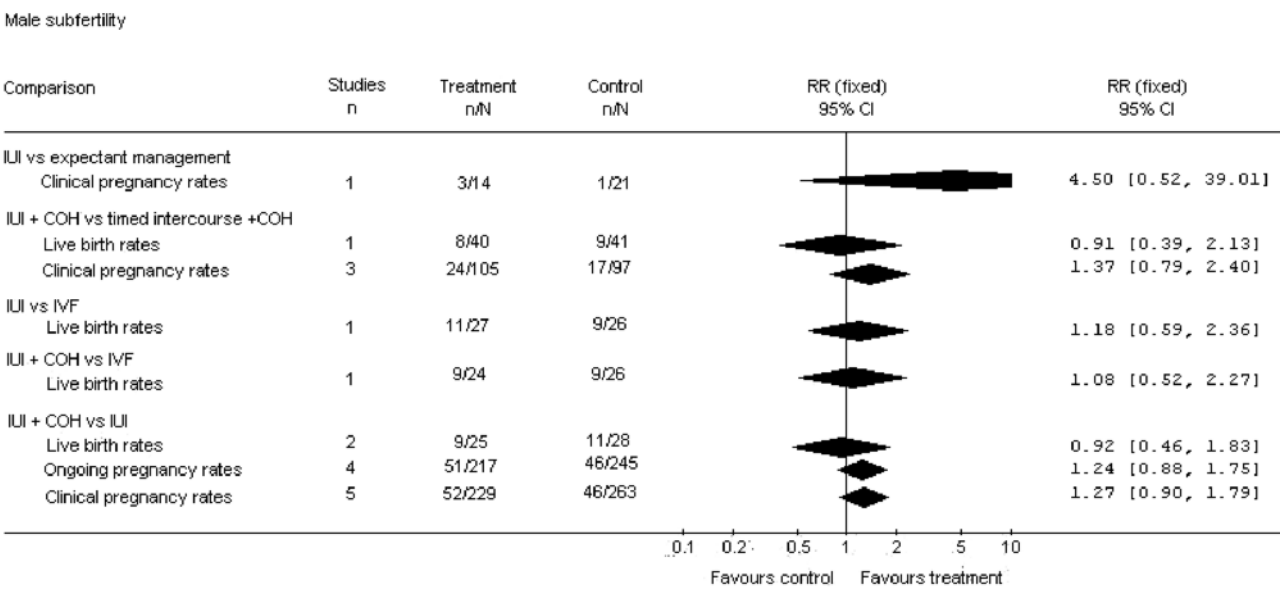

Fig. 3. — Summary of pregnancy results per couple for male subfertility

Table III. — Characteristics of randomised trials on the effectiveness of IUI in male subfertility

Trial n = number of randomised couples w = number of withdrawn couples	**Participants**	**Intervention**	**Comparison**	**Main Outcomes**	**Quality features**
Arici 1994 n = 75 w = 19 Analysed 56 Male sub: 26	Unexplained and male subfertility Male subfertility: concentration < 20 million/ml and/or motility < 50% and/or morphology < 50% (WHO 1987) Age: 33 (range 24-41) Duration subfertility: 3.5 (range 1-15) no previous treatment	IUI +COH 50 mg CC/day, day 5-9 Ovulation: 10000 IUI hCG, at least 1 follicle 18 mm Timing: 32 hr after hCG Cancel: unclear Duration 4 cycles max	IUI without COH - - Timing: On day of LH-surge and next day - Duration 4 cycles max	Live birth and PR per couple PR per 1 st cycle Multiple pregnancies Pregnancy: US showing gestational sac	Randomisation with random number table by computer in locked files Trial design: crossover (after 1 cycle) Single centre ITT- analysis: yes
Cohlen 1998 n = 74,36 versus 38 w = 0	Male subfertility: concentration < 20 million/ml and/or motility < 40% and/or morphology < 40% Age: 30.7 (range 24-39) Duration subfertility: 3.1 (range 2-9) previous treatment not stated	IUI +COH 75-150 IU hMG/day Ovulation: 5000 IU hCG leading follicle at least 18 mm or LH surge Timing: 38-40 hr after hCG Cancel: ≥ 4 follicles of ≥ 18 mm, or E2 level exceedd 1635 pg/ml Duration 6 cycles max	IUI without COH - - Timing: 26 hr after onset of LH-surge (≥ 24 IU/l) - Duration 6 cycles max	PR per couple in first cycle Multiple pregnancies Pregnancy: hCG urine tst and confirmation by US at gestation of 6-7 weeks	Randomisation not stated, allocation by sealed envelopes Trial design: Crossover, alternating cycles Single centre ITT- analysis: possible
Goverde 2000 n = 24 versus 27 w = unclear Analysed 50	Male and unexplained subfertility Male subfertility: 3 of 5 semen analyses TMC < 20 million progressive motile sperm in ejaculate and minimum of 1 million Age: 31.7 versus 31.6 Duration subfertility: 4.2 versus 3.9 previous treatment not stated	IUI + COH 75 IU/day FSH (starting dose) Ovulation: 10000 IU hCG, 1-3 follicles of 18 mm Timing: 40-42 hr after hCG Cancel > 3 follicles of 8 mm or > 6 follicles of 14 mm Duration 6 cycles max	IUI without COH - - Timing: 20-30 hr after LH surge Duration 6 cycles max	Live birth per couple	Randomisation computer generated randomisation schedule in sealed envelopes Trial design: Parallel Single centre ITT- analysis: yes

Table III — Continuation

Trial n = number of randomised couples w = number of withdrawn couples	**Participants**	**Intervention**	**Comparison**	**Main Outcomes**	**Quality features**
Goverde 2000 n = 27 versus 26 w = unclear Analysed 52	Male and unexplained subfertility Male subfertility: 3 of 5 semen analyses TMC < 20 million progressive motile sperm in ejaculate and minimum of 1 million Age: 31.7 versus 31.6 Duration subfertility: 4.2 versus 3.9 previous treatment not stated	IUI without COH - - Timing: 20-30 hr after LH surge Duration 6 cycles max	IVF 150-225 IU/day FSH with GnRH agonist Ovulation:10000 hCG, at least 1 follicle 18 mm, and minimum 3 follicle 16 mm Aspiration: 35 hr after hCG ET: 48-72 hr after retrievel, 2-3 embryo's Luteal phase: progesterone	Live birth per couple	Randomisation computer generated randomisation schedule in sealed envelopes Trial design: Parallel Single centre ITT- analysis: yes
Goverde 2000 n = 24 versus 26 w = unclear Analysed 50	Male and unexplained subfertility Male subfertility: 3 of 5 semen analyses TMC < 20 million progressive motile sperm in ejaculate and minimum of 1 million Age: 31.7 versus 31.6 Duration subfertility: 4.2 versus 3.9 previous treatment not stated	IUI + COH 75 IU/day FSH (starting dose) Ovulation: 1000 IU hCG, 1-3 follicles of 18 mm Timing: 40-42 hr after hCG Cancel > 3 follicles of 8 mm or > 6 follicles of 14 mm Duration 6 cycles max	IVF 150-225 IU/day FSH with GnRH agonist Ovulation:10000 hCG, at least 1 follicle 18 mm, and minimum 3 follicle 16 mm Aspiration: 35 hr after hCG ET: 48-72 hr after retrievel, 2-3 embryo's Luteal phase: progesterone	Live birth per couple	Randomisation computer generated randomisation schedule in sealed envelopes Trial design: Parallel Single centre ITT- analysis: yes
Gregoriou 1996 n = 62, 31 versus 31	Male subfertility: 3 samples concentration < 20 million/mL and/or motility < 30% and/or norm. morphology < 40% Age: 30.5 years Duration subfertility: 5.8 years previous treatment not stated	IUI + COH Stimulation: 75 IU hMG/day with adjustment (150 IU hMG/max) Ovulation: 10000 hCG Timing: 36-40 hr after hCG Cancel: ovarian hyperstimulation, not specified Duration 6 cycles max	TI + COH Stimulation: 75 IU hMG/day with adjustment (150 IU hMG/max) Ovulation: 10000 hCG Timing: 36-40 hr after hCG Cancel: ovarian hyperstimulation, not specified Duration 6 cycles max	PR per cycle couple Pregnancy: hCG urine tst and confirmation by US	Randomisation not clear Trial design: Crossover after 3 cycles Single centre ITT- analysis: possible

Guzick 1999 n = 932, of which 154 male factor and treated with IUI w = unclear	Unexplained subfertility & male subfertility Male subfertility: concentration < 20 million/ml and/or motility < 50% Age: 32 versus 32 Duration subfertility: 3.5 versus 3.8 no previous treatment	IUI + COH 150 IU FSH/day, day 3-7 Ovulation: 10000 IU hCG, 2 follicles > 18 mm Timing: 36-40 hr after hCG Cancel: E2 > 3000pg/ml Duration 4 cycles max	IUI without COH - - Timing: Day after urinary LH-surge Duration 4 cycles max	Live birth and PR per couple Multiple pregnancies Pregnancy: two positive hCG tests. Confirmed by live birh	Randomisation computer generated permuted block in locked files Trial design: Parallel Multi centre, 10 clinics ITT- analysis: unclear
Kerin 1984 n = 14 versus 21	Male subfertility: (in 3 samples, at least 2 abnormalities): concentration < 40 million/mL; motility < 45% and morphology < 40% Age: not stated Duration subfertility: ≥ 3 years previous treatment not stated Male & unexplained subfertility	IUI without COH Timing: day after LH-rise Duration 9 cycles max	TI without COH Timing: no timing or by LH tests, on day of LH-rise Duration 9 cycles max	Pregnancy per couples Pregnancy not stated	Randomisation not clear Trial design: Crossover alternating cycles Single centre ITT- analysis: possible
Melis 1995 n = 92 w = 11 analysed= 81 41 versus 40	Male subfertility: (2 samples): concentration 10-20 million/mL and/or progressive motility 15-25% and/or total motility 30-50 % and/or norm. morphology 30-50 % Age: 34.2 years Duration subfertility: 4.3 years previous treatment in all couples	IUI + COH 225 FSH/ day Ovulation: 10000 IU hCG,at least 2 follicles 16 mm Timing: 30-36 hr after hCG Cancel: E2 > 1500 pg/ml Duration 3 cycles max	TI + COH 225 FSH/ day Ovulation: 10000 IU hCG,at least 2 follicles 16 mm Timing: 12 hr after hCG Cancel: E2 > 1500pg/ml Duration 3 cycles max	Live birth and PR per couple Multiple pregnancies Pregnancy: fetal heart activity on US	Randomisation computer generated random number list, sealed envelopes Trial design: Parallel Single centre ITT- analysis: possible
Nan 1994 n = 76 first cycle: 34 versus 25	Male subfertility: (in 4 samples): concentration < 20 million/mL and/or motility < 40% and/or morphology < 40% Age: 32 years (range: 24-39) Duration subfertility: 4.5 years (2-10) previous treatment not stated	IUI + COH 150 IU hMG/day Ovulation: 10000 IU hCG Timing: 38-40 hr after hCG unless LH surge: 26 hr after detecting LH surge Cancel: > 4 follicles ≥ 18 mm or E2 > 6000 pmol/L Duration 6 cycles max	TI + COH 150 IU hMG/day Ovulation: 10000 IU hCG Timing: 24-28 hr after hCG unless LH surge: same evening as detection LH surge Cancel: > 4 follicles ≥ 18 mm or E2 > 6000 pmol/L Duration 6 cycles max	Live birth and PR per couple PR per cycle Multiple pregnancies Pregnancy: fetal heart activity on US	Randomisation: random number sequence, sealed envelopes Trial design: Crossover, alternating cycles Single centre ITT- analysis: not possible

Table III — Continuation

Trial n = number of randomised couples w = number of withdrawn couples	**Participants**	**Intervention**	**Comparison**	**Main Outcomes**	**Quality features**
Steures 2007 n = 136 versus 136 w = 4 versus 3 Analysed= 132 versus 133, of which 37 versus 46 had TMC < 10 million	Abnormal PCT due to cervical factor or male factor, taking the prognosis into account Male subfertility: TMC < 10 million Age: 33 versus 33 years Duration of subfertility: 2.5 vs 2.7 prognosis of a spontaneous pregnancy < 30%, no previous treatment, with one-sided tubal occlusion 8 versus 9 women	IUI with COH Mean 75 IU FSH/ day (range 37-150), minority used 50-150 CC/day for 5 days Ovulation: 5000 or 10000 IU hCG, at least 1 follicle 16 mm Timing: 36-40 hr after hCG Cancel: 3 follicles at least 16 mm, or 5 follicles at least 12 mm Duration: max 3 cycles	IUI without COH Timing: 20-30 hr after LH-surge or 36-40 hr after hCG hCG when follicle at least 16 mm Duration: max 3 cycles Live birth and ongoing PR per couple Multiple pregnancies	Ongoing pregnancy: fetal heart activity on US at gestation of 12 weeks	Randomisation computer generated in balanced blocks, sealed envelopes Trial design: Parallel Multi centre, 24 centres ITT- analysis: yes

IUI has been incorporated into clinical guidelines from 1996 onwards. Since then IUI was also officially established as the treatment of first choice. In view of the limited evidence, it is surprising that current clinical guidelines make rather firm recommendations about the use of IUI. The guideline made by The National Collaborating Centre for Women's and Children's Health, for example, stipulates that "Couples with mild male subfertility and unexplained subfertility should be offered IUI". On the issue of ovarian hyperstimulation it recommends that "IUI in male subfertility should not be offered with COH". Elsewhere it states that "in unexplained subfertility IUI without COH should be offered, even though this is associated with lower pregnancy rates than IUI with COH, because of the risk of multiple pregnancy after IUI with COH" (Nice Guideline, 2003).

Others authors have suggested that the risk of multiple pregnancies after IUI should encourage its replacement by IVF with single embryo transfer[4]. Still others proclaim that there is no place for the use of gonadotrophins in IUI treatment in unexplained and male subfertility (Goverde *et al.,* 2005).

This comprehensive review shows that there is very little data to ground the firmness of these recommendations, either in favour or against the use of IUI. More good quality trials with sufficient sample sizes are urgently needed to remedy the disturbing lack of evidence. Such studies should compare IUI with expectant management and IUI with IVF, with or without single embryo transfer.

So far, most studies included couples with a great variety in baseline characteristics. This makes a fair comparison between studies and extrapolation to daily practice a real challenge. We feel that, to make studies more generalizable, the prognosis of the couples should be taken into account in designing and analyzing trials. Incorporating the undeniable variability in prognosis provides us with the opportunity to compare and summarize study results in a more meaningful manner. Doing so may enable us to distinguish those couples who may benefit from treatment from those who are unlikely to.

Couples with an intermediate to good prognosis of a treatment independent pregnancy may be encouraged to participate in trials comparing IUI to expectant management, while couples with a poor prognosis are invited to participate in trials comparing IUI to IVF with or without single embryo transfer.

In conclusion, the evidence on the effectiveness of intrauterine insemination, the most frequently used treatment in subfertility, is surprisingly scarce and does not allow us to provide firm recommendations. Only two conclusions can be drawn; IUI with COH improves pregnancy rates over IUI without COH in unexplained subfertility and IUI with COH has not been shown to be effective in couples with unexplained subfertility and a good prognosis. Quality studies comparing IUI to expectant management and to IVF are urgently needed.

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