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The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a meta-analysis

Edward G.Hughes

Department of Obstetrics and Gynaecology, McMaster University, 1200 Main Street West, Hamilton, Ontario, L8N 3Z5, Canada

A systematic review was conducted to evaluate the effectiveness of intrauterine insemination (IUI) with or without ovarian stimulation using gonadotrophin in the treatment of persistent infertility. Relevant randomized controlled trials were identified by a diverse strategy including a hand search of 43 core journals from 1966 to the present. Two approaches to meta-analysis were used to summarize data. First, using a standard Mantel–Haenszel approach, eight trials comparing FSH/IUI with FSH/timed intercourse for unexplained infertility were combined. The common odds ratio for pregnancy was 2.37 [95% confidence interval (CI), 1.43, 3.90], suggesting a significant improvement with IUI following ovulation induction in this patient group. Although the data were statistically homogeneous, clinically important heterogeneity was present. Second, across all diagnostic groups, the independent effects of treatment with follicle stimulating hormone (FSH), clomiphene citrate, IUI, as well as the diagnoses of male factor and endometriosis were assessed using stepwise logistic regression. Based on 5214 cycles reported in 22 trials, the odds ratio for pregnancy associated with FSH use was 2.35 (95% CI, 1.87, 2.94) for IUI, 2.82 (95% CI, 2.18, 3.66) for male factor, 0.48 (95% CI, 0.37, 0.61), and for endometriosis 0.45 (95% CI, 0.27, 0.76). This summary of the best available evidence may prove useful in counselling couples who are considering FSH and/or IUI therapy.

Key words: gonadotrophin/insemination/intrauterine/persistent infertility/unexplained infertility

Introduction

The use of gonadotrophin [follicle stimulating hormone (FSH)] with or without intrauterine insemination (IUI) is widespread in the treatment of infertility. When less aggressive interventions have failed, couples frequently undergo one or more treatment cycles prior to considering in-vitro fertilization (IVF). The advantage of this approach is that some of the risks associated with IVF are avoided, particularly those relating to oocyte retrieval. However, significant risks of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy remain. In addition, there is a small but finite risk of infection following IUI. Understanding the effectiveness of FSH with or without IUI is therefore a priority. Regrettably, the majority of data relevant to these treatments comes from uncontrolled case series and cohort designs which tend to overestimate treatment effectiveness because of selection bias and incomplete follow-up. Also, cancelled cycles and other poor outcomes are generally excluded from the denominator, leading to inflated estimates of effect. A further problem in evaluating FSH and IUI is that although a significant number of trials have been published, they are clinically heterogeneous, comparing different types and combinations of treatments in different populations. Under these circumstances, standard meta-analysis with a simple combination of results across studies may be misleading. Despite these limitations, clinicians are constantly called upon to make use of these treatment techniques and to offer judgements about their effectiveness. Recognizing the need for a useful summary of these complex data, a systematic review was undertaken.

Materials and methods

The primary question posed was: what is the effectiveness of IUI, with or without ovarian hyperstimulation, compared with timed intercourse, in the treatment of persistent infertility? In refining this question further, the following interventions and diagnostic groups were considered separately: clomiphene citrate, FSH, persistent unexplained and persistent male factor infertility.

Criteria for considering trials for this review

All randomized controlled trials examining the use of IUI with or without clomiphene citrate and FSH, were considered. In each trial, one arm included IUI alone or in combination with FSH or clomiphene citrate. Comparisons could include clomiphene citrate, FSH, IUI or timed intercourse. Studies which compared IUI with intracervical insemination or more interventional treatments, such as direct intraperitoneal insemination (DIPI), tubal sperm perfusion, IVF or gamete intra-Fallopian transfer (GIFT) were excluded. Studies which compared two methodological variants of IUI treatment also were excluded.

Search strategy for identification of trials

The search strategy developed by the Cochrane Collaboration subfertility collaborative group was used to generate this overview. A combination of methods was used with close collaboration between the Leeds (UK) and McMaster (Canada) groups.

(i) A total of 43 core journals was divided between the two centres and searched systematically from 1966 to the present. The journal titles (abbreviated) are as follows: *Acta Endocrinol., Acta Eur. Fertil., Acta Obstet. Gynecol. Scand., Am. J. Obstet. Gynecol., Am. J. Reprod. Immunol. Microbiol., Andrologia, Arch. Androl., Aust. NZ J. Obstet. Gynaecol., Biol. Reprod., Br. J. Obstet. Gynaecol., Br. J. Urol., Br. Med. J., Clin. Endocrinol., Gynecol. Obstet. Invest., Horm. Res., Hum. Reprod., Int. J. Androl., Int. J. Fertil., Int. J. Gynecol. Obstet., J. Am. Med. Assoc., J. Androl., J. Clin. Endocrinol. Metab., J. Endocrinol., J. Gynaecol. Endocrinol., J. Obstet. Biol. Reprod., J.*

Gynaecol. Surg., J. In Vitro Fertil. Embryo Transfer, J. Obstet. Gynaecol., J. Reprod. Fertil., J. Reprod. Immunol., J. Reprod. Med., J. Urol., Lancet, Mol. Reprod. Dev., N. Engl. J. Med., Obstet. Gynecol., Surg. Gynecol. Obstet., Urology.

(ii) Bibliographies from potentially relevant studies were hand-searched for further trials.

(iii) The National Library of Medicine's MEDLINE database was systematically searched using a variety of keywords including 'infertility', 'insemination, homologous', 'insemination, intrauterine', 'ovulation induction', and 'randomized'. Studies were sought on the basis of methodology using key words 'comparative study', 'random allocation', and 'random'. From 1991 onward the subject heading 'randomized controlled trial' was used.

(iv) Abstracts from relevant North American and European scientific meetings were hand-searched for recent but as yet unpublished trials from 1986 to the present. Trials were coded in terms of their design, relevance to female or male sub-fertility or both, the indication or diagnosis leading to treatment and the overviews in which they were ultimately included. Reference Manager (Research Information Systems Inc., Carlsbad, CA, USA) was used as a bibliography management system. Reports were screened for relevance and data extracted by independent reviewers.

Results

Twenty-two relevant randomized controlled trials were identified (Ho *et al.*, 1989; te Velde *et al.*, 1989; Deaton *et al.*, 1990; Martinez *et al.*, 1990, 1991; Crosignani *et al.*, 1991; Doyle and DeCherney, 1991; Evans *et al.*, 1991; Kirby *et al.*, 1991; Ho *et al.*, 1992; Karlstrom *et al.*, 1993; Nulsen *et al.*, 1993; Zikopoulos *et al.*, 1993; Aribarg and Sukcharoen, 1995; Arici *et al.*, 1994; Balasch *et al.*, 1994; Nan *et al.*, 1994; Chung *et al.*, 1995; Gregoriou *et al.*, 1995; Karande *et al.*, 1995; Lahteenmaki *et al.*, 1995; Robinson *et al.*, 1995).

The multiple treatment comparisons considered in all studies are described in Figure 1 and their methodological features detailed in Table I.

Based on the extensive clinical heterogeneity between studies, two methodologies were chosen to address the following questions: (i) Is FSH plus IUI more effective than FSH plus timed intercourse in the treatment of persistent unexplained infertility? (ii) What are the independent effects of FSH, IUI, clomiphene citrate, male factor and endometriosis on fecundability in persistent infertility?

In answering question (i), the group of eight similar trials (Crosignani *et al.*, 1991; Doyle and DeCherney, 1991; Evans *et al.*, 1991; Martinez *et al.*, 1991; Karlstrom *et al.*, 1993; Zikopoulos *et al.*, 1993; Chung *et al.*, 1995; Gregoriou *et al.*, 1995) were considered to be amenable to a standard Mantel–Haenszel approach (Mantel and Haenszel, 1959), through which a sensible conclusion could at least be made from this small portion of the trial data. The Breslow–Day statistic was used to assess statistical heterogeneity (Breslow and Day, 1980).

In answering question (ii), logistic regression was used to evaluate the independent effects of FSH, clomiphene citrate and IUI in all diagnostic groups across all trials. The logistic models were constructed with and without scores for study quality.

In all, 14 trials were identified evaluating various combinations of IUI treatment in male factor patients (Ho *et al.*, 1989, 1992; te Velde *et al.*, 1989; Martinez *et al.*, 1990, 1991; Kirby *et al.*, 1991; Nulsen *et al.*, 1993; Arici *et al.*, 1994; Balasch *et al.*, 1994; Nan *et al.*, 1994; Aribarg and Sukcharoen, 1995; Karande *et al.*, 1995; Lahteenmaki *et al.*, 1995; Robinson *et al.*, 1995). A detailed summary of these and other trials for male factor infertility is currently in preparation (B.Cohlen and E.R.teVelde) and will be published elsewhere.

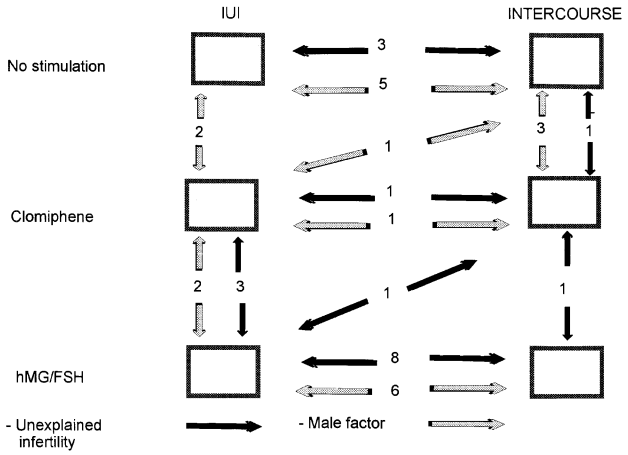

Figure 1. This matrix describes the comparisons tested in 22 relevant trials (5214 cycles). The interventions tested are broken down in terms of intrauterine insemination (IUI) and timed intercourse (columns), and no stimulation, clomiphene citrate and gonadotrophin (rows; HMG = human menopausal gonadotrophin, FSH = follicle stimulating hormone). Comparisons are shown separately for unexplained (solid arrow) and male factor infertility (shaded arrow), e.g. the first row shows that in unstimulated cycles, three studies compared IUI with timed intercourse in unexplained infertility and five studies compared the same interventions in male factor patients.

Methodological quality of included trials

Question (i) Eight randomized controlled trials compared FSH/IUI with FSH/timed intercourse in patients with unexplained infertility (Chung *et al.*, 1995; Crosignani *et al.*, 1991; Doyle and DeCherney, 1991; Evans *et al.*, 1991; Gregoriou *et al.*, 1995; Karlstrom *et al.*, 1993; Martinez *et al.*, 1991; Zikopoulos *et al.*, 1993). Crosignani *et al.* (1991) involved 19 centres and compared five different treatment approaches, allowing each centre to select only two treatments, and then randomize patients to receive one or other of these (Crosignani *et al.*, 1991). Data from the first treatment cycles were available and were selectively included in this overview. Evans *et al.* (1991) compared three treatment arms: clomiphene citrate/FSH plus IUI, clomiphene citrate/FSH plus timed intercourse and clomiphene citrate/FSH plus DIPI. Contamination occurred within groups post-randomization; when technical problems precluded an individual treatment, e.g. when IUI was not possible, DIPI was done instead. Zikopoulos *et al.* (1993) also used a cross-over design with a natural cycle between each stimulated cycle. Karlstrom *et al.* (1993) evaluated FSH, clomiphene citrate, IUI, DIPI and timed intercourse using a factorial design. Of the 157 couples with unexplained infertility, 51 women also had endometriosis. Two similar studies used a cross-over design without reporting pre- and post-cross-over data (Doyle and De Cherney, 1991; Gregoriou *et al.*, 1995). A more recent study using a parallel design evaluated a

gonadotrophin releasing hormone agonist (GnRHa)-based ovulation augmentation protocol (Chung *et al.*, 1995). This was the only study with and without IUI using a secure method of randomization — sealed envelopes.

Question (ii) Twenty-two randomized controlled trials including the eight listed above addressed the use of IUI/FSH/clomiphene citrate for persistent infertility (te Velde *et al.*, 1989; Ho *et al.*, 1989, 1992; Deaton *et al.*, 1990; Martinez *et al.*, 1990, 1991; Crosignani *et al.*, 1991; Doyle and DeCherney, 1991; Evans *et al.*, 1991; Kirby *et al.*, 1991; Karlstrom *et al.*, 1993; Nulsen *et al.*, 1993; Zikopoulos *et al.*, 1993; Aribarg and Sukcharoen, 1995; Arici *et al.*, 1994; Balasch *et al.*, 1994; Nan *et al.*, 1994; Chung *et al.*, 1995; Gregoriou *et al.*, 1995; Karande *et al.*, 1995; Lahteenmaki *et al.*, 1995; Robinson *et al.*, 1995) (Table I). Several randomized controlled trials compared more than two treatment arms. Only the treatments relevant to the hypotheses under study were included in this analysis. These randomized controlled trials uniformly compared IUI with timed intercourse rather than with natural coital activity.

Only three trials reported details of the method of randomization (Arici *et al.*, 1994; Evans *et al.*, 1991; Nulsen *et al.*, 1993) and only two avoided the use of a cross-over design (Chung *et al.*, 1995; Karlstrom *et al.*, 1993). In the remainder, random allocation was used in choosing the first treatment approach, with the alternate assignment after one to four cycles. Two trials made use of a latin square design (Martinez *et al.*, 1990, 1991). Although, in FSH-stimulated cycles, induction failure or cycle cancellations occur in up to 10% of cycles (Hartz *et al.*, 1991), none of these trials appeared to include failed cycles in the denominator. Studies among anovulatory women recently summarized elsewhere (Collins and Hughes, 1995) were more likely to address rates of adverse events such as early pregnancy loss, OHSS and multiple gestation. None of these studies was on economic evaluation.

Trials excluded

Trials were excluded for various reasons. These included: relevant data on unexplained infertility patients reported in the methods section of the text and in tables were inconsistent (Chaffkin *et al.*, 1991); no control comparison (Dodson and Haney, 1991); no IUI arm (Harrison and O'Moore, 1983; Cruz *et al.*, 1986; Glazener *et al.*, 1987, 1990; Hughes *et al.*, 1987; Fisch *et al.*, 1989; Fedele *et al.*, 1992; Hogerzeil *et al.*, 1992; Mascarenhas *et al.*, 1994) more interventional comparison (Hovatta *et al.*, 1990; Abyholm *et al.*, 1992; Campos-Liete *et al.*, 1992); IUI methodology comparison only (Friedman *et al.*, 1989; Silverberg *et al.*, 1992; Kahn *et al.*, 1993; Ransom *et al.*, 1994).

Treatment effectiveness

Question (i) The data from eight trials comparing FSH/IUI with FSH/timed intercourse cycles are summarized in Figure 2 (Crosignani *et al.*, 1991; Doyle and DeCherney, 1991; Evans *et al.*, 1991; Martinez *et al.*, 1991; Karlstrom *et al.*, 1993; Zikopoulos *et al.*, 1993; Chung *et al.*, 1995; Gregoriou *et al.*, 1995). The common odds ratio for pregnancy per treatment cycle was 2.37 [95% confidence interval (CI), 1.43, 3.90],

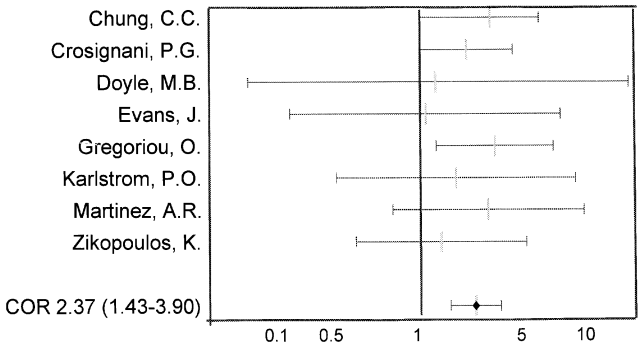

Figure 2. The effectiveness of follicle stimulating hormone (FSH)/intrauterine insemination versus FSH/timed intercourse in the treatment of persistent unexplained infertility as analysed in eight studies. The common odds ratio (COR) for fecundity was generated using the Mantel–Haenszel method. The 95% confidence interval is also shown for each study.

suggesting a significant improvement with IUI following ovulation induction for unexplained infertility. While the Breslow–Day statistic suggested no statistically significant heterogeneity (1.67, $P = 0.44$), low event rates reduced the power of this test. Certainly some heterogeneity existed, particularly in terms of populations and interventions highlighted in Table I. These should be borne in mind when considering the combined estimate of effect size.

Concerns have been raised about the methodological rigour of two studies [Crosignani *et al.* (1991) and Evans *et al.* (1991)]. Sensitivity analysis was therefore performed excluding these trials from meta-analysis. The resultant common odds ratio was 2.56 (95% CI, 1.41, 4.65). Again no significant statistical heterogeneity was noted. Thus, exclusion of these two trials from the analysis did not significantly change its overall conclusions.

Question (ii) The unadjusted aggregate results of treatment from all 22 studies (5214 cycles) are listed in Table II. A logistic regression analysis estimated the likelihood of conception expressed as adjusted odds ratios and 95% CI for study, diagnostic group, type of ovarian stimulation and whether insemination was done (Table III). The likelihood of conception was ~2-fold higher with FSH and nearly 3-fold higher with IUI. This is consistent with the unadjusted data: 4.6% in all clomiphene citrate and unstimulated cycles versus 11.7% in all FSH cycles; similarly, the ratios are 3.7% with timed intercourse and 9.4% with IUI. An interaction term for FSH and IUI was the first covariate to enter the model in forward stepwise regression, but with FSH and IUI in the model, this term was the first to be removed during backward stepwise regression, suggesting that the effects of FSH and IUI are independent. A diagnosis of endometriosis or male factor infertility reduced treatment effectiveness approximately by half (Table III).

Discussion

This summary of published studies of IUI, with or without ovarian stimulation for persistent infertility, indicates that IUI and FSH both significantly improve fecundity. The trial designs do not exclude bias, however, and high quality studies are

Table I. Methodological features of included trials

Authors (year)	Design	Participants	Intervention	Notes
Aribarg *et al.* (1995)	Random allocation method not described. Cross-over study	pelvis; sperm conc. $1–20\times10^6$/ml; >2 years infertile; $n = 50$ couples	Ovulatory female with normal CC 100 mg ×5 days plus IUI versus timed intercourse	No CC in control cycles
Arici *et al.* (1994)	Random allocation by computer table, concealment not described. Cross-over study	Ovulatory female with normal pelvis (including surgically treated endometriosis); normal sperm. $n = 26$ couples male factor infertility (WHO); $n = 30$ couples	CC 50 mg × 5 days plus IUI × 1 versus IUI × 2	Cointervention with HCG, used only in CC/IUI group. Also extra IUI used in most control cycles. Pre-cross-over data available.
Balasch *et al.* (1994)	Random allocation method not described. Parallel study	Male factor infertility with two abnormal analyses two abnormal analyses (WHO); $n = 60$ couples, 114 cycles. Unexplained infertility ⩾2 years $n = 40$ couples, 78 cycles	FSH plus IUI versus CC 50 mg ×5 days plus IUI	HCG luteal support in both groups. Up to three treatment cycles per arm
Chung *et al.* (1995)	Random allocation by sealed envelope. Parallel study	Unexplained infertility >3 years duration; ovulatory; normal pelvis; $>15\times10^6$ total motile spermatozoa per ejaculate; $n = 100$ couples, 257 cycles	GnRHa/FSH plus IUI versus GnRHa/FSH plus timed intercourse	Intercourse discouraged in post-ovulatory period
Crosignani *et al.* (1991)	Random allocation method not described. Cross-over study	Unexplained infertility >3 years duration; ovulatory; normal pelvis; normal sperm (WHO); $n = 236$ couples	HMG/IUI versus HMG plus timed intercourse (IPI, GIFT and IVF other interventions in this study)	Pre and post cross-over data available. 19 centres chose two HMG-based interventions to compare
Deaton *et al.* (1990)	Random allocation method not described. Cross-over study	Unexplained infertility; normal ovulation, pelvis and sperm (WHO); $n = 67$ couples, 298 cycles	CC 50 mg × 5 days plus IUI versus timed intercourse	No CC in control. Women with surgically treated endometriosis Pre-cross-over data not available
Doyle and DeCherney (1991)	Random allocation method not described. Cross-over study	Unexplained infertility 13–68 months duration; $n = 30$ cycles	FSH plus IUI versus FSH plus timed intercourse	Pre- and post-cross-over data not separable. Published in abstract
Gregoriou *et al.* (1995)	Random allocation method not described. Cross-over study	Unexplained infertility; normal ovulation, androgens, TSH, PRL, laparoscopy, HSG, post-coital test, sperm penetration assay,		
		immunobead testing and semen analysis (WHO); $n = 46$ couples, 141 cycles	FSH plus timed intercourse versus FSH plus IUI	Pre- and post-cross-over data not separable
Ho *et al.* (1989)	Random allocation method not described. Cross-over study	Male factor infertility (WHO); ovulatory female, patent tubes; $n = 47$ couples, 238 cycles	LH timed IUI versus LH timed intercourse	CC used in some women with irregular cycles. Pre- and post-cross-over data not separable
Ho *et al.* (1992)	Random allocation method not described. Cross-over study	Male factor infertility criteria as above; $n = 15$ couples, 84 cycles	FSH plus IUI versus intercourse	Intercourse alternate days in control group, not LH timed
Karande *et al.* (1995)	Random allocation method not described. Cross-over study	Consecutive patients treated with COH; Unexplained $n = 39$ cycles	FSH plus IUI versus CC plus IUI (FSP treatment also included study)	Four arm factorial design evaluating CC, FSH, IUI and tubal perfusion
Karlstrom *et al.* (1993)	Random allocation method not described. Parallel study	Unexplained infertility $n = 148$ couples and cycles	FSH plus IUI versus CC plus IUI versus IUI alone (DIPI also included in study)	Factorial design, single treatment cycle. 51 women had minimal/mild endometriosis
Kirby *et al.* (1991)	Random allocation method not described. Cross-over study	Unexplained infertility >2 years duration. Normal ovulation and pelvis. Sperm concentration $>40 \times 10^6$/ml, $n = 73$ couples, 123 cycles; male factor $n = 188$ couples, 331 cycles	IUI versus timed intercourse	IUI and insemination 40 h post-LH surge. Pre- and post-cross-over data available for total sample but not by diagnostic groups.

Table I. *Continued*

Authors (year)	Design	Participants	Intervention	Notes
Lahteenmaki *et al*. (1995)	Random allocation using sealed envelopes. Cross-over study	Male antisperm antibodies; female age <40; n = 46 couples, 204 cycles	IUI versus timed intercourse plus prednisone 20 mg × 10 days	CC co-intervention in 62% of IUI cycles and 54% of prednisone/intercourse cycles. Pre- and post-cross-over data available
Martinez *et al*. (1990)	Random allocation method not described. Cross-over study	Unexplained infertility n = 21 couples, 144 cycles; male factor n = 17 couples, 106 cycles	CC 100 x 5 days plus IUI versus CC plus timed intercourse versus timed IUI versus timed intercourse	Latin square design
Martinez *et al*. (1991)	Random allocation method not described. Cross-over study	Unexplained infertility n = 32 couples; male factor infertility n = 16 couples	FSH plus IUI versus FSH plus timed intercourse	Eight factorial design with HCG and LH surge timing
Nan *et al*. (1994)	Random allocation method not described. Cross-over study	Male factor; four SAs (WHO); ovulatory; normal pelvis and PCT; n = 76 couples, 249 cycles	FSH plus IUI versus FSH plus timed intercourse	Pre- and post-cross-over data available; three pregnancies in 173 rest cycles (1.7%)
Nulsen *et al*. (1993)	Random allocation method not described. Cross-over study	Persistent infertility, male factor (WHO); unexplained; endometriosis after surgical treatment; mixed diagnoses; n = 119 couples	FSH plus IUI versus IUI alone	FSH cycles included HCG. IUI cycles timed using urine LH testing
Robinson *et al*. (1995)	Random allocation method not described. Cross-over study	Male antisperm antibodies 50% (immunobead); normal female FSH and LH; patent Fallopian tubes; n = 30 couples	CC 100 mg × 5 days/FSH plus IUI versus timed intercourse. Both arms included male treatment with prednisone 40 mg daily × 10 days per cycle	Pre and post-cross-over data not separable. FSH regime fixed: eight ampoules total
te Velde *et al*. (1989)	Random allocation method not described. Cross-over study	Male factor, mild to severe n = 30 couples; sperm-mucus n = 27 couples	IUI versus timed intercourse	No stimulation used. Pre- and post-cross-over data not separable
Zikopoulos *et al*. (1993)	Random allocation method not described. Cross-over study	Unexplained; normal ovulation, sperm (WHO) laparoscopy, sperm-mucus interaction, n = 48 couples, 250 cycle	GnRHa/FSH plus IUI versus GmRHa/FSH plus timed intercourse	Endometriosis and fibroids excluded. Pre- and post-cross-over data not available

Conc. = concentration, CC = clomiphene citrate, IUI = intrauterine insemination, SA = WHO = World Health Organization, HCG = human chorionic gonadotrophin, FSH = follicle stimulating hormone; FSP = Fallopian sperm fusion; GnRHa = gonadotrophin releasing hormone agonist, HMG = human menopausal gonadotrophin, IPI = intraperitoneal insemination, GIFT = gamete intra-Fallopian transfer, IVF = in-vitro fertilization, TSH = thyroid stimulating hormone, PRL = prolactin, HSG = hysterosalpingography, LH = luteinizing hormone, OS = ovarian stimulation, DIPI = direct IPI, PCT = post-coital test, SA = semen analyses.

Table II. Crude aggregate data from 22 relevant trials (5214 cycles). Values in parentheses are percentages.

	No. of pregnancies per cycle	
Ovulation stimulation	IUI cycles	No IUI
No stimulation	80/1306 (6)	27/1354 (2)
Clomiphene	42/644 (7)	5/54 (9)
FSH	171/1156 (15)	47/700 (7)
Total	293/3106 (9.8)	79/2108 (3.7)

FSH = follicle stimulating hormone, IUI = intrauterine insemination.

Table III. Adjusted odds ratios for the likelihood of conception per cycle, generated using stepwise logistic aggression. Twenty-two trials contributed a total of 5214 cycles to this analysis

Independent variable	Adjusted odds ratio (± 95% CI)[a]
FSH	2.35 (1.87–2.94)
IUI	2.82 (2.18–3.66)
Seminal defect	0.48 (0.37–0.60)
Endometriosis	0.45 (0.27–0.76)

[a]Logistic regression model.
FSH = follicle stimulating hormone, IUI = intrauterine insemination, CI = confidence interval.

needed to estimate confidently the true effects of IUI and FSH treatment. For now, the best available evidence indicates that average fecundability is more than 2-fold higher in a cycle with either treatment and ~5-fold higher when both treatments are used compared with untreated cycles. These findings are consistent with the results of a previous meta-analysis comparing IUI with timed intercourse or intracervical insemination among couples with oligozoospermic infertility. This combination of somewhat different trials demonstrated a 2-fold increase in fecundity following IUI (O'Donovan *et al.*, 1993).

In summarizing these complex data, a standard fixed effects meta-analysis model could be meaningfully applied only to a small sub-group of studies: the relatively homogeneous group of eight trials comparing FSH/IUI with FSH/timed intercourse.

At least for this comparison, a reasonably precise estimate of effect could be made. There was no evidence of statistical heterogeneity, suggesting that factors which may have differed between studies had little effect on the overall conclusions. Certainly there were differences, particularly in terms of the definition of unexplained infertility and, in some cases, the intervention that was used, e.g. GnRHa was included in the ovulation induction protocol of only one study (Chung *et al.*, 1995). As was mentioned previously, statistical tests of heterogeneity have limited power, particularly when dealing with low event rates, as was the case here. However, given the apparent statistical homogeneity of these findings, the clinical differences identified may actually serve to increase the external validity or generalizability of their findings.

In considering all of the relevant data about these frequently combined therapies, 22 germane but diverse randomized controlled trials were identified, evaluating IUI with or without ovarian stimulation. Although the different interventions ruled out aggregation by standard meta-analysis, summarizing these data remains a priority, particularly because individual trials have insufficient power to adequately address the questions posed. The largest study identified in this review included 257 cycles (Chung *et al.*, 1995). In order to detect a clinically significant improvement in cycle fecundity from 2% in a control group to 8% among those treated, ~500 treatment cycles would be required (with the conventional assumptions of $\alpha = 0.05$ and $\beta = 0.20$). Logistic regression proved a useful tool in determining the independent effects of important variables such as FSH, IUI, clomiphene citrate, male factor and endometrosis associated infertility. With this technique it was possible to evaluate whether an interaction existed between FSH and IUI. It was also possible to estimate the effects of FSH and IUI treatment while holding constant the effects of diagnosis. The odds ratios generated for FSH and IUI use were between 2 and 3, in agreement with the crude aggregate data. As expected, these values are lower than those generally reported in uncontrolled studies which are far more prone to various types of bias, particularly in the selection of patients and inclusion of cycles for study.

The fact that clomiphene citrate failed to enter this regression model is interesting, given the results of a recent meta-analysis of six randomized controlled trials evaluating the use of clomiphene citrate in unexplained infertility (Hughes and Vandekerckhove, 1996). That review included trials with or without IUI and demonstrated a clinically and statistically significant benefit following clomiphene citrate treatment, with a common odds ratio for pregnancy per cycle of 2.5 (95% CI, 1.20, 4.6). Why did the current review fail to confirm this effect? First, different studies were included, based on the use of IUI as a criterion for the current report. As a result, only two studies (Deaton *et al.*, 1990; Arici *et al.*, 1994) were included in both reviews. Second, the relatively small number of cycles that these two trials contributed to the current review reduces the impact of any independent contribution of clomiphene citrate on overall fecundity. The difference between the conclusions of these two reviews with respect to clomiphene effectiveness underlines the importance of two critical steps in meta-analysis: adherence to explicit trial inclusion criteria and making inferences only on the basis of the specific question posed.

How should this overview be used in counselling patients with persistent infertility? In a couple with 4 years of primary male factor infertility, fecundability rate of 1% would be expected without treatment (Collins *et al.*, 1995). Here, the independent effects of FSH or IUI would increase fecundability to 2–3% and when used in combination to 5%. In a couple with 2 years of unexplained secondary infertility with an expected untreated cycle fecundity rate of 4% per month, FSH should double this value to 8%. When used in combination with IUI, a 5-fold increase to 20% would be expected. Particularly in the former group, in the light of the limited potential for enhancing fecundity and the risks of serious side-effects such as multiple pregnancy and OHSS, a clear presentation of the effectiveness of treatment is essential in obtaining fully informed consent.

One of the key findings of this review is that further studies of FSH/IUI versus no treatment are urgently needed. Significant side-effects require careful evaluation. In addition, comparisons of standard high intensity and reduced intensity trials are required to assess the appropriate degree of ovarian stimulation for maximum benefit with least risk and cost. Future therapy options may include further refinements of gonadotrophin preparations; also clinical applications may arise from the far-reaching research in the regulation of follicular development and ovulation. As new FSH/IUI trials are designed and treatment methods emerge for use in clinical practice, there is a need for controlled studies with superior designs. Positive features of such designs would include strict adherence to a secure method of randomization, since inadequate concealment may inflate estimates of effectiveness by as much as 30–40% (Schulz *et al.*, 1995). The use of parallel rather than cross-over designs is also favourable in the study of events, since the latter may exaggerate effectiveness of treatment by up to 35% (Khan *et al.*, 1996). Inclusion of all cycles in the denominator is clearly important, since selective exclusion of cycles with poor outcomes again tends to exaggerate effectiveness. Along the same lines, it is essential that the planned length of observation is equal for all comparison groups. While all of these features are desirable in future studies, the 22 trials summarized here provide the best available current evidence on which to give counsel and base clinical decisions.

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