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Intrauterine insemination: a systematic review on determinants of success

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Intrauterine insemination (IUI) is a frequently indicated therapeutic modality in infertility. Here, a systematic review of the literature was performed to examine the current status of clinical and laboratory methodologies used in IUI and the impact of female and male factors on pregnancy success. Emphasis was centred in questioning the following: (i) the value of IUI against timed intercourse; (ii) IUI application with or without controlled ovarian hyperstimulation; (iii) timing and frequency of IUI; and (iv) impact of various parameters (male/female) on the prediction of pregnancy outcome. The odds of multiple pregnancy occurrence and its risk factors, as well as the cost-effectiveness of IUI treatment compared with more complex assisted reproductive technologies are discussed. A computerized literature search was performed including Medline and the Cochrane library, as well as a crossover search from retrieved papers. It is concluded that although IUI is a successful contemporary treatment for appropriately selected cases of female and/or male infertility, further research is needed through well-designed studies to improve the methodologies currently utilized. Importantly, the clinical management of the infertile couple should be performed in an expedited manner taking into consideration the age of the woman, the presence of multifactorial infertility and cost-effectiveness of the available treatment alternatives.

Key words: cost-effectiveness/double insemination/female or male factors/intrauterine insemination/timed intercourse

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Introduction

Intrauterine insemination (IUI) is frequently used in the treatment of infertile couples with various causes of infertility, including cervical factor, ovulatory dysfunction, endometriosis, immunological causes, male factor and unexplained infertility. It is also the mode of treatment for various ejaculatory and coital problems. IUI is generally considered to be an intermediate step of low to moderate complexity before the application of more sophisticated assisted reproductive technologies (ART) such as IVF with or without ICSI (Oehninger, 2001).

The overall success rate of IUI remains controversial and depends on several factors, with published pregnancy rates ranging from as low as 5% to as high as 70% per patient; however, a 10–20% clinical pregnancy per cycle is an acceptable range for all aetiologies (Allen *et al*., 1985; Ombelet *et al*., 1995). IUI may be performed in natural cycles, as well as in conjunction with controlled ovarian hyperstimulation (COH). When combined with COH in unexplained infertility, cumulative pregnancy rates may approach those of ART (Hannoun *et al*., 1998; Aboulghar *et al*., 1999; Goverde *et al*., 2000).

In this review, daily dilemmas that the physician confronts in the clinical setting when indicating IUI therapy were examined, with special emphasis on the analysis of success and cost-efficiency of IUI performed for male and unexplained infertility. The objectives were to: (i) compare the success rate of IUI with that of timed intercourse (TI) and intracervical insemination (ICI); (ii) compare the success rate of IUI cycles according to the management strategy (natural versus COH); (iii) review the methods and strategies used to time IUI with ovulation; (iv)

identify the factors reported to determine IUI outcome; (v) review the risk factors reported for multiple pregnancy as a major drawback of IUI; and (vi) evaluate the cost-effectiveness of IUI as an option for infertility management

Research methods

A computerized search of the published literature was carried out, including Medline and the Cochrane library. The search was not limited to English language literature. Key words used for the search included: intrauterine insemination, IUI, timed intercourse, human, randomized controlled trial, pregnancy, success, prognosis, sperm, intracervical insemination, natural, controlled ovarian hyperstimulation, ovulation induction, double, repeat, frequency, logistic regression, morphology, method, separation, preparation, selection, wash, density, gradient, swim-up, sperm stimulants, pentoxifylline, multiple pregnancy and cost-effectiveness. Retrieved articles were reviewed for content and their references were used to identify other articles of interest. For the selected objectives (i–iii, vi), there were various randomized controlled trials as well as meta-analyses of them; therefore, studies with other types of design were not included. However, for the other objectives (iv, v) all published articles that could be retrieved were reviewed. The Breslow–Day method (Breslow and Day, 1980) was used to test statistical heterogeneity. If statistically homogeneous, data were pooled for each comparison and overall combined odds ratios (OR) with 95% confidence intervals (CI) were calculated using the Peto method (a fixed-effects model).

IUI versus TI/ICI

It has been documented that IUI is superior to TI in couples with male subfertility (Cohlen *et al*., 2000). The results obtained from six randomized controlled trials indicated that IUI significantly improved the probability of conception compared with TI with an OR of 2.5 and 95% CI of 1.6–3.9 in natural cycles (Kerin *et al*., 1984; Kerin and Quinn, 1987; Ho *et al*., 1989; te Velde *et al*., 1989; Martinez *et al*., 1990; Kirby *et al*., 1991). Seven randomized controlled trials showed a similar improvement in pregnancy with an OR of 2.2 (95% CI 1.4–3.6), in cycles of IUI combined with COH, against TI (Martinez *et al*., 1990, 1991; Evans *et al*., 1991; Crosignani and Walters, 1994; Nan *et al*., 1994; Melis *et al*., 1995; Gregoriou *et al*., 1996).

IUI is slightly more beneficial than TI or ICI in couples with unexplained infertility, in natural cycles. Based on two trials evaluating this issue in 1691 cycles, a borderline benefit was obtained by IUI over TI or ICI (OR = 2.7, 95% CI 1.0–4.4) (Kirby *et al*., 1991; Guzick *et al*., 1999). Intrauterine insemination combined with COH in unexplained infertility has also been proven to be superior to TI. A total of 980 cycles in seven prospective randomized studies (Crosignani *et al*., 1991; Evans *et al*., 1991; Martinez *et al*., 1991; Karlstrom *et al*., 1993; Zikopoulos *et al*., 1993; Gregoriou *et al*., 1995; Melis *et al*., 1995) yielded an improved probability of pregnancy (OR = 1.8, 95% CI 1.3–2.6) for couples with unexplained infertility treated with COH/IUI (Zeyneloglu *et al*., 1998). The studies included for this section and the level of evidence they provided are summarized in Table I.

Natural cycle versus ovarian stimulation in conjunction with IUI

In general, clomiphene citrate (CC) and/or gonadotrophins are used for COH in conjunction with IUI. For male subfertility, COH obtained by CC does not seem to increase the efficiency of IUI. Two randomized controlled trials (Martinez *et al*., 1990; Arici *et al*., 1994) were combined, which indicated the inefficiency of CC as a mode of COH for male subfertility (OR = 0.78, 95% CI 0.14–4.3). When gonadotrophins were used for COH/IUI on the other hand (Nulsen *et al*., 1993; Cohlen *et al*., 1998), the probability of conception was increased (OR = 2.0, 95% CI 1.1–3.8) as compared with IUI only (Cohlen *et al*., 2000). For unexplained infertility, COH by either CC (Arici *et al*., 1994) or gonadotrophins (Nulsen *et al*., 1993) improves the fecundity rate when compared with IUI alone. This is further supported by others (Guzick *et al*., 1999) who showed that the probability of pregnancy was 1.7 times more likely (95% CI 1.2–2.6) for COH/IUI when compared with IUI alone. In addition, pregnancy was 3.2 times more likely to occur (95% CI 2.0–5.3) when COH/IUI was compared with ICI (Guzick *et al*., 1999).

The studies included for this section and the level of evidence they provided are summarized in Table II, with the exception of two (Martinez *et al*., 1990; Guzick *et al*., 1999), which were already listed in Table I.

Timing/induction of ovulation, frequency of insemination

Timing of ovulation appears to be one of the crucial factors to determine the success of IUI therapy. It is the major goal of treatment to provide sperm that are capable of fertilizing the oocyte at the site of fertilization during a narrow time window, the so-called periovulatory period. Various strategies have been developed to achieve this goal. Urinary LH peak monitoring, hCG injection to stimulate ovulation and scheduling IUI with different frequencies at different time points are some of those strategies. hCG injection is a well-documented and accurate means of triggering ovulation by the time of optimal follicle maturation. However, it does not have superiority against spontaneous ovulation detected by urinary LH detection kits (Deaton *et al*., 1997; Zreik *et al*., 1999). Its main advantage is to give the physician a better control in the management of the cycle.

Several retrospective investigations in donor insemination programmes provided conflicting results on the impact of insemination frequency (single versus double) on pregnancy outcome (Matthews *et al*., 1979; Centola *et al*., 1990; Khalifa *et al*., 1995; Lincoln *et al*., 1995; Matilsky *et al*., 1998). In this review, three randomized controlled trials were found in the literature which aimed to investigate this topic on IUIs performed with husband's sperm (Table III). The earliest of these was conducted on 49 cycles of COH/IUI (in cycles stimulated with hMG), and a higher cycle fecundity rate in favour of double insemination was reported (Silverberg *et al*., 1992). The next prospective randomized study on 169 cycles similarly managed, however, did not report a difference in outcome between these two options of management (Ransom *et al*., 1994).

The most recent prospective randomized study on 449 COH/IUI cycles (with CC and gonadotrophins) indicated an increased cycle fecundity for double insemination performed 12 and 34 h

Table I. Studies that compared the efficiency of intrauterine insemination (IUI) and timed intercourse (TI) for patients with male subfertility or unexplained infertility

Reference	Study design	n[a]	Interventions	Outcomes	Comments
Crosignani *et al*., 1991	Random, cross-over, multicentre	90 (130)	IUI vs TI, COH cycles (method not specified), unexplained infertility	PR per completed cycle, 10/65 for IUI, 5/65 for TI, NSD	Randomization method, concealment of allocation, dropouts NS
Crosignani and Walters, 1994	Random, cross-over, multicentre	NS (97)	IUI vs TI, COH cycles (method not specified), male subfertility	PR per completed cycle, 7/48 for IUI, 0/49 for TI, $P = 0.006$	Drawing black or white disk from a blinded bag, dropouts NS
Evans *et al*., 1991	Random, cross-over, single centre	22 (44)	IUI vs TI, COH cycles by CC+hMG, male subfertility (including men with antisperm Ab), unexplained infertility	PR per completed cycle, 0/22 for IUI, 1/22 for TI, NSD	Sealed opaque envelopes, dropouts >10%
Gregoriou *et al*., 1996	Random, cross-over, single centre	62 (158)	IUI vs TI, COH cycles by hMG, male subfertility	PR per completed cycle, 15/130 for IUI, 5/128 for TI ($P < 0.05$)	Randomization method, concealment of allocation, dropouts NS
Guzick *et al*. , 1999	Random, parallel, multicentre	932 (2678)	IUI vs ICI, natural and COH cycles by pure FSH, male subfertility, unexplained infertility	PR per completed cycle, 35/717 for IUI, 14/706 for ICI, 54/618 for COH+IUI, 26/637 for COH+ICI ($P \leqslant 0.01$)	Permutated block procedure, concealment of allocation NS, dropouts >10%
Ho *et al*., 1989	Random, cross-over, single centre	47 (238)	IUI vs TI, natural cycles, male subfertility	PR per completed cycle, 0/114 for IUI, 1/124 for TI, NSD PR per completed cycle, 4/32 for IUI, 7/47 for TI, NSD	Randomization method, concealment of allocation, dropouts NS
Karlström *et al*., 1993	Random, multicentre	148 (148)	IUI vs TI, COH cycles by CC+hMG	PR per completed cycle, 4/32 for IUI, 7/47 for TI, NSD	Randomization method, concealment of allocation NS, dropouts <10%
Kerin *et al*., 1984	Random, cross-over, single centre	35 (77)	IUI vs TI, natural cycles, male subfertility	PR per completed cycle, 8/39 for IUI, 0/38 for TI by LH ($P < 0.05$), 1/34 for TI by sympto-thermal methods ($P = 0.02$)	Randomization method, concealment of allocation, dropouts NS
Kerin and Quinn, 1987	Random, cross-over, single centre	NS (509)	IUI vs TI, natural cycles, male subfertility	PR per completed cycle, 26/296 for IUI, 6/213 for TI ($P = 0.01$)	Randomization method, concealment of allocation, dropouts NS
Kirby *et al*., 1991	Random, cross-over, single centre	261 (996)	IUI vs TI natural cycles, male subfertility, unexplained infertility, cervical factor	PR per completed cycle, 30/542 for IUI, 13/453 for TI, NSD	Randomization method, concealment of allocation, dropouts NS
Martinez *et al*., 1990	Random, cross-over, single centre	38 (115)	IUI vs TI, natural and COH cycles by CC, male subfertility, unexplained infertility, cervical factor	PR per completed cycle, natural cycles: 3/32 for IUI, 0/34 for TI COH cycles: 5/35 for IUI, 1/31 for TI, NSD for both comparisons	Randomization method, concealment of allocation NS, dropouts 10%
Martinez *et al*., 1991	Random, cross-over, single centre	16 (56)	IUI vs TI, COH cycles by hMG, male subfertility, unexplained infertility	PR per completed cycle, 3/40 for IUI, 2/37 for TI by hCG injection, 3/34 for TI by LH surge, NSD	Randomization method, concealment of allocation NS, dropouts <10%
Melis *et al*., 1995	Random, parallel, single centre	184 (462)	IUI vs TI, COH cycles by pure FSH, male subfertility, unexplained infertility	PR per completed cycle, 33/226 for IUI, 35/236 for TI, NSD	Numbered, sealed envelopes
Nan *et al*., 1994	Random, cross-over, single centre	76 (202)	IUI vs TI, COH cycles by hMG, male subfertility	PR per completed cycle, 11/107 for IUI, 4/95 for TI, NSD	Sealed opaque envelopes, dropouts NS
te Velde *et al*., 1989	Random, cross-over, single centre	30 (202)	IUI vs TI, natural cycles, male subfertility, cervical factor	PR per completed cycle, 3/112 for IUI, 2/90 for TI, NSD	Sealed opaque envelopes, dropouts NS
Zikopoulos *et al*., 1993	Random, cross-over, single centre	48 (85)	IUI vs TI, COH cycles by GnRH (long luteal)+hMG	PR per completed cycle, 8/40 for IUI, 9/45 for TI, NSD	Randomization method, concealment of allocation, dropouts NS

[a]Values not in parentheses indicate number of couples; values in parentheses indicate number of completed cycles.
CC = clomiphene citrate; COH = controlled ovarian hyperstimulation; ICI = intracervical insemination; NS = not stated; NSD = no significant difference; PR = pregnancy rate.

Table II. Studies that compared the efficiency of natural and controlled ovarian hyperstimulation (COH) cycles, both in conjunction with intrauterine insemination (IUI), for patients with male subfertility or unexplained infertility[a]

Reference	Study design	n[b]	Interventions	Outcomes	Comments
Arici *et al*., 1994	Random, cross-over, single centre	29 (95)	Natural vs COH cycles by CC, both in conjunction with IUI, male subfertility, unexplained infertility	PR per completed cycle, male subfertility: 1/26 for COH, 1/26 for natural cycles; unexplained: 6/23 for COH, 1/20 for natural cycles, $P < 0.05$	Random number tables, concealment of allocation NS, very high dropout rate (61%)
Cohlen *et al*., 1998	Random, cross-over, single centre	74 (308)	Natural vs COH cycles by hMG, both in conjunction with IUI, male subfertility	PR per completed cycle, 21/153 for COH, 13/155 for natural cycles, NSD	Sealed opaque envelopes, dropout rate >10%
Nulsen *et al*., 1993	Random, cross-over, single centre	41 (111)	Natural vs COH cycles by hMG, both in conjunction with IUI, male subfertility, unexplained infertility, endometriosis	PR per completed cycle, male subfertility: 7/54 for COH, 1/41 for natural cycles, NSD; unexplained: 11/57 for COH, 1/41 for natural cycles, $P < 0.05$	Randomization method, concealment of allocation, dropouts NS

[a]Two of the studies included for this comparison are listed in Table I (Martinez *et al*., 1990 and Guzick *et al*., 1999).
[b]Values not in parentheses indicate number of couples; values in parentheses indicate number of completed cycles.
CC = clomiphene citrate; NS = not stated; NSD = no significant difference; PR = pregnancy rate.

after hCG administration, as compared with both single and double inseminations performed 34 and 60 h after hCG injection (Ragni *et al*., 1999). Combining all the cycles with single IUI (n = 265) and those with double IUI that were performed 12–43 h after hCG injection (n = 241) from these three studies, a double IUI seems to increase the probability of pregnancy (OR = 2.3, 95% CI 1.4–3.9). However, further randomized controlled trials with better design are needed to confirm this finding.

Prediction of pregnancy

Factors related to the couple

Despite the evident effectiveness of IUI for various causes of infertility—particularly cervical factor, ovulatory dysfunction and unexplained infertility—there is no consensus on the parameters that determine pregnancy success. Of several parameters that are claimed to have an important effect on IUI outcome, a parameter related to the couple is duration of infertility. In a retrospective analysis of 260 IUI cycles, logistic regression analysis revealed a 10% conception rate per cycle if the duration of fertility exceeded 72 months. For a shorter history of infertility, the conception rate was >20% (Tomlinson *et al*., 1996). However, another study, which was a randomized controlled trial based on a higher number of couples (and cycles), failed to demonstrate such an association (Goverde *et al*., 2000).

Female parameters

Another set of factors associated with IUI success is the aetiology of female infertility. It is a difficult task to isolate the influence of female factors on IUI outcome. One of the methods to achieve this goal is to select couples with no known cause of male infertility, prospectively. Another way to fulfil this task is by using logistic regression analysis, generally on retrospective data. This latter method was preferred in most of the studies mentioned in this section. In a retrospective review of 1728 cycles of IUI (Hendin *et al*., 2000), with data analysed by logistic regression, it was reported that the absence of history of any pelvic corrective surgery was one of the factors directly associated with a successful IUI outcome.

A recent retrospective report of 2473 cycles identified unexplained infertility and anovulation as favourable factors to predict the likelihood of pregnancy as compared with other aetiological factors, also by logistic regression analysis (Khalil *et al*., 2001). Another recent analysis of 495 cycles reviewed retrospectively by stepwise regression analysis revealed a negative impact of the diagnoses of endometriosis or tubal factor on IUI outcome (Montanaro *et al*., 2001). Based on these findings, a history of pelvic inflammation, regardless of the cause and whether its consequences are corrected or not, seems to decrease the likelihood of conception by IUI. On the contrary, unexplained and anovulatory causes of infertility are aetiologies with relatively better prognostic value in terms of pregnancy. Further data, preferentially in prospective format, are needed to reveal the impact of other types of female aetiological problems on IUI success.

Other significant female factors that are associated with a positive IUI outcome are age, number of pre-ovulatory follicles and endometrial thickness by the time of ovulation, as well as indicators of vascular compliance in ovarian, uterine and spiral arteries (Campana *et al*., 1996; Tomlinson *et al*., 1996; Tohma *et al*., 1997; Stone *et al*., 1999; Hendin *et al*., 2000; Tsai *et al*., 2000; Khalil *et al*., 2001). The age of the female partner is a well known, indirect indicator of oocyte quality, a consensus that was reached as a result of several reports of ART. Evidence from several studies also indicates it as a determinant of IUI outcome (Campana *et al*., 1996; Kang and Wu, 1996; Stone *et al*., 1999; Hendin *et al*., 2000; Khalil *et al*., 2001; Montanaro *et al*., 2001). Other factors reported generally depend on the presence of COH in conjunction with IUI. In this respect, most of the female parameters claimed to affect IUI outcome are secondary indicators of the presence, as well as the impact, of COH.

Table III. Studies that compared the efficiency of single and double intrauterine insemination (IUI)

Reference	Study design	n[a]	Interventions	Outcomes	Comments
Silverberg *et al*., 1992	Random, parallel, single centre	31 (37)	Single (34 h after hCG) vs double IUI (18 and 42 h after hCG), COH by hMG; male subfertility, unexplained infertility, ovulatory dysfunction, endometriosis, cervical factor	PR per completed cycle, 9/18 for double IUI, 2/19 for single IUI, $P = 0.02$	Computer-generated random numbers, concealment of allocation NS, dropout rate <10%
Ransom *et al*., 1994	Random, parallel, single centre	120 (169)	Single (35 h after hCG) vs double IUI (19 and 43 h after hCG), COH by hMG; male subfertility, unexplained infertility, ovulatory dysfunction, endometriosis, cervical factor, corrected tubal factor and other	PR per completed cycle, 11/79 for double IUI, 10/90 for single IUI, NSD	Random number table, concealment of allocation, dropouts NS
Ragni *et al*., 1999	Random, single centre	273 (449)	Single (34 h after hCG) vs double IUI (12 and 34 h after hCG) vs double IUI (34 and 60 h after hCG), COH by CC+pure FSH; male subfertility, unexplained infertility	PR per completed cycle, 10/149 for double IUI (34–60 h), 28/144 for double IUI (12–34 h), 13/156 for single IUI, $P < 0.01$ between double IUI (12–34 h) and others	Randomization method, concealment of allocation, dropout rate NS

[a]Values not in parentheses indicate number of couples; values in parentheses indicate number of completed cycles.
CC = clomiphene citrate; COH = controlled ovarian stimulation; NS = not stated; NSD = no significant difference; PR = pregnancy rate.

Male parameters

Similar to female determinants of IUI outcome, it is also difficult to isolate individual male parameters that influence the likelihood of pregnancy. To assess the real impact of male parameters to the outcome prospectively, all possible female factors should be eliminated in couples undergoing IUI therapy. It is quite impracticable to design and maintain such a study, and therefore most of the reports in the literature aiming to illuminate male determinants of IUI outcome are based upon regression analyses of retrospective data (Table IV).

Another factor which makes the review of literature difficult on this topic is a lack of standardization of semen analysis. Currently, criteria set by the World Health Organization seem to be the best standardization method for most of the parameters (World Health Organization, 1999), although different thresholds for some of these parameters have recently been proposed (Guzick *et al*., 2001). On the other hand, various counting chambers are used with different methodologies (e.g. manual versus computerized) to calculate these parameters. Consequently, the variation of results among centres may well be beyond acceptable, weakening the results reported by several studies. All in all, there is still a long way to go to standardize the methodology of basic semen analysis on a global basis.

The presence of severe male factor infertility is an indication to proceed to ART, rather than IUI (Oehninger, 2000). For male subfertility, however, IUI has a proven role as a clinical treatment modality, even though it has a lower success rate for this type of infertility (Oehninger *et al*., 1997; Khalil *et al*., 2001). Therefore, male parameters, especially those related to the ejaculate, may be more determinative for IUI outcome, especially for couples with known male subfertility. A combination of post-semen preparation sperm motility and concentration seems to be the major predictive factor, although other variables have also been proposed.

A total motile sperm count (TMSC) per insemination was reported to affect IUI outcome in 1115 cycles, with pregnancy rates of 2.1 and 6.7% for samples with TMSC per insemination $<1\times10^6$ and $\geqslant1\times10^6$ respectively (Campana *et al*., 1996). Another report on a retrospective analysis of 9963 IUI cycles also identified sperm motility in the inseminate as a major determinant of outcome, with <20% motility in inseminate significantly decreasing the possibility of pregnancy (pregnancy rates of 5.5 and 14.0% for motility in inseminate <20 and ⩾20% respectively) (Stone *et al*., 1999). The total number of motile sperm inseminated was the only variable found by a group of European investigators to significantly affect the pregnancy rate; values $<2\times10^6$ resulted in the poorest outcome (pregnancy rates of 4.6 and 9.2% for TMSC per insemination $<2\times10^6$ and $\geqslant2\times10^6$ respectively) (van der Westerlaken *et al*., 1998).

Logistic regression analysis of 1728 cycles also indicated post-wash sperm motility to be a determinant of IUI outcome, with a threshold of 40% (Hendin *et al*., 2000). The number of inseminated motile sperm was also reported as one of the six variables best predicting IUI outcome in a logistic regression analysis of 2473 cycles of the Scandinavian population (pregnancy rates 5.3 and 12.8% for TMSC per insemination $<5\times10^6$ and $\geqslant5\times10^6$ respectively) (Khalil *et al*., 2001).

It is very difficult to suggest a universal threshold for these parameters, since the inclusion criteria, methods of evaluation and even the pregnancy rate per cycle vary considerably among the studies mentioned. However, we believe that it would not be prejudiced to claim that the total motile sperm count and/or motility after semen processing are the parameters that have been cited most commonly as the predictors of IUI outcome. Instead of

Table IV. Studies that described male-derived determinants of IUI outcome

Reference	Study design	n[a]	Interventions	Statistics	Described determinants of IUI outcome
Campana *et al*., 1996	Retrospective analysis of IUI cycles during a 5 year period	332 (1115)	Natural and COH cycles by CC or hMG	χ^2, trend and life-table analyses	Cycle no. (first three cycles), age of woman (≤39 years), TMSC per insemination ($\geq 1\times10^6$)
Hendin *et al*., 2000	Retrospective analysis of IUI cycles during a 3 year period	533 (1728)	Cycle management not stated	Logistic regression, life-table analyses with Kaplan–Meier methods	Age of woman (<38 years), history of corrective pelvic surgery, motility in the inseminate (≥40%)
Karabinus and Gelety, 1997	Retrospective analysis of IUI cycles during a 2.5 year period	193 (538)	COH cycles by CC, hMG or CC+hMG; male subfertility, unexplained infertility, cervical factor, tubal factor, endometriosis, ovulation dysfunction	Least-squares methods using the general linear models	None. (No difference in PRs of groups with sperm morphology cut-off of 5, 10, 20 and ≥30%)
Khalil *et al*., 2001	Retrospective analysis of IUI cycles during a 9 year period	893 (2473)	COH cycles by CC, CC+FSH, CC+hMG, hMG, GnRHa+hMG Male subfertility, unexplained infertility, ovulatory dysfunction, one-sided tubopathology	Logistic regression, χ^2 analyses	Cycle no. (first cycle), number of follicles at the time of IUI (>1), COH protocol (CC+FSH and CC+hMG better than CC), TMSC per insemination ($\geq 5\times10^6$), time of insemination (day 13–16 of cycle), aetiology of infertility (ovulation dysfunction and unexplained infertility better than male subfertility)
Lindheim *et al*., 1996	Retrospective analysis of IUI cycles during a 4.5 year period. Couples who did not achieve pregnancy with <4 cycles, woman aged >40 years or with tubal disease, oligo-, astheno- or oligoasthenozoo-spermic men were not included	42 (176)	COH cycles by hMG, pure FSH, hMG+pure FSH	Student's *t*-test, χ^2 analyses	Sperm morphology by strict criteria (≥4%)
Matorras *et al*., 1995	Prospective analysis of IUI cycles during a 2 year period. Male partners' sperm morphology evaluated 1 month before the first IUI cycle	74 (271)	COH cycles by hMG or FSH; male subfertility, cervical factor, tubal factor, endometriosis, ovulatory dysfunction	Kolmogorov–Smirnov, Student *t*-tests, χ^2 analyses	None. (No difference in PRs of groups with sperm morphology cut-off of 4% or normal+slightly amorphous forms cut-off of 10%. This applies to both couples with male subfertility and whole population)
Montanaro *et al*., 2001	Retrospective analysis of IUI cycles during a 5.5 year period	273 (495)	Natural and COH cycles by CC, hMG or CC+hMG. Male subfertility, unexplained infertility, ovulatory dysfunction, cervical factor, endometriosis, combined male and female factors	Student's *t*-test, logistic regression	Age of woman (≤35 years), number of follicles (≥2), motility before sperm preparation (>50%), sperm morphology by strict criteria (>4%), absence of endometriosis or tubal factor
Ombelet *et al*., 1997	Retrospective analysis of IUI cycles during a 7 year period	373 (792)	COH cycles by CC; male subfertility, unexplained infertility, cervical factor, endometriosis, ovulatory dysfunction, combined male and female factors	χ^2, Student's *t*-test, ROC curve analyses	Sperm morphology by strict criteria (≥4%) in cases where TMSC per insemination $<1\times10^6$
Stone *et al*., 1999	Retrospective analysis of IUI cycles during a 6 year period	~3200 (9963)	Natural and COH cycles by CC, CC+FSH, CC+hMG, CC+FSH+hMG, Estrace+FSH+hMG, FSH, FSH+hMG, GnRHa+FSH+hMG, hMG	ANOVA, χ^2 analyses	Cycle no. (first three cycles), age of woman (≤32 years), number of follicles at the time of IUI (≥2), TMSC per insemination ($\geq 2\times10^6$), motility in the inseminate (≥20%)

Table IV. *Continued*

Reference	Study design	n[a]	Interventions	Statistics	Described determinants of IUI outcome
Toner *et al*., 1995	Retrospective analysis of IUI cycles during a 1 year period	126 (395)	COH cycles by CC or hMG; male subfertility, unexplained infertility, ovulatory dysfunction, cervical factor, peritoneal factor, endometriosis	ANCOVA, χ^2 analyses, logistic regression, ROC analyses	Sperm morphology by strict criteria (>14%), linearity of movement TMSC per inseminate ($\geq 2\times10^6$)
van der Westerlaken *et al*., 1998	Retrospective analysis of IUI cycles during a 8 year period	566 (1763)	COH cycles by CC; male subfertility, unexplained infertility, ovulatory dysfunction, one-sided tubopathology	χ^2 analysis	TMSC per inseminate ($\geq 2\times10^6$)

[a]Values not in parentheses indicate number of couples; values in parentheses indicate number of completed cycles.
CC = clomiphene citrate; COH = controlled ovarian hyperstimulation; PR = pregnancy rate; ROC = receiver-operating characteristic; TMSC = total motile sperm count.

trying to determine a universal threshold, therefore, we recommend that each centre should evaluate its results and define a threshold for its population and laboratory.

Evidently, morphology of sperm assessed by strict criteria is one of the best predictors of IVF (Kruger *et al*., 1986; Oehninger *et al*., 1988; Enginsu *et al*., 1993). However, its predictive power for IUI outcome is not a matter of consensus. One of the reports claiming it as a predictive factor for IUI outcome relies on the data obtained from 176 cycles of 42 couples, indicating a 28.3-fold (95% CI 3.2–250.5) greater likelihood of achieving pregnancy with a favourable sperm morphology (Lindheim *et al*., 1996). Similarly, previous data from 395 IUI cycles accomplished at one of our centres also indicated a predictive capacity for sperm morphology (Toner *et al*., 1995). A recent logistic regression analysis of 495 cycles also demonstrated sperm morphology as one of the four variables to predict IUI outcome (Montanaro *et al*., 2001). Morphology has also been proposed to have a good predictivity for cases with $<1\times10^6$ sperm in the inseminate (Ombelet *et al*., 1997). However, similar pregnancy rates were also reported for samples with poor and normal morphology in both prospective (271 cycles) (Matorras *et al*., 1995) and retrospective studies (538 cycles) (Karabinus and Gelety, 1997).

Based on existing data from the six studies mentioned above, a recent meta-analysis yielded a risk difference of –0.07 (95% CI –0.11 to –0.03) between pregnancy rates achieved in patients with poor (≤4%) and normal (>4%) sperm morphology (Van Waart *et al*., 2001). A risk difference of zero indicated the absence of any effect of poor sperm morphology on the outcome, whereas a negative risk difference—which was the case here—indicated a negative impact of poor sperm morphology on the outcome. The exclusion of zero from the 95% CI made this impact significant. The higher the absolute value of risk difference, the higher is the impact. Since both the impact calculated was relatively small and the majority of the studies evaluated were retrospective, we believe that prospective, more powerful, well-designed studies are needed to definitively establish the role of sperm morphology in predicting IUI outcome.

Several other parameters related to other features of sperm are currently under investigation. So far, motion characteristics evaluated by computer-assisted sperm analysis have not indicated a consistent prognostic value. With the advent of different methods of evaluation, prognostic values of several other sperm parameters, such as those related to energy metabolism, membrane characteristics and nuclear maturity/normality of sperm, will yet need to be determined. More data are also needed to examine the predictive value of the more validated available sperm functional assays, i.e. sperm–zona pellucida binding tests and induced-acrosome reaction testing, on IUI outcome (ESHRE Andrology Special Interest Group, 1996; Oehninger *et al*., 2000).

Sperm processing methods

There is no consensus on the use of sperm processing methodologies for IUI. Although most centres perform a simple wash in culture medium with or without protein supplementation, other programmes perform IUI following separation of purified sperm populations after swim-up, density gradient centrifugation (DGC) or other methods (Daya *et al*., 1987; Gonzales and Pella, 1993; Zimmerman *et al*., 1994; Centola *et al*., 1998). Only three published randomized controlled trials could be found which compared different methods of sperm preparation for IUI (Karlstrom *et al*., 1991; Carrell *et al*., 1998; Dodson *et al*., 1998). The first two studies were included to compare the efficiencies of two methods, wash and DGC (Table V), and the third study (Karlström *et al*., 1991) was excluded as it compared swim-up with self-migration in sodium hyaluronate. Combined data from the two studies (465 cycles in 443 couples) yielded a borderline benefit (OR = 1.7, 95% CI 1.0–2.9) in favour of DGC. Further randomized controlled comparisons are warranted to confirm these results. Until then, the selection of the sperm processing technique should be tailored to the individual case.

Unfortunately, the in-vitro use of substances to stimulate sperm functions and/or metabolic activities has not yielded expected results. Such stimulants have included, among others, xanthine derivatives (e.g. caffeine, pentoxifylline and others), adenosine derivatives and analogues, kinin-enhancing drugs, follicular fluid and prostaglandins (Cummins and Yovich, 1993; Mbizvo *et al*., 1993; Nassar *et al*., 1998, 1999; Vandekerckhove *et al*., 2000; Brown *et al*., 2001; Toner *et*

Table V. Studies that compared wash and density gradient centrifugation as sperm preparation methods for intrauterine insemination

Reference	Study design	n[a]	Interventions	Outcomes	Comments
Carrell *et al*., 1998	Random, cross-over, multicentre	363 (361)	Wash vs DGC (90 and 35% double-layer Percoll); natural and COH cycles (CC or gonadotrophins); male subfertility, unexplained infertility, wide range of male- and/or female-related disorders; samples with $<20\times10^6$ progressive motile sperm not included	PR per completed cycle, 33/204 for DGC, 14/157 for wash, $P=0.04$	Randomization method, concealment of allocation, dropout rate NS
Dodson *et al*., 1998	Random, neither cross-over nor parallel (cycle-specific randomization), single centre infertility, endometriosis, minor pelvic adhesions; patients with severe oligo-zoospermia not included (threshold NS)	80 (153)	Wash vs DGC (90 and 45% double-layer Percoll); COH cycles only (gonadotrophins); male subfertility, unexplained	PR per completed cycle, 10/51 for DGC, 8/53 for wash, NSD	Computer-generated random numbers, concealment of allocation, dropout rate NS

[a]Values not in parentheses indicate number of couples; values in parentheses indicate number of completed cycles.
COH = controlled ovarian hyperstimulation; DGC = density gradient centrifugation; NS = not stated; NSD = no significant difference; PR = pregnancy rate.

al., 2001). Although some of these substances clearly improve sperm functions under in-vitro conditions, their generalized use in the IUI setting has not been successful. More studies are needed to optimize such treatments.

Multiple pregnancy

Multiple pregnancy imposes a less favourable obstetric and perinatal outcome. There has been an increased prevalence of multiple births during the past two decades. A population survey from The Netherlands indicated that the delay in achieving pregnancy and the use of fertility-promoting therapies were responsible for this increase in prevalence in a given country (Steegers-Theunissen *et al*., 1998). The attitudes of couples undergoing IUI are especially more favourable towards multiple gestational pregnancies than those of IVF patients, although they have an accompanied increase in tendency for multifetal pregnancy reduction (Goldfarb *et al*., 1996). Thus, a multiple pregnancy rate of 14–39% has been reported in this high-risk group of couples (Valbuena *et al*., 1996; Goldfarb *et al*., 1997; Tur *et al*., 1997).

Major factors identified to predict multiple pregnancy outcome include peak estradiol level and number of pre-ovulatory follicles on the day of hCG, which are basically indirect indicators of COH (Pasqualotto *et al*., 1999; Dickey *et al*., 2001). Aspiration of supernumerary follicles before IUI has been associated with a multiple pregnancy rate of 10.4% without decreasing the overall pregnancy rate, though it has not been accepted as a routine practice (De Geyter *et al*., 1996).

Cost-effectiveness

One group (Peterson *et al*., 1994) compared COH/IUI (using hMG) to ART [IVF, gamete intra-Fallopian transfer (GIFT) and zygote intra-Fallopian transfer (ZIFT)] as a treatment modality in a prospective, non-randomized fashion. Using meta-analysis and theoretical assumptions, these authors found that one cycle of COH/IUI was inferior to that of ART, two cycles were comparable with IVF or ZIFT and inferior to GIFT, three cycles were superior to IVF or ZIFT and comparable with GIFT, and four cycles were superior to ART. They also reported that one cycle of IVF was more expensive than four cycles of COH/IUI (with hMG). Other investigators analysed the cost-effective treatment of the infertile couple. Of these, one group (Van Voorhis *et al*., 1998) concluded that IUI and COH/IUI (with CC or hMG) were similar procedures in terms of cost per delivery and all were more cost-effective than ART. Some factors, such as age of the female partner and number of inseminated motile sperm, were found to be determinants of cost for individual couples.

Two randomized controlled trials supported the cost-effectiveness of IUI and COH/IUI against IVF (Table VI). The first suggested IVF not to be a cost-effective first-line treatment in couples with unexplained infertility compared with a standard infertility treatment algorithm, with mean costs per pregnancy of US$38 021 and US$16 725 respectively (Karande *et al*., 1999). The second randomized controlled trial did not find any difference between cumulative pregnancy rates of IUI and COH/IUI, as well as those of both and IVF for unexplained and non-severe male infertility (Goverde *et al*., 2000). The mean costs per pregnancy resulting in at least one live birth were 10 661 and 27 409 Dutch guilders (US$5108 and US$13 132) for COH/IUI and IVF respectively. The impact of the female partner's age on the cost of any treatment was also confirmed. The differences in costs between these two trials might result from the health policies administered in the countries where trials have been undertaken.

Unfortunately, neither of these studies evaluated the costs resulting from the antenatal care—an important issue that would contribute to the costs of the treatment options—and especially to

Table VI. Studies that compared the cost-efficiency of intrauterine insemination (IUI) and IVF

Reference	Design	n[a]	Interventions	Outcomes	Cost[b]			Comments
					Group I	Group II	Group III	
Karande *et al.*, 1999	Random, parallel, single centre (USA)	96 (157)	SITA vs IVF; SITA includes six cycles of COH/IUI (three by CC, three by gonadotrophins) followed by four IVF cycles (stimulation protocols NS); male subfertility, unexplained infertility, ovulatory dysfunction, endometriosis, tubal factor, pelvic adhesions, uterine factor or combined	Cost per pregnancy, multiple pregnancy rates: SITA: 18% (three pairs of twins + two sets of triplets); IVF: 38% (three pairs of twins +two sets of triplets)	SITA 16 725	– –	IVF 38 021	Sealed envelopes, dropout rate: 34% (28% for SITA, 41% for IVF)
Goverde *et al.*, 2000	Random, parallel, single centre (Europe)	258 (963)	IUI vs COH/IUI vs IVF COH by pure FSH for IUI, GnRHa (triptorelin) long luteal or flare-up+hMG or pure FSH for IVF; male subfertility, unexplained infertility	Cost per pregnancy resulting in at least one live birth; multiple pregnancy rates: IUI 0%; COH/IUI 29% (nine pairs of twins). IVF 21% (six pairs of twins + one set of triplets)	IUI 4035	COH/IUI 5108	IVF 13 132	Computer-generated random numbers, numbered, masked and sealed envelopes, drop-out rate: 29% (22% for IUI, 19% for COH/IUI, 45% for IVF)

[a]Values not in parentheses indicate number of couples; values in parentheses indicate number of started cycles.
[b]Costs in US$.
CC = clomiphene citrate; COH = controlled ovarian hyperstimulation; NS = not stated; SITA = standard infertility treatment algorithm.

that of multiple pregnancies achieved. In addition to antenatal care, other costs such as those of neonatal intensive care should also be taken into account, since most multiple pregnancies end with premature delivery. We are not aware of any published study investigating such further outcomes of various treatment modalities for infertility. In order to establish more realistic numbers for cost-efficiency analysis, as well as to understand the consequences of different therapeutic options in a public health perspective, there is a current need for such studies with a comprehensive design. These results also need to be re-examined in the light of the continuing increase in pregnancy rates in IVF, especially in women aged <35 years (35% live birth/cycle) (Society for Assisted Reproductive Technology, American Society for Reproductive Medicine, 2002).

Conclusions

The treatment of infertility with IUI is a very frequently used approach. In our programmes, twice as many IUI cycles are performed on a yearly basis than ART procedures. There are, however, no national registries or reports that depict IUI numbers and success. This review demonstrates that there are consolidated facts about IUI therapy, but generally speaking more questions have been raised than questions answered. It can be concluded that IUI is a very useful and cost-effective treatment modality for some infertility aetiologies. Cumulative pregnancy rates by the fourth to sixth cycle are generally considered as optimal. IUI is superior to TI for non-severe male factor and unexplained infertility.

Several factors have been proposed to influence the likelihood of pregnancy after IUI. Of these, duration of infertility, age of the female partner, history of pelvic inflammation (such as pelvic inflammatory disease, surgery or endometriosis) and presence of a severe male factor have a negative impact on outcome, whereas cervical factor, unexplained and anovulatory causes of infertility are more favourable. The addition of COH to IUI, especially with gonadotrophins, increases its efficiency at the cost of increased expense and risk of multiple pregnancies, which is the major drawback of this mode of treatment. The use of GnRH agonists as adjuvants in gonadotrophin-treated cases, or GnRH antagonists in cycles treated with CC/gonadotrophins or gonadotrophins alone, may be indicated in selected cases to optimize ovarian response. The optimal timing of insemination(s) after hCG administration and the need and adequacy of luteal phase support should be further investigated.

Of the parameters related to the inseminate, those related to motility—such as percentage or actual number of motile sperm—appear to have an important impact on outcome. The percentage of sperm with normal morphology according to strict criteria also seems to be correlated with a favourable IUI outcome, although this correlation needs further confirmation. Other semen parameters related to a successful IUI outcome need to be evaluated.

These include, but are not limited to, volume of the inseminate, the degree of sperm DNA fragmentation, plasma membrane characteristics, motion parameters and metabolism, and the impact of functional deficiencies such as an impaired zona pellucida binding capacity and limited response to the physiological agonists of the acrosome reaction (Oehninger, 2000).

Purification of selected sperm populations by new methodologies and use of stimulants of defined sperm functions will hopefully be added to the clinical armamentarium in the near future. In addition, efforts should be geared toward the identification of local molecular regulatory factors within the uterine cavity and Fallopian tubes that determine the optimum environment for fertilization at the time of insemination, followed by successful implantation, likely to play a significant role in determining IUI success.

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