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Intrauterine insemination after ovarian stimulation with clomiphene citrate: predictive potential of inseminating motile count and sperm morphology

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This retrospective study aimed to evaluate the prognostic value of the inseminating motile count (IMC) and sperm morphology (using strict criteria) on success rates after homologous intrauterine insemination (IUI) combined with clomiphene citrate (CC) stimulation. A total of 373 couples underwent 792 IUI cycles in a predominantly (87.4%) male subfertility group. The overall cycle fecundity (CF) and baby take-home rate (BTH) was 14.6 and 9.9% respectively. The cumulative CF and BTH (per couple) after three cycles were 30.6 and 21.1% respectively. Overall, sperm morphology and IMC were of no prognostic value using receiver operating characteristic (ROC) curve analysis, but after classifying the study population into different subgroups according to IMC, sperm morphology turned out to be a valuable prognostic parameter in subgroup 1, i.e. IMC $<1\times10^6$. In this subgroup, no pregnancies were seen when the morphology score was <4% and the mean value of sperm morphology was significantly different in the pregnant (8.3%) versus non-pregnant group (5.0%; $P<0.05$). The cumulative CF and BTH after three IUI cycles were comparable for all couples with the exception of those cases in which the IMC was $<1\times10^6$ with a morphology score of <4% normal forms. We recorded only two twin pregnancies (2.5%) and no moderate or severe ovarian hyperstimulation syndrome. We conclude that in a selected group of patients without CC resistance and normal ovarian response following CC stimulation [maximum of three follicles with a diameter of >16 mm at the time of administration of human chorionic gonadotrophin (HCG)], IUI combined with CC–HCG can be offered as a very safe and non-expensive first-line treatment, at least with an IMC of $>1\times10^6$ spermatozoa. In cases with $<1\times10^6$ spermatozoa, CC–IUI remains important as a first-choice therapy provided the morphology score is 4%.

Key words: clomiphene citrate/HCG/intrauterine insemination/ovarian stimulation/sperm morphology

Introduction

The rationale for homologous intrauterine insemination (IUI) with washed spermatozoa involves bypassing the cervical mucus barrier resulting in an increased gamete density at the site of fertilization.

Renewed interest in IUI is undoubtedly the consequence of better washing procedures, enhancing the quality of a sperm sample. These washing procedures are necessary to remove prostaglandins, infectious agents and antigenic proteins. Another substantial advantage of these techniques is the removal of non-motile spermatozoa, leukocytes and immature germ cells. This might contribute to enhanced sperm quality by decreased release of lymphokines and/or cytokines and a reduction in the formation of free oxygen radicals after sperm preparation. This results in better sperm fertilizing ability *in vitro* and *in vivo* (Aitken and Clarkson, 1987). Finally, this may lead to higher success rates after IUI in male subfertility cases, as described previously by Martinez *et al.* (1993) and Ombelet *et al.* (1995b).

Despite the extensive literature on the subject of artificial homologous insemination, controversy still surrounds the effectiveness of this very popular treatment procedure (Kerin *et al.*, 1984; Cruz *et al.*, 1986; Dodson *et al.*, 1987; Sunde *et al.*, 1988; te Velde *et al.*, 1989; Horvath *et al.*, 1989; Ho *et al.*, 1992; Crosignani and Walters, 1994; Nan *et al.*, 1994; Aribarg and Sukcharoen, 1995; Melis *et al.*, 1995; Ombelet *et al.*, 1995b; Tomlinson *et al.*, 1996).

We certainly need controlled prospective trials to determine the real value of this less expensive method of infertility treatment. At the start of assisted reproductive technologies (ART) in a certain couple, we should be able to give a realistic prognosis as to what the couple may expect from first-step options such as the combination of IUI and clomiphene citrate (CC) stimulation. Tomlinson *et al.* (1996) reported on a statistical model for IUI success, but in this study male factor subfertility was largely excluded. According to this study, follicle number, endometrial thickness, duration of subfertility and progressive motility (in the initial sample) were the most significant IUI variables in predicting success.

Previous reports have demonstrated poor results when IUI was performed in natural cycles and these negative findings were independent of the indication for IUI (Irianni *et al.*, 1990; DiMarzo *et al.*, 1992). Furthermore, other studies on IUI results after ovarian stimulation showed a significantly higher monthly fecundity after human menopausal gonadotrophin (HMG) compared with CC treatment (Tarlatzis *et al.*, 1991; Irianni *et al.*, 1993; Martinez *et al.*, 1993; Ombelet *et al.*, 1996).

Published data concerning the important issue of cost–benefit analysis, comparing different methods of ART are rare. According to these studies (Robinson *et al.*, 1992; Peterson *et al.*, 1994; Comhaire, 1995; Dodson, 1995), the costs of in-vitro fertilization (IVF) with embryo transfer, gamete intra-

Table I. Main characteristics of the study-population (mean value ± SD). For the diagnostic classification, total number and percentages (in parentheses) of couples are indicated.

	Total	Pregnant	Not pregnant	Significance (*t*-test)
No. subjects	373	116	257	
Female age (years)	29.5 ± 3.4	29.1 ± 3.1	29.7 ± 3.5	NS
Male age (years)	31.6 ± 4.7	30.8 ± 4.6	31.6 ± 4.7	NS
Duration of subfertility (months)	32.3 ± 22.4	30.6 ± 23.5	33.9 ± 21.8	$P < 0.05$
Sperm parameters				
Concentration ($\times 10^6$)	43.6 ± 43.8	44.2 ± 52.2	43.2 ± 39.6	NS
Total motility (%)	50.5 ± 18.8	52.7 ± 17.7	49.5 ± 19.2	NS
Morphology (%)	7.4 ± 4.0	7.8 ± 3.9	7.2 ± 4.0	NS
IMC ($\times 10^6$) (after washing)	10.5 ± 14.0	11.4 ± 12.8	10.2 ± 14.5	NS
Diagnostic classification				
Idiopathic	29 (7.8)	7 (6.0)	22 (8.6)	NS
Male factor only	206 (55.2)	68 (58.6)	138 (53.3)	NS
Female factor only				
cervical	10 (2.7)	3 (2.6)	7 (2.7)	NS
endometriosis	7 (1.9)	2 (1.7)	5 (1.9)	NS
Male + female factor	121 (32.4)	36 (31.0)	85 (33.1)	NS

IMC = inseminating motile count, NS = not significant.

Fallopian transfer (GIFT) and zygote intra-Fallopian transfer (ZIFT) are four to seven times the cost of a single HMG/IUI cycle. Since ovarian stimulation with CC is undoubtedly less expensive when compared with HMG, once again, results with IUI after CC–human chorionic gonadotrophin (HCG) stimulation should be very interesting.

Considering the increased incidence of multiple gestation after HMG–IUI versus CC–IUI (Ombelet *et al.*, 1996) and taking into account the higher risk of ovarian hyperstimulation after HMG versus CC, we believe that the use of IUI after clomiphene citrate stimulation can be regarded as a first-step procedure in selected cases of human subfertility. Most interesting would be to determine the influence of the inseminating motile count (after sperm washing procedure) and sperm morphology in an IUI programme with the husband's semen.

This retrospective study aimed to establish the influence of the inseminating motile count (IMC) and sperm morphology on the success rate in CC–IUI cycles in a selected group of patients with normal ovarian response to CC stimulation, in order to determine limits below which the chances of IUI success are limited.

Materials and methods

During a period of 64 months, from January 1989 until December 1995, homologous artificial insemination combined with CC stimulation was used in 373 subfertile couples during 792 treatment cycles. Therapeutic data were compiled and analysed retrospectively.

The average subfertility period for our couples was 32.3 months (range 13–180) with a mean age of 31.6 years for men (range 23–62) and 29.5 years for their partners (range 20–41) (Table I).

All patients had undergone an infertility work-up including ultrasound monitoring of folliculogenesis, luteal phase concentrations of progesterone, hysterosalpingogram indicating a normal uterine cavity and at least one patent tube, and a mid-cycle post-coital test. Antisperm antibodies were analysed in both partners using an enzyme-linked immunosorbent assay (IBL,RE 52029; Eurogenetics, Tessenderlo, Belgium). Male subfertility was diagnosed when sperm abnormalities were found on at least two recent sperm examinations.

Semen specimens were collected by masturbation in a plastic container after an abstinence period of 2–4 days for the first sample and 24 h for the second sample. It was delivered to the laboratory within 1 h of collection and, after complete liquefaction, the semen was analysed according to the World Health Organization guidelines (WHO, 1987), except for sperm morphology. For this parameter we used the strict criteria as described by Kruger *et al.* (1986, 1988). Our cut-off level for normality was 10%; this value was based on a prospective study comparing fertile and subfertile populations, using receiver operating characteristic (ROC) analysis as the statistical tool (Ombelet *et al*., 1997).

In the majority of cases (652/792 cycles, 82.3%), a double insemination was performed periovulatory, as described before (Ombelet *et al.*, 1996). Since we found no significant difference between the first and second sample and because a previous study showed no difference in success between double and single insemination in the CC stimulated cycles (Ombelet *et al.*, 1995a), only the results of the semen sample inseminated 36–40 h after HCG were considered for evaluation. A laparoscopy and hysteroscopy were performed when endometriosis was suspected, with a history of previous abdominal surgery or when the hysterosalpingogram revealed no clear diagnosis of bilateral tubal patency.

Patient selection

The couples were grouped into four major categories:

Unexplained infertility

This was considered if no abnormalities could be found during the infertility work-up.

Female factor

(i) Cervical factor: this diagnosis was made only when a well-timed post-coital test was negative (fewer than three motile spermatozoa per high power field) and no signs of infection or cervical antisperm antibodies were present; (ii) endometriosis: in almost 50% of our patients a laparoscopy was performed, mostly because endometriosis was suspected after history of patient's complaints. We classified our patients according to the revised American Fertility Society guidelines (AFS, 1985); (iii) ovulatory dysfunction: patients with a history of oligomenorrhoea or amenorrhoea, an abnormal basal body temperature (BBT) chart, abnormal findings midcycle (ultrasonography, hormonal) and a low serum progesterone concentration in the pre-menstrual period were categorized as having ovulatory disorders.

Table II. Cycle fecundity (CF) and baby take-home rate (BTH) in the different inseminating motile count (IMC) subgroups (1, 2, 3, 4)[a], according to the cycle number (χ^2 statistics for differences among subgroups). Figures in parentheses are percentages

IMC Cycle number	Subgroup 1			Subgroup 2			Subgroup 3			Subgroup 4			Total		
	n	CF	BTH	*n*	CF	BTH	*n*	CF	BTH	*n*	CF	BTH	*n*	CF	BTH
1	56	4 (7.1)[b]	3 (5.4)[b]	37	5 (13.5)	3 (8.1)	156	29 (18.6)	19 (12.2)	124	31 (25.0)[b]	22 (17.7)[b]	373	69 (18.5)	47 (12.6)
2	52	5 (9.6)	3 (5.8)	31	6 (19.4)	4 (12.9)	125	17 (13.6)	13 (10.4)	92	9 (9.8)	7 (7.6)	300	37 (12.3)	27 (9.0)
3	13	1 (7.7)	1 (7.7)	12	1 (8.3)	1 (8.3)	37	3 (8.1)	2 (5.4)	20	3 (15.0)	1 (5.0)	82	8 (9.8)	5 (6.1)
4 or more	7	0	0	6	1 (8.3)	0	15	1 (6.7)	0	9	0	0	37	2 (5.4)	0
	128	10 (7.8)[c]	7 (5.5)[c]	86	13 (15.1)	8 (9.3)	333	50 (15.0)	34 (10.2)	245	43 (17.6)[c]	30 (12.2)[c]	792	116 (14.6)	79 (10.0)

[a]Subgroups defined by number of motile spermatozoa recovered after washing. Subgroup 1: $<1\times10^6$; subgroup 2: $\geqslant1-<2\times10^6$; subgroup 3: $\geqslant2-<10\times10^6$; subgroup 4: $\geqslant10\times10^6$.
[b]Cycle 1, subgroup 1 versus subgroup 4: $P < 0.05$ for CF and BTH.
[c]All cycles, subgroup 1 versus subgroup 4: $P < 0.05$ for CF and BTH.

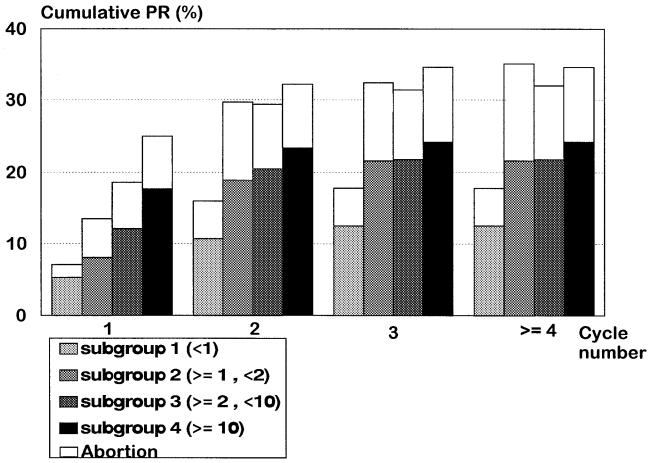

Figure 1. Cumulative cycle fecundity (CF) and baby take-home rate (BTH) in the different subgroups (1, 2, 3, 4).

Male factor

A male factor was diagnosed if the sperm concentration was $<20\times10^6$/ml, total progressive motility (grade a + b) <50% and/or sperm morphology <10% normal forms according to the strict criteria. We only excluded those patients with a pre-treatment trial recovery of <100 000 motile spermatozoa after washing procedure.

Combined female and male factor

Immunological male subfertility cases due to seminal sperm surface antibodies (>50% binding) were excluded from the study.

Ovarian stimulation

For ovarian stimulation all patients received CC–HCG. A daily dose of 50 mg was administered for 5 days starting on day 4–5 of the cycle. At the 10th day of the cycle, follicular ultrasonography and serum oestradiol determination was carried out. HCG (5000 IU; Profasi,® Serono, Brussels, Belgium or Pregnyl,® Organon, Oss, The Netherlands) was given when the average diameter of the dominant follicle was ⩾19 mm in diameter. The patients received no luteal support. Only patients with a normal ovarian response (absence of CC resistance and maximum of three follicles with a diameter of >16 mm at the time of HCG administration) and at least two consecutive IUI procedures (if no pregnancy occurred during the first cycle), were included.

Insemination procedure

In most cycles (632 or 79.8%), two inseminations were performed on two consecutive days in the periovulatory period. The inseminations were timed 14–18 h and 36–40 h post-HCG (Ombelet *et al.*, 1996).

The washed motile fraction was inserted up to the uterine fundus and the spermatozoa were gently expelled into the uterine cavity (defined as high intrauterine insemination). Subsequently the catheter was withdrawn and the patient remained in the supine position for 30 min after the insemination.

Semen examination and preparation

Semen samples were analysed after complete liquefaction according to the WHO guidelines, except for sperm morphology. At least 200 spermatozoa situated in more than five different fields were evaluated and the percentage of sperm cells with complete normal forms was defined as the morphology index. Morphology scores (percentage of normal forms) used in this study were: (i) the morphology score of the treatment cycle in which the patient became pregnant or (ii) the mean of different morphology scores during consecutive IUI trials when no pregnancy occurred. The same applied to the inseminated motile count.

Since no significant difference was found between sperm parameters of the first versus second day sample (when double insemination was performed), we examined only the results of the second sample during investigation of the influences of sperm morphology and IMC on success rate after IUI.

Spermatozoa were prepared by the conventional swim-up technique. After liquefaction all fresh semen samples were diluted with 5 ml Earle's balanced salt solution (EBSS; Life Sciences International, Paisley, UK) supplemented with penicillin, streptomycin and pyruvate (1 ml sample to 2 ml EBSS) and centrifuged at 200 *g* for 10 min. The pelleted spermatozoa were centrifuged once more after resuspension in supplemented EBSS. Supernatants were discarded again. For normal semen specimens (count $>20\times10^6$/ml and total progressive motility >50%) the pellets were gently layered over with 2 ml EBSS supplemented with penicillin, pyruvate and 0.3% human serum albumin (HSA; Sigma Chemical Co., St Louis, USA) and incubated at 37°C. The most motile fraction was selected by gentle aspiration of 1–1.5 ml of the supernatant. Sperm concentration and motility were counted once again. Finally this fraction was concentrated to 0.3 ml by centrifugation.

For subnormal sperm samples (count $<20\times10^6$/ml and initial total progressive motility <50%), we performed only one wash procedure, followed by centrifugation of the pellets on a mini-Percoll gradient (1 ml 95%–1 ml 50% Percoll; Fertipro, Lotenhulle, Belgium) at 200 *g* for 20 min. The 95% fraction was recovered and washed twice with EBSS + penicillin and pyruvate (penicillin and pyruvate; Life Science International, Paisley, UK). The pellet was resuspended in 1 ml EBSS + 0.3% HSA. Motility and concentration were determined (total motile sperm count) and the samples were concentrated to 0.3 ml.

To investigate the value of sperm morphology as a predictive tool

Table III. Comparison of the morphology score (mean value ± SD) in the different subgroups (1, 2, 3, 4)[a] for pregnant and non-pregnant couples

	Morphology score				Significance (unpaired *t*-test)
	Pregnant (n = 116)		Not pregnant		
	Range	Mean (± SD)	Range	Mean(± SD)	
Subgroup 1 (n = 56)	3.5–17	8.3 ± 4.0	0–16	5.0 ± 3.8	$P < 0.05$
Subgroup 2 (n = 37)	1–11	5.8 ± 2.6	1–16	6.9 ± 3.8	NS
Subgroup 3 (n = 156)	0–18	7.3 ± 4.0	0–15	6.6 ± 3.5	NS
Subgroup 4 (n = 124)	2–18	8.8 ± 3.7	2–22	9.2 ± 4.2	NS

NS = not significant.
[a]Subgroups defined by number of motile spermatozoa recovered after washing. Subgroup 1: $<1\times10^6$; subgroup 2: $\geqslant1-<2\times10^6$; subgroup 3: $\geqslant2-<10\times10^6$; subgroup 4: $\geqslant10\times10^6$.

Table IV. Diagnostic potential of sperm morphology in the study population and the different subgroups[a] through receiver operating characteristic (ROC) curve analysis. Cut-off value denotes for the value with optimal sensitivity and specificity

	Area under ROC curve	SE	95% confidence interval	Cut-off value (%)	Sensitivity	Specificity
All patients	0.54	0.033	0.496–0.601	6	46.6	66.4
Subgroup 1	0.77	0.092	0.639–0.880	7.3	83.3	70.0
Subgroup 2	0.56	0.099	0.392–0.730	7.7	34.9	84.6
Subgroup 3	0.54	0.051	0.459–0.622	5.5	44.3	68.1
Subgroup 4	0.53	0.055	0.442–0.626	7.5	64.9	48.8

[a]Subgroups defined by number of motile spermatozoa recovered after washing. Subgroup 1: $<1\times10^6$; subgroup 2: $\geqslant1-<2\times10^6$; subgroup 3: $\geqslant2-<10\times10^6$; subgroup 4: $\geqslant10\times10^6$.

through ROC analysis, our study population was divided in four subgroups depending on the inseminating motile count: group 1: $<1\times10^6$; group 2: $\geqslant1-<2\times10^6$; group 3: $\geqslant2-<10\times10^6$; group 4: $\geqslant10\times10^6$ motile spermatozoa recovered after washing.

Definition of pregnancies

Chemical and clinical pregnancies were taken into account. Only offspring with a birth weight of >500 g were considered positive cases in the final data of the baby take-home rate.

Statistical analysis

ROC curve analysis was used to determine the predictive power of the investigated sperm parameters (total motile sperm count, sperm morphology). Differences between non-conception and conception cycles were tested by a paired *t*-test for unpaired samples and by the χ^2 test after classification of patients by function of semen analysis results (IMC) in contingency tables.

Results

Characteristics of the groups

The main characteristics of the pregnancy (n = 116) and non-pregnancy (n = 257) groups were similar as shown in Table I. Comparing both groups, we found no significant difference in female age (29.1 ± 3.1 versus 29.7 ± 3.5), male age (30.8 ± 4.6 versus 31.6 ± 4.7) and diagnostic classification (number and percentages of idiopathic, female and male subfertility cases in the two groups) (Table I). The mean duration of subfertility was significantly lower (P <0.05) in the pregnancy versus non-pregnancy group (30.6 ± 23.5 versus 33.9 ± 21.8), but this difference was not present comparing subgroups 1, 2, 3 and 4.

In the studied population, male subfertility was observed in 87.7% (327/373) of cases. Idiopathic subfertility and a pure cervical factor were only present in 39 couples (10.5%) (Table I).

Overall clinical results

Overall, during the period considered, 792 CC–IUI treatment cycles in 373 couples were analysed (mean: 2.1 cycles per couple). The first cycle was the most successful one with a pregnancy rate (PR) and baby take-home rate (BTH) of 18.5 and 12.6% respectively, declining in the second and third cycles (Table II).

A total of 114 patients (30.6%) became pregnant within 1–3 treatment cycles. Of these 114, only 79 delivered a baby (BTH: 21.2% per couple, 10.0% per cycle) (Table II, Figure 1).

Comparing the mean values of semen characteristics (initial sample and post-washing) of the pregnant and non-pregnant group, we could demonstrate no significant difference in: (i) initial concentration; (ii) initial total motility; (iii) sperm morphology and (iv) inseminating motile count (IMC) after washing (Table I).

Although the best PR and BTH results were obtained in subgroup 4, sperm morphology and the number of motile spermatozoa inseminated were of no value in predicting conception for the whole group of patients, using ROC curve analysis (area under ROC curve for the whole group: <56%).

After dividing the patients into the four different subgroups, sperm morphology turned out to be a very important discriminant when the IMC was $<1\times10^6$ (subgroup 1). In this subgroup, no pregnancies occurred when the morphology score was <4%. Furthermore, the mean value of sperm morphology was significantly different between the pregnancy (8.3%) versus non-pregnancy group (5.0%) (Table III). Only for this subgroup, morphology was a very important tool using ROC curve analysis (area under ROC curve: 77.6%, cut-off value with optimal sensitivity and specificity: 7.3%) (Table IV). For subgroups 2, 3 and 4, sperm morphology was of no additional benefit in predicting the IUI outcome and mean values were not different in the pregnancy and non-pregnancy groups (Tables III and IV).

The PR and BTH were lower in subgroup 1 (7.8 and 5.5%) versus subgroup 2 (15.1 and 9.3%), 3 (15.0 and 10.2%) and 4 (17.6 and 12.2%), but significance was only reached ($P < 0.05$) when subgroup 1 was compared to subgroup 4 (Table II). The cumulative PR and BTH rate per patient after three treatment cycles were 17.9 and 12.5% respectively for subgroup 1, 32.4 and 21.6% for subgroup 2, 31.4 and 21.8% for subgroup 3 and 34.6 and 24.2% for subgroup 4 (Figure 1). Considering only patients with a sperm morphology score of ⩾4% normal forms, cycle fecundity and BTH per couple were 13.6% (9/66) and 21.9% (7/32) respectively, comparable with the results of subgroups 2, 3 and 4.

The use of a swim-up procedure or a mini-Percoll technique for sperm washing did not influence the success rate, taking into account that the mini-Percoll technique was only used for the male subfertility cases. A study comparing the success rates in subgroup 4 for swim-up versus mini-Percoll cases did not reveal any differences. Nor was the success rate influenced by the different indications for IUI (female causes, idiopathic subfertility, male subfertility and combined problems).

Our miscarriage rate (chemical and clinical abortions) was 31.9% (37/116) and equally distributed throughout the four subgroups. The incidence of multiple (twin) pregnancies was only 2.5% (2/79) and none of our patients was admitted for moderate or severe ovarian hyperstimulation syndrome (OHSS).

Discussion

In this study, we tried to investigate the power of two important post-wash semen parameters [inseminating motile count (IMC) and sperm morphology] to predict success rates in an intrauterine insemination programme.

Previous studies showed a trend towards increasing conception rates with increasing inseminating motile count, but the cut-off value above which IUI seems to be more successful varies between $0.25–5\times10^6$ (Horvath *et al.*, 1989; Dodson and Haney, 1991; Mathieu *et al.*, 1995; Huang *et al.*, 1996) for HMG-stimulated cycles and 20×10^6 (Brasch *et al.*, 1994) for IUI in natural cycles. Only a few pregnancies have been reported with an IMC of $<1\times10^6$ (Kerin *et al.*, 1984; Allen *et al.*, 1985; Confino *et al.*, 1986; Ho *et al.*, 1989; Brasch *et al.*, 1994; Mathieu *et al.*, 1995; Burr *et al.*, 1996).

According to their findings in HMG-stimulated IUI cycles, Burr *et al.* (1996) recently reported no significant influence of total motile sperm count on monthly fecundity. On the other hand, sperm morphology turned out to be a good predictive parameter in this study (⩽10% normal forms = poor outcome), a confirmation of previous reports (Comhaire *et al.*, 1994; Toner *et al.*, 1994; Ombelet *et al.*, 1996).

In the present study, we investigated the influence of both parameters in a very selected group of patients with normal ovarian response to CC stimulation. IUI was always provided as first-line treatment in a predominantly male subfertility group of patients.

Using ROC curve analysis, IMC and sperm morphology turned out to be of little prognostic value in predicting success for the group as a whole. However, the finding that sperm morphology only becomes a very useful predictive tool in a subgroup of patients with an IMC of $<1\times10^6$ may be a very important message. In terms of therapeutic strategy, this means that above a cut-off limit of 1×10^6 motile spermatozoa recovered after washing, CC–IUI can be promoted as a first-line therapy with an expected BTH rate of 21–25% after three cycles. Furthermore, in cases with $<1\times10^6$ motile spermatozoa, CC–IUI remains important as a first-line option provided the sperm morphology score is ⩾4%.

We are aware of the disadvantages of a retrospective analysis, but our results highlight the importance of performing a well-organized prospective study on this matter. Considering the increasing demand for cost–benefit analysis and taking into account the very low complication rate of CC–IUI treatment cycles, we believe that even in cases of severe male subfertility, CC–IUI can be offered to subfertile couples, especially in centres with a waiting list for IVF, but also in regions where patients can easily reach and visit the fertility centre for careful monitoring. We agree with Cohlen *et al.* (1995) that the addition of controlled ovarian stimulation to IUI increases not only the pregnancy, but also the complication rate. In a previous reported study we found a significant difference in success between the CC–IUI and HMG–IUI groups, but almost all complications were seen in the HMG-stimulated patients. In this series, we observed a very low complication rate indicating that careful monitoring and strict cancellation criteria indeed minimize the risk for complications, such as multiple gestation and ovarian hyperstimulation, as described by Cohlen *et al.* (1995).

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References

Aitken, R.J. and Clarkson, J.S. (1987) Cellular basis of defective sperm function and its association with the genesis of reactive oxygen species by human spermatozoa. *J. Reprod. Fertil.*, **81,** 459–469.

Allen, N.C., Herbert, C.M., Maxon, W.S. *et al.* (1985) Intrauterine insemination: a critical review. *Fertil. Steril.*, **44,** 569–580.

American Fertility Society (1985) Revised American Fertility Society classification of endometriosis. *Fertil. Steril.*, **43,** 351–352.

Aribarg, A. and Sukcharoen, N. (1995) Intrauterine insemination of washed spermatozoa for treatment of oligozoospermia. *Int. J. Androl.*, **18** (Suppl. 1), 62–66.

Brasch, J.G., Rawlins, R., Tarchala, S. and Radwanska, E. (1994) The relationship between total motile sperm count and the success of intrauterine insemination. *Fertil. Steril.*, **62,** 150–154.

Burr, R.W., Siegberg, R., Flaherty, S.P. *et al.* (1996) The influence of sperm morphology and the number of motile sperm inseminated on the outcome of intrauterine insemination combined with mild ovarian stimulation. *Fertil. Steril.*, **65,** 127–132.

Cohlen, B.J., te Velde, E.R. and Van Kooij, R.J. (1995) Is there still a place for intra-uterine insemination as a treatment for male subfertility? A review. *Int. J. Androl.*, **18** (Suppl. 2), 72–75.

Comhaire, F. (1995) Economic strategies in modern male subfertility treatment. *Hum. Reprod.*, **10** (Suppl. 1), 103–106.

Comhaire, F., Milingos, S., Liapi, A. *et al.* (1994) The effective cumulative pregnancy rate of different modes of treatment of male infertility. *Andrologia*, **27,** 217–221.

Confino, E., Friberg, J., Dudkiewicz, A.B. and Gleicher, N. (1986) Intrauterine inseminations with washed human spermatozoa. *Fertil. Steril.*, **46,** 55–60.

Crosignani, P.G. and Walters, D.E. (1994) Clinical pregnancy and male subfertility; the ESHRE multicentre trial on the treatment of male subfertility. *Hum. Reprod.*, **9,** 1112–1118.

Cruz, R.I., Kemman, E., Brandeis, V.T. *et al.* (1986) A prospective study of intrauterine insemination of processed sperm from men with oligoasthenospermia in superovulated women. *Fertil. Steril.*, **46,** 673–677.

DiMarzo, S.J., Kennedy, J.F., Young, Ph.E. *et al.* (1992) Effect of controlled ovarian hyperstimulation on pregnancy rates after intrauterine insemination. *Am. J. Obstet. Gynecol.*, **166,** 1607–1613.

Dodson, W.C. (1995) Is superovulation and intrauterine insemination really an alternative to assisted reproductive technology? *Semin. Reprod. Endocrinol.*, **13,** 85–89.

Dodson, W.C. and Haney, A.F. (1991) Controlled ovarian hyperstimulation and intrauterine insemination for treatment of infertility. *Fertil. Steril.*, **55,** 457–467.

Dodson, W.C., Whitesides, D.B., Hughes, C.L. *et al.* (1987) Superovulation with intrauterine insemination in the treatment of infertility: A possible alternative to gamete intrafallopian transfer and *in vitro* fertilization. *Fertil. Steril.*, **48,** 441–445.

Ho, P.-C., Poon, I.M.L., Chan, S.Y.W. and Wang, C. (1989) Intrauterine insemination is not useful in oligoasthenospermia. *Fertil. Steril.*, **51,** 682–684.

Ho, P.-C., So, W.-K., Chan, Y.-F. and Yeung, W.S.-B. (1992) Intrauterine insemination after ovarian stimulation as the treatment of subfertility because of subnormal semen: a prospective randomized controlled trial. *Fertil. Steril.*, **58,** 995–999.

Horvath, P.M., Bohrer, M., Shelden, R.M. and Kemmann, E. (1989) The relationship of sperm parameters to cycle fecundity in superovulated women undergoing intrauterine insemination. *Fertil. Steril.*, **52,** 288–294.

Huang, H.-Y., Lee, C.-L., Lai, Y.-M. *et al.* (1996) The impact of the total motile sperm count on the success of intrauterine insemination with husband's spermatozoa. *J. Assist. Reprod. Genet.*, **13,** 56–63.

Irianni, F.M., Acosta, A.A., Oehninger, S. and Acosta, M.R. (1990) Evaluation and preparation of spermatozoa for intrauterine insemination: clinical aspects. In Acosta, A.A., Swanson, R.J., Ackerman, S.B. *et al.* (eds), *Human Spermatozoa in Assisted Reproduction.* Williams and Wilkins, Baltimore, pp. 265–279.

Irianni, F.M., Ramey, J., Vaintraub, M.T. *et al.* (1993) Therapeutic insemination improves with gonadotropin ovarian stimulation. *Arch. Androl.*, **31,** 55–62.

Kerin, J.F.P., Peek, J., Warnes, G.M. *et al.* (1984) Improved conception rate after intrauterine insemination of washed spermatozoa from men with poor quality semen. *Lancet*, **i,** 533–534.

Kruger, T.F., Menkveld, R., Stander, F.S.H. *et al.* (1986) Sperm morphologic features as a prognostic factor in *in vitro* fertilization. *Fertil. Steril.*, **46,** 1118–1123.

Kruger, T.F., Acosta, A.A., Simmons, K.F. *et al.* (1988) Predictive value of abnormal sperm morphology in *in vitro* fertilization. *Fertil. Steril.*, **49,** 112–117.

Martinez, A.R., Bernardus, R.E., Vermeiden, J.P.W. and Schoemaker, J. (1993) Basis questions on intrauterine insemination: an update. *Obstet. Gynecol. Surv.*, **48,** 811–828.

Mathieu, C., Ecochard, R., Bied, V. *et al.* (1995) Cumulative conception rate following intrauterine artificial insemination with husband's spermatozoa: influence of husband's age. *Hum. Reprod.*, **10,** 1090–1097.

Melis, G.B., Paoletti, A.M., Ajossa, S. *et al.* (1995) Ovulation induction with gonadotrophins as sole treatment in infertile couples with open tubes: a randomized prospective comparison between intrauterine insemination and timed vaginal intercourse. *Fertil. Steril.*, **64,** 1088–1093.

Nan, P.M., Cohlen, B.J., te Velde, E.R. *et al.* (1994) Intra-uterine insemination or timed intercourse after ovarian stimulation for male subfertility? A controlled study. *Hum. Reprod.*, **9,** 2022–2026.

Ombelet, W., Cox, A., Jansen, M. *et al.* (1995a) Intrauterine insemination (IUI) following superovulation: pregnancy rates after single versus repeated inseminations. A prospective randomized study. Proceedings of the 11th meeting of ESHRE. [Abstr. no. 290.] *Hum. Reprod.*, **10** (Abstr. Book 2), 134.

Ombelet, W., Puttemans, P. and Brosens, I. (1995b) Intrauterine insemination: a first-step procedure in the algorithm of male subfertility treatment. *Hum. Reprod.*, **10** (Suppl. 1), 90–102.

Ombelet, W., Cox, A., Janssen, M. *et al.* (1996) Artificial Insemination (AIH) Artificial insemination 2: using the husband's sperm. In Acosta, A.A. and Kruger, T.F. (eds), *Diagnosis and Therapy of Male Factor In Assisted Reproduction.* Parthenon Publishing, Carnforth, UK, pp. 397–410.

Ombelet, W., Bosmans, E., Janssen, M. *et al.* (1997) Semen parameters in a fertile versus subfertile population: A need for change in interpretation of semen testing. *Hum. Reprod.*, **12,** 987–993.

Peterson, C.M., Hatasaka, H.H., Jones, K.P. *et al.* (1994) Ovulation induction with gonadotropins and intrauterine insemination compared with *in vitro* fertilization and no therapy: a prospective, nonrandomized, cohort study and meta-analysis. *Fertil. Steril.*, **62,** 535–544.

Robinson, D., Syrop, C.H. and Hammitt, D.G. (1992) After superovulation-intrauterine insemination fails: the prognosis for treatment by gamete intrafallopian transfer/pronuclear stage transfer. *Fertil. Steril.*, **57,** 606–612.

Sunde, A., Kahn, J. and Molne, K. (1988) Intrauterine insemination. *Hum. Reprod.*, **3,** 97–99.

Tarlatzis, B.C., Bontis, J., Kolibianakis, E.M. *et al.* (1991) Evaluation of intrauterine insemination with washed spermatozoa from the husband in the treatment of infertility. *Hum. Reprod.*, **6,** 1241–1246.

te Velde, E.R., van Kooy, R.J. and Waterreus, J.J.H. (1989) Intrauterine insemination of washed husband's spermatozoa: a controlled study. *Fertil. Steril.*, **51,** 182–185.

Tomlinson, M.J., Amissah-Arthur, J.B., Thompson, K.A. *et al.* (1996) Prognostic indicators for intrauterine insemination (IUI): statistical model for IUI success. *Hum. Reprod.*, **11,** 1892–1896.

Toner, J.P., Mossad, H., Grow, D.R. *et al.* (1994) Value of sperm morphology assessed by strict criteria for prediction of the outcome of artificial (intrauterine) insemination. *Andrologia*, **27,** 143–148.

World Health Organization (1987) *WHO Laboratory Manual for the Examination of Human Semen and Semen–Cervical Mucus Interaction.* 2nd edn. Cambridge University Press, Cambridge, UK.

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