Human Reproduction vol.14 no.3 pp.698–703, 1999

Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome

Sinikka Nuojua-Huttunen[1,4], Candido Tomas[2], Risto Bloigu[3], Leena Tuomivaara[1] and Hannu Martikainen[2]

[1]The Family Federation of Finland (The Oulu Infertility Clinic), Kiviharjuntie 11, FIN-90220 Oulu, [2]Department of Obstetrics and Gynecology, Oulu University Hospital, Kajaanintie 50, FIN-90220 Oulu, and [3]Medical Informatics, Faculty of Medicine, University of Oulu, Kajaanintie 52, FIN-90220 Oulu, Finland

[4]To whom correspondence should be addressed

A total of 811 intrauterine insemination (IUI) cycles in which clomiphene citrate/human menopausal gonadotrophin (HMG) was used for ovarian stimulation were analysed retrospectively to identify prognostic factors regarding treatment outcome. The overall pregnancy rate was 12.6% per cycle, the multiple pregnancy rate 13.7%, and the miscarriage rate 23.5%. Logistic regression analysis revealed five predictive variables as regards pregnancy: number of the treatment cycle ($P = 0.009$), duration of infertility ($P = 0.017$), age ($P = 0.028$), number of follicles ($P = 0.031$) and infertility aetiology ($P = 0.045$). The odds ratios for age <40 years, unexplained infertility aetiology (versus endometriosis) and duration of infertility ≤6 years were 3.24, 2.79 and 2.33, respectively. A multifollicular ovarian response to clomiphene citrate/HMG resulted in better treatment success than a monofollicular response, and 97% of the pregnancies were obtained in the first four treatment cycles. The results indicate that clomiphene citrate/HMG/IUI is a useful and cost-effective treatment option in women <40 years of age with infertility duration ≤6 years, who do not suffer from endometriosis.

Key words: clomiphene citrate/human menopausal gonadotrophin/infertility/intrauterine insemination/prognostic factors

Introduction

Most couples seeking infertility treatment are subfertile, with a decreased monthly conception rate, but natural pregnancy is possible (ESHRE Capri Workshop group, 1996). In planning the treatment policy of subfertility, over-treatment should be avoided, thereby minimizing the possible health risks associated with ovarian stimulation and the total cost of infertility treatment. Presently, numerous treatment modes of assisted reproductive technology are widely used for subfertility. For example, in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) were initially used for those with bilateral tubal damage or severe male factor infertility, but they are now used for a variety of infertility diagnoses. Despite the high success rates of new treatment options, it would be cost-effective to consider less-demanding treatments for subfertile couples before undergoing expensive and invasive IVF (Peterson *et al.*, 1994; Zayed *et al.*, 1997). When the treatment outcome is evaluated the possibility of multiple pregnancy needs also to be taken into consideration.

Intrauterine insemination (IUI) together with ovarian stimulation is a simple and inexpensive treatment for subfertility. The reported pregnancy rates per cycle have usually varied between 8% and 22% (Sunde *et al.*, 1988; Dodson and Haney, 1991; Peterson *et al.*, 1994; Brzechffa *et al.*, 1998; Cohlen *et al.*, 1998), but very low (4%) and high (40%) pregnancy rates have also been published (Karlström *et al.*, 1993; Fanchin *et al.*, 1995). The great variance in pregnancy rate achieved may be due to the small size of the study populations, variability in characteristics of the subjects, ovarian stimulation protocols, and insemination techniques.

Previously, only in a few studies have different variables affecting IUI outcome been adequately examined (Dickey *et al.*, 1991, 1992; Mathieu *et al.*, 1995; Tomlinson *et al.*, 1996). In particular, data on the prognostic factors related to IUI treatment in which clomiphene citrate/human menopausal gonadotrophin (HMG)/human chorionic gonadotrophin (HCG) is used for ovarian stimulation are rare. In this retrospective study we have attempted to identify in detail the variables that contribute to the success of clomiphene citrate/HMG/IUI treatment. These data would be valuable in planning subfertility treatment and predicting the success rate of IUI therapy in individual couples.

Materials and methods

Subjects

In the present study we have evaluated a total of 924 IUI cycles in which a clomiphene citrate/HMG/HCG stimulation protocol and a standard IUI technique with partner's spermatozoa were used. All cycles were carried out between January 1992 and December 1996 at the Infertility Clinic of the Family Federation of Finland in Oulu.

The study couples had at least 1 year of infertility, and had undergone a basic infertility evaluation consisting of anamnesis, measurement of mid-luteal serum progesterone, prolactin and thyroid hormone concentrations and semen analysis. Tubal patency was confirmed by laparoscopy or hysterosalpingography. Among women with a short duration of infertility (maximum of 2 years) or intrauterine pregnancy in the immediate past and no signs of tubo-peritoneal disease suggested by the history, physical examination or other diagnostic methods, examination of tubal patency was not always carried out before the first IUI treatment. If pregnancy was not achieved after two to three ovarian stimulation/IUI cycles, tubal patency was investigated. All women with only one tube open or other tubal abnormalities were excluded from the study (113 cycles), and 811 IUI cycles were included in the analysis. The median female age and duration of infertility was 32 (range 20–46) years and 3 (range 1–15) years, respectively.

The categories of infertility aetiology were unexplained infertility (51%), male factor (28%), minimal (stage I) to mild (stage II) endometriosis (17%) and ovulatory disorders (4%). Patients with polycystic ovarian syndrome were excluded from the study because they underwent stimulation according to a protocol other than clomiphene citrate/HMG/HCG. Male factor was defined as: (i) a sperm count of $<20\times10^6$/ml; (ii) normal forms <30%; or (iii) progressive motility (grade A+B) <40% before sperm preparation modifying World Health Organization guidelines (1987). If the progressively motile sperm count after preparation was $<1\times10^6$/ml in the basic infertility evaluation, couples were not enrolled in IUI treatment. The median value of sperm concentration and the percentage of progressive motility (grade A+B) after preparation was 28×10^6/ml (range <1–200×10^6/ml) and 63% (range 6–100%), respectively. Endometriosis was diagnosed by laparoscopy and classified in accordance with the revised classification of the American Fertility Society (1985). Infertility was primary in 56% of cycles and secondary in 44%.

Ovarian stimulation

All women in the study underwent ovarian stimulation using clomiphene citrate (Clomifen; Leiras, Tampere, Finland) and HMG (Humegon; Organon, Oss, The Netherlands; or Pergonal; Serono, Aubonne, Switzerland). The women were given 50 or 100 mg of clomiphene citrate on cycle days 3 to 7, followed by 1–2 ampoules (75–150 IU) of HMG daily. Ovarian and endometrial responses were monitored by vaginal ultrasonography on cycle days 9 to 13 and 5000–10 000 IU of HCG (Pregnyl; Organon or Profasi; Serono) was administered when at least one follicle was >16 mm in mean diameter. Standard IUI was performed 36 h after administration of HCG. No luteal support was given.

Sperm preparation

Semen was collected by masturbation into a sterile jar after 2–4 days of sexual abstinence. After liquefaction and initial sperm analysis, the standard swim-up or Percoll gradient technique was used for preparation, employing Earle's balanced salt solution or Medi-Cult medium supplemented with human serum albumin (Medi-Cult a/s, Copenhagen, Denmark). Briefly, in the swim-up technique the sperm sample was centrifuged at 500 *g* for 15 min. The supernatant was discarded and the pellet diluted in 2.5 ml of medium and re-centrifuged. After removing the supernatant the final pellet was gently covered with medium and incubated for 1 h at 37°C in an incubator. In the Percoll technique, semen was layered onto a discontinuous Percoll gradient (40%, 90%; Pharmacia, Bio Process Technology AB, Uppsala, Sweden) containing Medi-Cult medium and centrifuged at 500 *g* for 20 min. The lowest (90%) fraction was then suspended in 6 ml of medium and re-centrifuged (500 *g* for 10 min). The remaining pellet was diluted in 0.5–1 ml of medium and incubated as in the swim-up technique.

Intrauterine insemination

Intrauterine insemination was performed using an intrauterine catheter (Kremer Delafontaine; Prodimed, Neuilly-en-Thelle, France) with a 1- or 2-ml syringe. The catheter was gently passed through the cervical canal and the sperm suspension expelled into the uterine cavity. Insemination volumes ranged from 0.5 to 2 ml. The women remained supine for 10–15 min after IUI.

Table I. Pregnancy outcome of the intrauterine insemination cycles

Pregnancy outcome	No. of patients
Pregnancies/cycle (%)	102/811 (12.6)
Live births	72 (70.6)
Miscarriages	24 (23.5)
Ectopic pregnancies	6 (5.9)
Multiple pregnancies	14 (13.7)
Multiple births/live births	12/72 (16.7)

Values in parentheses are percentages

If menstruation was delayed after IUI, a urinary pregnancy test was performed. All pregnancies were confirmed by ultrasonography.

Statistical analysis

A logistic regression method was used to identify significant variables that contribute to the success of ovarian stimulation/IUI treatment and to predict the probability of pregnancy for each treatment cycle. The variables selected for the initial analysis were female age, duration of infertility, type and diagnosis of infertility, sperm concentration and progressive motility (grade A+B) after preparation, number of pre-ovulatory follicles (>16 mm in diameter), thickness of the endometrium and number of the treatment cycle. Female age and duration of infertility were treated as dichotomous variables, <40 or ⩾40 years and ⩽6 or >6 years, respectively. The categories of sperm concentration and progressive motility (grade A+B) were $<5\times10^6$, 5–10×10^6 or $>10\times10^6$/ml and <40 or ⩾40%, respectively. The number of follicles and treatment cycles were categorized as follows: 1, 2, 3 or 4 (more than four follicles was recorded as four) and 1, 2, 3, 4 or 5 (more than five treatments was recorded as five). The thickness of the endometrium was also treated as a categorical variable, <6, 6–10 or >10 mm. Other variables were nominal.

Only statistically significant variables were included in the final model. The Hosmer–Lemeshow goodness of fit statistic (1989) was used for assessment of the final model.

Logistic regression analysis was performed using the PC version of the SPSS Inc. Professional Statistics, Release 6.1 (Chicago, IL, USA). Differences in pregnancy rates between groups were tested by using Student's *t*-test and χ^2 test. The chosen level of significance was $P < 0.05$.

Results

General results

A total of 811 IUI cycles were analysed. The overall pregnancy rate per cycle was 12.6% (102/811). Of the 102 pregnancies, 70.6% were viable, 23.5% resulted in spontaneous abortion, and 5.9% were ectopic. The multiple pregnancy rate was 13.7% (12 pairs of twins and two sets of triplets). Pregnancy outcome is presented in Table I.

The pregnancy rates according to the female characteristics and sperm parameters after preparation are summarized in Table II. The pregnancy rate in women <40 years old was significantly higher than in older women (13.7 versus 4.1%). The live birth rate was 3.1% (3/98) per cycle in women ⩾40 years old. No pregnancies were achieved among women >42 years old. In addition, an infertility duration of ⩽6 years was associated with a significantly better pregnancy rate compared with a longer duration of infertility (14.2 and 6.1% respectively). As regards the diagnosis of infertility, the highest

Table II. Intrauterine insemination pregnancy rate according to female characteristics and sperm parameters (after preparation)

	Pregnancies/cycle (%)
Age (years)[a]	
<40	98/713 (13.7)
⩾40	4/98 (4.1)
Infertility duration (years)[b]	
⩽6	92/646 (14.2)
>6	10/165 (6.1)
Infertility aetiology[c]	
Unexplained	63/413 (15.3)
Male factor	27/229 (11.8)
Endometriosis	9/138 (6.5)
Ovarian dysfunction	3/31 (9.7)
Type of infertility	
Primary	52/457 (11.4)
Secondary	50/354 (14.1)
Sperm count ($\times 10^6$/ml)	
<5	6/84 (7.1)
5–10	12/91 (13.2)
>10	84/636 (13.2)
Progressive motility (%)	
<40	6/63 (9.5)
⩾40	96/748 (12.8)

[a]$P = 0.007$; [b]$P = 0.005$; [c]$P = 0.05$.

Table III. Intrauterine insemination pregnancy rate according to number of follicles, thickness of endometrium and number of treatment cycle

	Pregnancies/cycle (%)
Number of follicles (>16 mm)[a]	
1	10/177 (5.7)
2	36/265 (13.6)
3	32/196 (16.3)
⩾4	24/173 (13.9)
Thickness of endometrium (mm)	
<6	3/27 (11.1)
6–10	87/683 (12.7)
>10	12/101 (11.9)
Number of treatment cycle[b]	
1	51/283 (18.0)
2	26/228 (11.4)
3	15/160 (9.4)
4	7/73 (9.6)
⩾5	3/67 (4.5)

[a]$P = 0.013$; [b]$P = 0.007$.

pregnancy rate (15.3%) was achieved in women with unexplained infertility, and the lowest (6.5%) in women suffering from endometriosis. Infertility type (primary or secondary) and sperm parameters did not significantly affect the outcome of IUI treatment.

The median number of pre-ovulatory follicles (>16 mm in diameter) on the HCG day was 2 (range 1–8) and the median endometrial thickness was 8 mm (range 4–17 mm). In cycles with a single pre-ovulatory follicle (>16 mm in diameter) the pregnancy rate (5.7%) was significantly lower than in cycles with more follicles. The highest pregnancy rate (16.3%) in this regard was observed with three pre-ovulatory follicles. There was no correlation between the number of follicles and multiple pregnancy rate. The thickness of the endometrium was not related to treatment outcome (Table III).

The highest pregnancy rate per cycle (18%) was achieved in the first treatment cycle. Almost all of the pregnancies (99/102; 97%), occurred within the first four treatment cycles and no pregnancies were achieved in the sixth and seventh cycles (Table III).

Table IV. Logistic regression model for predicting the success of intrauterine insemination

Variable	OR[a]	CI[b]	*P*
Age[c]			0.028
<40 (years)	3.24	(1.14, 9.23)	
Infertility duration[c]			0.017
⩽6 (years)	2.33	(1.16, 4.66)	
Infertility aetiology[c]			0.045
unexplained	2.79	(1.33, 5.87)	
Number of follicles (>16 mm)[c]			0.031
2	2.45	(1.16, 5.18)	
3	3.18	(1.48, 6.81)	
⩾4	2.51	(1.13, 5.55)	
Number of treatment cycle[d]			0.009
2	0.57	(0.34, 0.96)	
3	0.44	(0.24, 0.83)	
4	0.43	(0.19, 1.03)	
⩾5	0.22	(0.07, 0.75)	

[a]Odds ratio.
[b]95% confidence interval.
[c]Odds ratio in contrast to the poorest category.
[d]Odds ratio in contrast to the best category.

Logistic regression

Logistic regression analysis revealed five predictive variables for IUI success. These were the number of the treatment cycle ($P = 0.009$), duration of infertility ($P = 0.017$), age ($P = 0.028$), number of follicles ($P = 0.031$) and aetiology of infertility ($P = 0.045$). The results of the final model are presented as odds ratios (OR) and 95% confidence intervals (CI) in Table IV. When the analysis included only cycles in women <40 years old ($n = 713$), age did not affect the outcome of IUI treatment, while the other predictive variables remained significant. Our data fitted logistic regression analysis well, as indicated by the Hosmer and Lemeshow goodness-of-fit test ($P = 0.57$). Using this model, the probability of pregnancy can be estimated for each treatment cycle.

Discussion

In this study we attempted to discover prognostic factors associated with success in clomiphene citrate/HMG/IUI treatment. We carried out logistic regression analysis of 811 IUI cycles and identified five significant variables. These are the age of the woman, duration of infertility, aetiology of infertility, number of the treatment cycle and number of pre-ovulatory follicles.

The age-related decline in female fecundity has been well documented, particularly in women undergoing IUI with donor spermatozoa (van Noord-Zaadstra *et al.*, 1991; Kang and Wu, 1996). This decline has been suggested to be a result of reduced uterine receptivity (Flamigni *et al.*, 1993; Cano *et al.*, 1995) and/or decreased oocyte quality (Navot *et al.*, 1991; Abdalla *et al.*, 1993). Accordingly, the success rates of IVF and ICSI (Devroey *et al.*, 1996; Hull *et al.*, 1996) have been reported to decrease with advancing female age, indicating that the negative impact of age can be overcome only partly by assisted reproductive technology. In our study, the success rate of IUI with partner's semen was reduced significantly in women aged ⩾40 years, which is in agreement with the results of earlier studies (Dodson and Haney, 1991; Frederick *et al.*, 1994; Campana *et al.*, 1996; Tomlinson *et al.*, 1996). However, in contrast to the results of some previous studies (Agarwal and Buyalos, 1996; Brzechffa and Buyalos, 1997; Brzechffa *et al.*, 1998), age was not predictive of IUI success in women <40 years old. The reported livebirth rates per IUI cycle in women aged ⩾40 years are low, varying from 1.4% to 5.2% (Dickey *et al.*, 1992; Frederick *et al.*, 1994; Corsan *et al.*, 1996), which is in line with the results of our study (3.1%). Put together, all these results indicate that IUI is a poor treatment option for women over 40 years of age.

We found a significant decrease in pregnancy rate with an increasing duration of infertility, as also shown previously in some (Nulsen *et al.*, 1993; Crosignani and Walters, 1994; Mathieu *et al.*, 1995; Tomlinson *et al.*, 1996), but not all studies (McGovern *et al.*, 1989; Dodson and Haney, 1991). Although the precise limits of the duration of infertility after which IUI success has been shown to decrease vary, IUI cannot be recommended to patients with a long-standing duration of infertility.

When the effect of infertility aetiology was assessed, a significantly lower pregnancy rate was found in endometriosis patients compared with women with unexplained infertility. In our study the pregnancy rate was 6.5% per cycle in the endometriosis group, which is slightly lower than reported previously (9–16%) (Chaffkin *et al.*, 1991; Dodson and Haney, 1991; Tummon *et al.*, 1997). The negative impact of endometriosis on IUI success has also been reported by other authors (Dickey *et al.*, 1992; Crosignani and Walters, 1994), and Hughes (1997) concluded in his meta-analysis that a diagnosis of endometriosis reduced the effectiveness of ovarian stimulation/IUI by approximately half in the treatment of persistent infertility (unexplained infertility, male factor and endometriosis), which is in accordance with the present data.

The factors that decrease fertility in endometriosis without tubal involvement are not clearly known. An altered follicular environment (Harlow *et al.*, 1996), impaired oocyte quality (Pellicer *et al.*, 1995) and reduced implantation rate (Arici *et al.*, 1996) have been found in endometriosis. A gametotoxic effect induced by endometriosis has also been suggested to affect fertility negatively (Martinez-Roman *et al.*, 1997). The present data and the published IVF results (Geber *et al.*, 1995) suggest that IVF would be more effective than IUI in women with endometriosis.

In unexplained infertility, ovarian stimulation and IUI appears to be effective (Crosignani *et al.*, 1991; Chung *et al.*, 1995). In a meta-analysis carried out by Peterson *et al.* (1994), the average pregnancy rate per cycle for unexplained infertility, using HMG/IUI, was 18%. Our present and previous results (Nuojua-Huttunen *et al.*, 1997a,b) are in agreement with this. A decreased fertilization rate has been suggested to be the cause of failure to conceive among women with unexplained infertility (Templeton *et al.*, 1996), which possibly can be overcome by superovulation therapy associated with an increased number of fertilizable oocytes in IUI (Nulsen *et al.*, 1993; Arici *et al.*, 1994). However, other factors may also be operative, since the combination of IUI with ovarian stimulation has been found to give better results than ovarian stimulation with timed intercourse (Hughes, 1997). The information available at present indicates that IUI should be considered for the first line of approach prior to more expensive IVF in patients with unexplained infertility.

In our study the number of follicles was a good prognostic predictor of IUI outcome. In this regard the highest pregnancy rate (16.3%) was seen in cycles with three pre-ovulatory follicles, this being remarkably higher than in cycles with only one follicle (5.7%). Multifollicular development may result in an increased number of fertilizable oocytes and a better quality endometrium and luteal phase, thereby improving fertilization and implantation rates. The poor outcome in cycles with only one pre-ovulatory follicle, also confirmed in other studies (Dodson and Haney, 1991; Tomlinson *et al.*, 1996; Hughes *et al.*, 1998), indicates the necessity of using ovarian stimulation in combination with IUI.

Multiple gestation is an important aspect that needs to be taken into account when an assisted reproduction technique is evaluated. We found an overall multiple pregnancy rate of 13.7% in our study, which is similar to that found in earlier studies (6.5% to 25%) (Chaffkin *et al.*, 1991; Dodson and Haney, 1991; Dickey *et al.*, 1992; Nulsen *et al.*, 1993). Less than 2% of the pregnancies were triplets. The multiple pregnancy rate in our study was lower than that generally reported in IVF treatment (25–30%) (American Society for Reproductive Medicine, 1995; Gissler *et al.*, 1995). These results emphasize the clinical value of IUI treatment compared with IVF, since the total costs associated with multifetal pregnancies are considerably lower in IUI treatment. We found no correlation between the number of large follicles and multiple pregnancies. This is in agreement with the results published by Dodson and Haney (1991), Dickey *et al.* (1992) and Goldfarb *et al.* (1997), but contradictory results have also been published (Valbuena *et al.*, 1996). However, IUI cycles with more than three to four large follicles should be cancelled or converted to IVF, or supernumerary mature follicles should be aspirated in order to decrease the possibility of multiple pregnancy.

In the present study the pregnancy rate per cycle was highest in the first treatment cycle (18%) and thereafter it remained about 10% up to the fourth cycle. In the literature, cycle fecundity has been reported to be relatively constant for the first three to seven cycles (Chaffkin *et al.*, 1991; Dickey *et al.*, 1992; Nulsen *et al.*, 1993), but decreasing pregnancy rates with an increased number of treatment cycles have also been shown, in accordance with our results (Burr *et al.*, 1996; Tomlinson *et al.*, 1996). In this and previous studies (Dodson and Haney, 1991; Dickey *et al.*, 1992), most pregnancies occurred within the first four treatment cycles, favouring a maximum of four IUI cycles before IVF.

Sperm concentration and progressive motility (grade A+B) after preparation were not predictive of IUI success. This is obviously due to pre-treatment sperm screening and exclusion of couples with a progressively motile sperm count after preparation of $<1\times10^6$/ml.

The cost-effectiveness of the treatment is important in making decisions regarding different treatment options in cases of infertility. In our unit the average cost per live birth has been £1670 for clomiphene citrate/HMG/IUI, and over two-fold greater (£4450) for IVF treatment conducted during the same time period. In addition, longer time off work and higher multiple pregnancy rates resulting in added costs during pregnancy, delivery and the neonatal period (not taken into account in these calculations) after IVF treatment further favour the cost-effectiveness of IUI treatment.

In conclusion, clomiphene citrate/HMG/IUI is a useful treatment option for subfertility in a selected patient category. Favourable patient characteristics for treatment success are age <40 years, duration of infertility ≤6 years and a cause of subfertility other than endometriosis. A multifollicular response results in better treatment outcome than a monofollicular response, indicating the necessity of ovarian stimulation combined with IUI. Most pregnancies occur during a course of four clomiphene citrate/HMG/IUI cycles. Importantly, the risk of multiple pregnancy is considerably lower than in IVF. This information is helpful in counselling subfertile couples entering infertility treatment, and makes it possible to carry out more precise patient selection and thereby further increase the cost-effectiveness of IUI therapy.

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Received on July 8, 1998; accepted on November 12, 1998