ANALYSIS OF PROGNOSTIC FACTORS FOR SUCCESSFUL OUTCOME IN PATIENTS UNDERGONING INTRAUTERINE INSEMINATION

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Abstract- Intrauterine insemination (IUI) has been widely used for the treatment of infertility. Several prognostic factors for IUI outcome have been proposed, including the endometrial thickness and follicle numbers, etiology and duration of infertility and morphology, type and motility of sperms. A total of 463 IUI cycles in which clomiphene citrate and/or human menopausal gonadotrophin (HMG) were used for ovarian stimulation analyzed retrospectively to identify prognostic factors regarding treatment outcome. The overall pregnancy rate was 13% per cycle. Logistic regression analyses were done on 14 sets of data, including age, Duration of infertility, Type of infertility, The etiology of infertility, Sperm count, Sperm motility before and after processing, The method of ovarian stimulation, Endometrial thickness, Type of catheter, Use of tenaculum, Season of IUI performing , The number of dominant follicle and cycle number. Logistic regression analysis revealed two predictive variables as regards pregnancy: number of the dominant follicles ($P = 0.003$) and the thickness of endometrium ($P = 0.001$). The odds ratios for number of the dominant follicles and thickness of endometrium were 1.41 and 1.78 respectively. The results indicate that controlled ovarian hyperstimulation (COH) and IUI achieves the best results with increased number of preovulatory follicles and endometrial thickness.

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Key words: Intrauterine insemination, pregnancy rate, prognostic factors

INTRODUCTION

Intrauterine insemination (IUI) with husband's sperm has been widely used for the treatment of infertility with a variety of indications, such as non-severe male factor infertility, unexplained infertility, cervical mucus hostility and ovulatory disturbances. To obtain a higher likelihood of achieving pregnancy, IUI is usually synchronized with ovulation, either in a natural or a stimulated cycle. It also involves fractionating and/or washing of motile sperm, before being injected into the uterine cavity. The overall success of IUI varies, with pregnancy rates between 5 and 26% per cycle (1).

Several prognostic factors for IUI outcome have been proposed, including the age of the woman (2-4), endometrial thickness and follicle number by the time of ovulation (3, 5, 6), etiology and duration of infertility (4-6), presence and type of ovarian stimulation (6), time and number of inseminations (6-8), percentage of sperm with normal morphology (9, 10), type and percentage of sperm motility (3-5, 11) and total number of motile sperm inseminated (6, 12).

In this retrospective study we have attempted to evaluate intrauterine insemination results obtained in our clinic and identify prognostic factors for the chance of pregnancy.

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MATERIALS AND METHODS

In this study we have evaluated a total of 463 IUI cycles In Fatemieh infertility research center from March 2001 to November 2003. We obtained informed consent from all participants.

Cycles were either natural or stimulated in which clomiphene citrate and/or gonadotrophins (HMG/HCG) were used for controlled ovarian stimulation. For clomiphene citrate-stimulated cycles, 100 mg Clomiphene citrate was given between days 3 and 7. For Clomiphene citrate plus gonadotrophin stimulation, 100 mg clomiphene citrate was given between days 3 and 7, followed by 150 IU of gonadotrophins added by day 9. For cycles managed by gonadotrophins only, stimulation was started on day 3 with 75–150 IU HMG daily. Follicle maturation was monitored by serial transvaginal ultrasonography.

Ovarian and endometrial responses were monitored by vaginal ultrasonography on cycle days 9 to 13 and 5000–10000 IU of HCG was administered when at least one follicle was >18 mm in mean diameter. Standard IUI was performed 36 h after administration of HCG. 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.

The categories of infertility etiology were unexplained infertility (3.45%), male factor (38.78%), endometriosis identified by laparoscope (2.8%), ovulatory disorders (23.32%), cervical factor (7.77%), male and cervical factor (2.8%), Mail factor and ovulatory disorders (18.79%) and other combined factors (2.15%). Male factor was defined as: (i) a sperm count of $< 20 \times 10^6$/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 $< 1 \times 10^6$/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 were 49×10^6/ml (range < 1–200 $\times 10^6$/ml) and 70% (range 60–99%), respectively. Infertility was primary in 72.78% of cycles and secondary in 27.22%.

Semen was obtained from male partners of couples who were undergoing IUI for treatment of infertility. The specimen 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 technique, employing Hams F10 Medium supplemented with 10% human serum albumin was used for preparation. Briefly, 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.

Intrauterine insemination was performed using an intrauterine catheter (Wallace) or Metallic catheter with a 1 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 1 ml. The women remained supine for 10–15 min after IUI. Luteal phase was supported by daily vaginal administration of 50 mg progesterone for 14 days. Plasma β-hCG levels were measured routinely, 2 weeks after IUI. Clinical pregnancy was defined as transvaginal ultrasonographic visualization of intrauterine gestational sac(s).

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 of infertility, sperm concentration and progressive motility before and after preparation, the number of pre-ovulatory follicles (>16 mm in diameter), thickness of the endometrium and number of the treatment cycle, the etiology of infertility, The method of ovarian stimulation, type of catheter, use of tenacious, season of IUI performing. Female age and duration of infertility were treated as dichotomous variables, < 35 or ≥ 35 years and ≤ 4 or > 4 years, respectively. The categories of sperm concentration and progressive motility (grade A+B) were $< 10 \times 10^6$,

10–20 × 10^6 or > 20 × 10^6/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 were 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.

Logistic regression analysis was performed using SPSS 10. Differences in pregnancy rates between groups were tested by using Student's *t* test and λ^2 test. The chosen level of significance was $P < 0.05$.

RESULTS

A total of 463 IUI cycles were analyzed. The overall pregnancy rate per cycle was 13% (60/463). The pregnancy rates according to the female characteristics are summarized in Table 1.

The pregnancy rate in women < 35 years old was significantly higher than in older women (14% versus 4.2%). No pregnancies were achieved among women > 40 years old. In addition, infertility duration of ≤ 4 years was associated with a significantly better pregnancy rate compared with a longer duration of infertility (14.4 and 11.5% respectively). As regards the diagnosis of infertility, the highest pregnancy rate (23.1%) was achieved in women with ovulatory disorders and the lowest (7.7%) in women suffering from endometriosis.

According to the method of ovarian stimulation, the highest pregnancy rate (15.7%) was obtained in the women whom were given gonadotrophin. The pregnancy rates in clomiphene citrate and clomiphene citrate plus HMG groups were 11.8% and 11.3% respectively. No pregnancy achieved in natural cycles.

Infertility type (primary or secondary) did not significantly affect the outcome of IUI treatment (Table 1). As shown in Table 2 the median number of pre-ovulatory follicles (> 16 mm in diameter) on the HCG day among the pregnant patents was 3 (± 1.6) and in non pregnant cases was 1.79 (± 1.2). The median endometrial thickness in the pregnant and non pregnant cases were 10.76 (± 2.1) and 7.08 (± 2.03) mm, respectively.

Table 1. Intrauterine insemination pregnancy rate according to female characteristics*

Characteristic	Pregnancies/cycle
Age (years)	
<35	58/415 (14)
≥35	2/48 (4.2)
Infertility duration (years)	
≤ 4	34/236 (14.4)
>4	26/227 (11.5)
Infertility aetiology	
Unexplained	3/16 (18.8)
Male factor	17/180 (9.4)
Endometriosis	1/13 (7.7)
Ovulatory disorder	25/108 (23.1)
Cervical factor	6/36 (16.7)
Male + Cervical factor	1/13 (7.7)
Male + Ovarian dysfunction	7/87 (8%)
Type of infertility	
Primary	45/337 (13.4)
Secondary	15/126 (11.9)
Method of ovarian stimulation	
Clomiphene citrate	17/144 (11.8)
Gonadotrophin	30/191 (15.7)
Clomiphene citrate + gonadotrophin	13/115 (11.3)
Natural cycle	0/133 (0)
Type of catheter	
Metallic	31/249 (12.4)
Disposable	29/213(13.6)
Endometrial thickness (mm)	
< 6+ 6-10	6(88) (6.8%)
10	54/375(14.4)
Use of tenaculum	
Yes	34/289(11.8)
No	26/174(14.9)
Season of performing IUI	
Spring	13/118 (11)
Summer	30/208 (14.4)
Autumn	10/76 (13.2)
Winter	7/54 (11.5)

Abbreviation: IUI, Intrauterine insemination.
*Data are given as number (percent).

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. There were not any significant differences in total sperm concentration and sperm motility before and after processing among pregnant and not pregnant study population (Table 2).

Table 2. The follicles, endometrium, treatment cycle and sperm characteristics in pregnant and not pregnant groups*

Characteristics	Pregnant	Not Pregnant
The of number of follicles (>16 mm)	3 ± 1.6	1.79 ± 1.2
Thickness of endometrium (mm)	10.76 ± 2.1	7.08 ± 2.03
Total sperm concentration (*10^6)	92.5 ± 47	78.8 ± 47.6
Sperm progressive motility before processing (%)	33.87 ± 7.6	34.06 ± 8.6
Sperm progressive motility after processing (%)	83.5 ± 14.6	84.7 ± 15

* Data are given as mean ± SD.

As shown in Table 3, logistic regression analysis revealed two predictive variables as regards pregnancy: The number of the dominant follicles and the thickness of endometrium. The odds ratios for number of the dominant follicles and thickness of endometrium were 1.41 and 1.78, respectively.

Table 3. Logistic regression model for predicting the success of intrauterine insemination

Variable	CR	Odds	*P*
Age	-0.065	0.93	0.13
Duration of infertility	-0.072	0.93	0.24
Type of infertility	0.132	0.87	0.77
Etiology of infertility	-0.60	0.93	0.87
Total sperm count.	0.003	1.003	0.47
Sperm motility before processing	-0.015	0.98	0.58
Sperm motility after processing	-0.007	0.99	0.76
The method of ovarian stimulation	0.36	1.4	0.19
The endometrial thickness	0.58	1.78	0.001
Type of catheter	-0.43	0.65	0.24
Use of tenaculum	-0.031	0.97	0.93
Season of IUI performing	0.96	1.1	0.80
The number of dominant follicle (>16 mm)	0.34	1.41	0.003
The cycle number	0.079	1.08	0.7

Abbreviation: CR, confidence ratio; Odds, odds ratio; IUI, intrauterine insemination.

DISCUSSION

In this study we attempted to discover prognostic factors associated with success in intrauterine insemination. We carried out logistic regression analysis of 463 IUI cycles and identified two significant variables. These are the thickness of endometrium and the number of pre-ovulatory follicles.

The most of pregnancies were seen in cycles with three or more pre-ovulatory follicles, this being remarkably higher than in cycles with only one follicle. The poor outcome in cycles with only one pre-ovulatory follicle has also confirmed in other studies (5, 13-15). The positive association between pregnancy and the number of preovulatory follicles (> 16 mm) on HCG day is in accordance with that reported in other studies (13-17) and it is indicates the number of follicles is a good prognostic predictor of IUI outcome. However, our result shave shown that the pregnancy was significantly higher in women < 35 years old but it was not predictive of IUI success. In regard to duration of infertility, we found a significant decrease in pregnancy rate with an increasing duration of infertility, as also shown previously in some studies (5, 18-20), but it also was not predictive of IUI success. This study indicates that the result of IUI will be better by using induction ovulation compared to natural ovulatory cycle. In our program use of HMG for ovarian stimulation yielded a higher rate of pregnancy rate compared with clomiphene citrate or clomiphene citrate + HMG. However, it was not predictive of IUI success. This is in agreement with the other published results (17, 21, 22) and it is may be due to that HMG cause multifollicular development and a better quality endometrium and luteal phase, thereby improving fertilization and implantation rates.

In contrary to other studies (23) and in agreement with the results published by Sinikka *et al.* (13), we found no association between pregnancy rate and sperm parameters. 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 $< 1 \times 10^6$/ml.

In conclusion, HMG/IUI is a useful treatment option for subfertility in a selected patient category. Favorable patient characteristics for treatment success are age < 35 years, duration of infertility ≤ 4 years and a cause of subfertility other than endometriosis. A multifollicular response results in better treatment outcome than a monomolecular response, indicating the necessity of ovarian stimulation combined with IUI. Most pregnancies occur during a course of four HMG/IUI cycles. This information is helpful in counseling 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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Conflict of interests

The authors declare that they have no competing interests.

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