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Evaluation of ten years of intrauterine insemination results at a tertiary center

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Summary

Purpose: To report on ten years of intrauterine insemination (IUI) practice at Haseki Training and Research Hospital to determine retrospectively, the impact of IUI on the management of subfertile couples. *Materials and Methods:* This study was a retrospective analsis of all IUI cycles completed from June 1, 2003, to July 1, 2013, at the Haseki Training and Research Hospital, Istanbul, Turkey. Baseline clinical characteristics, drugs used for ovulation induction, and triggering ovulation were reviewed. The primary outcome was clinical pregnancy. *Results:* The overall clinical pregnancy rate was 10.2% (26/253). Improved success was significantly associated with a shorter period of infertility (4.8 ± 3.9 years *vs* 3.2±2.4 years; $p = 0.01$). Clinical pregnancy rates were significantly higher when recombinant FSH was used for ovulation induction than clomiphene citrate (CC) (22% *vs* 5.6%; $p = 0.002$). Patients were also analysed for the drug used for triggering ovulation. The clinical pregnancy rate was 27.2% in the recombinant hCG group compared with 8.6% in the urinary hCG group ($p = 0.006$). *Conclusions:* IUI may be a safe and cost-effective option for mild male factor infertility or unexplained infertility. Better results may be obtained when recombinant FSH and recombinant hCG are used and when the duration of infertility is short.

Key words: Intrauterine insemination; Clinical pregnancy rate; Ovulation induction; Ovulation triggering; Unexplained infertility.

Introduction

Intrauterine insemination (IUI) is an assisted reproduction procedure that places sperm directly into the uterus. This method is indicated in cases of cervical infertility, relative male factor infertility, anovulation, mild endometriosis, and unexplained infertility [1]. Ovulation induction with clomiphene citrate (CC) prior to IUI is commonly recommended in couples, especially with unexplained infertility. More commonly, gonadotropin therapy is combined with IUI for the treatment of unexplained infertility. IUI involves timed insemination of spermatozoa into the uterus in natural cycles or insemination following stimulation of the ovaries using CC or gonadotropins [2]. It is modestly effective and reasonable to consider in couples who fail to conceive during IUI cycles combined with clomiphene [3]. Controlled ovarian hyperstimulation is a technique commonly utilized with assisted reproductive technologies. It has the advantage of increasing the number of oocytes available for fertilization, thus improving pregnancy rates per stimulated cycle [4].

The aim of this retrospective study was to report on ten years of IUI practice at Haseki Training and Research Hospital to determine the impact of IUI on the management of subfertile couples with regards to success rate and to identify prognostic factors associated with successful outcome.

Materials and Methods

The authors analysed all IUI cycles completed from June 1, 2003, to July 1, 2013, at the Haseki Training and Research Hospital, Istanbul, Turkey. All couples had unexplained or male factor infertility and had been referred to the infertility clinic. Unexplained infertility was defined if no abnormality was found during primary infertility investigations with regards to ovarian, tubal, uterine, and male factors. The inclusion criteria of this study were as follows: female aged between 20 and 45 years, unexplained infertility for at least 12 months, and patent fallopian tubes documented by hysterosalpingography. Patients who had endometriosis (classification stage III and IV of the American Infertility Society) [5], contraindication to one of the used drugs, persistent ovarian cyst (a cyst of at least 30 mm persisting for longer than two months), and having a total motile sperm count less than a million in prepared semen, were excluded from the study.

All participants underwent a baseline transvaginal ultrasound using a 7.5-MH transvaginal probe on the second or third day of the menstrual cycle to rule out the presence of an ovarian cyst.

Ovarian stimulation

All women in their first ovulation induction/IUI cycle underwent transvaginal ultrasound monitoring between cycle days 11 and 13 after recieving five days of treatment with 100 mg of CC daily starting on days 3 to 5. At the time of the ultrasound, the mean diameter of the follicle was calculated from measurements in two perpendicular planes for any follicles measuring greater than 16 mm. If at least one follicle ≥ 18 mm in mean diameter was detected, hCG was administered and IUI was scheduled 36 hours later. If follicular maturation was not successful with CC, these women underwent ovulation induction with gonadotropins.

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The treatment was initiated on the third day of the cycle and was continued until ovulation. The authors used recombinant FSH. The administration of GnRH agonist or antagonist was not required. The initial dose of gonadotropin prescribed (37.5-100 IU/day) depended on the woman's hormonal profile, age, and the duration of infertility. The initial dose was maintained until the first sixth day of stimulation and thereafter adapted as a function of the ovarian response.

To evaluate the patients, the authors used vaginal ultrasound examination evaluating follicle number and size and sperm parameters, ovulation triggering was achieved by SC injection of 250 mcg of recombinant hCG or 10,000 IU u-hCG. Insemination was performed 36 hours after the hCG injection. The criteria used for triggering ovulation was at least one follicle measuring ≥ 18 mm. Participants did not receive luteal phase support.

IUI

Semen specimens were produced by masturbation at the laboratory, following 48-72 hours of abstinence, two hours before the insemination. After a motility determination, the spermatozoa were washed free from seminal liquid and prepared for insemination (postwash TMS - number of spermatozoa inseminated). Abnormal spermatozoa were rated according to the WHO criteria [6].

A soft catheter was used for the insemination process. The end of the catheter was placed in the center of the uterine cavity, and the sperm preparation (0.2-0.4 ml) was injected slowly (over 20 seconds). The authors did not use progesterone therapy after insemination. After insemination, the woman was allowed to perform a pregnancy test (serum beta-hCG assay). If the test was positive, it was repeated seven days later to check the beta-hCG time course. Clinical pregnancies were defined as those with a fetal heart beat on ultrasound. The pregnancy was qualified as ongoing when it reached 12 weeks.

Numerical variables were reported as mean ± standard deviation (SD) when normally distributed, otherwise as median plus range. All variables were tested for normal distribution with Kolmogorov-Smirnov test. Continuous variables were compared with the *t*-test for independent samples on the Mann-Whitney *U*-test depending on the normality of their distribution. Proportions were compared with the Fischer's exact test or the chi-squared test where appropriate. A p-value ≤ 0.05 was considered statistically significant. All analyses were performed using SPSS version 21.0. The endpoints were clinical pregnancy rate (defined as ultrasound evidence of pregnancy) per cycle. The study protocol was approved by the local independent ethics committee.

Table 1. — *Baseline characteristics of all patients.*

	Median	Mean ± SD
Age (years)	29.6 ± 5.9	20−45
BMI (kg/m^2)	25.7	19−38
Infertility duration (years)	4.6 ± 3.8	1−27
Cause of infertility:		
Idiopathic	199 (78.7%)	
Male	54 (21.3%)	
Primary infertility	204 (80.6%)	
Drug used for ovulation induction:		
CC	159 ± 62.8	
Recombinant FSH	94 ± 37.2	
Drug used for triggering ovulation:		
Choriogonadotropin	230 (90.9%)	
Choriogonadotropin alfa	23 (9.1%)	

Results

The authors studied a total of 253 IUI cycles in 235 couples; 235 couples underwent one IUI cycle and 18 couples underwent two IUI cycles. Of these patients, 159 received CC and 94 received recombinant FSH for ovulation stimulation. Descriptive summaries of all the patients can be seen in Table 1.

The group treated with recombinant FSH was found to have significantly higher pregnancy rates. There was a difference in pregnancy outcomes between the two groups. Higher pregnancy rates were achieved with recombinant FSH in comparison with CC. Cycles of ovulation induction

Table 2. — *Factors affecting pregnancy rates in intrauterine insemination.*

		Pregnancy -		Pregnancy +		
		Mean ± SD	Min-max	Mean ± SD	Min-max	p
Age (years)		29.7 ± 5.9	20-45	28.5 ± 4.9	21-38	0.29
BMI (kg/m^2)		25.2 ± 2.1	19-29	25.4 ± 2.4	29-30	0.3
Infertility duration		4.8 ± 3.9	1-27	3.2 ± 2.4	1-13	0.01
Cause of infertility	Idiopatic	179		21		0.7
	Male	48		5		
Type of infertilty	Primer	183		21		0.9
	Seconder	44		5		
Drug used for ovulation induction	CC	150		9		0.002
	Recombinant FSH	77		17		
Drug used for triggering ovulation	u-hCG	210		20		0.006
	Recombinant hCG	16		6		
Leading follicle diameter at the time of hCG (mm)		19.9 ± 1.8	16-30	20.6 ± 1.9	18-26	0.06
Number of follicles		1.2 ± 0.5	1-4	1.3 ± 0.5	1-3	0.7
Sperm count (mil/ml)		31.7 ± 29.1	1-138	35.9 ± 23.4	4-85	0.1
Sperm motility		77.1 ± 16.1	10-100	75.9 ± 15.2	22-95	0.6
Sperm morphology		74.8 ± 16.1	2-98	69.1 ± 20.9	3-89	0.3

with CC had a 5.6% pregnancy rate, whereas cycles with recombinant FSH had a 22% pregnancy rate ($p = 0.002$). There was no statistical significant difference in pregnancy rates according to patient's age, body mass index or type of infertility (Table 2). Duration of infertility was significantly shorter for the pregnant group than non-pregnant group. (4.8 *vs* 3.2, $p = 0.01$)

When pregnancy rates were compared to the drug used for ovulation induction, pregnancy rates were significantly higher with recombinant hCG group than u-hCG group (27.2% *vs* 8.6% respectively, $p = 0.006$). When comparing the cycles that resulted in pregnancy versus those that did not, there was no statistical significant difference in the sperm count, motility, and morphology of the males.

Discussion

In this study, the authors found that duration of infertility, drug used for ovulation induction and drug used for triggering ovulation significantly affects the pregnancy rates after IUI. The overall pregnancy rate was found as 10.2% and this result was similar to other studies. Wainer *et al.* reported the pregnancy rate as 12.91%, Iberico *et al.* reported the pregnancy rate as 9.2% per cycle [7, 8]. Consequently, the present authors decided to evaluate their results and search for prognostic factors associated with successful outcome after IUI.

Predictors of IUI cycle success in achieving pregnancy have been examined by several studies [9-12]. Factors that were considered to be prognostic included the age of patients, duration of the infertility, primary infertility diagnosis, number of mature follicles, and sperm parameters. In this study, the authors examined the optimal follicular size before hCG administration and drug used to trigger ovulation to yield the highest pregnancy rates in IUI cycles. In both groups, the diameter of the leading follicle at the time of hCG administration was not statistically different (19.9 *vs* 20.6 mm); however, when the patients were evaluated according to drug used to trigger the ovulation, there was a statistically significant difference favoring recombinant hCG when compared with u-hCG (27.2% *vs* 8.6% respectively, $p = 0.006$). Similarly Abdelmassih *et al.* found a higher frequency of positive beta hCG values and clinical pregnancy rate in the recombinant hCG group, but their differences did not reach statistical significance [13]. Hugues *et al.* also reported the recombinant hCG products ensure a better hormonal environment during the luteal phase and thought to be related with better pregnancy results [14].

In the present study, the most important step for pregnancy occurrence was the drug used for ovulation induction. Cycles of ovulation induction with CC had a 5.6% pregnancy rate, whereas cycles with recombinant FSH had a 22% pregnancy rate ($p = 0.002$). Similarly Hughes analyzed the data from 22 studies and a total of 5,214 cycles [15]. The pregnancy rate per cycle for unexplained infertility was 15% for stimulation with gonadotropin, 6% in natural cycles, and 7% for stimulation with CC. Also Guzyck *et al.* published a meta-analysis of 45 studies and 1,806 IUI cycles [16]. The pregnancy rates in natural cycles and those stimulated with CC or hMG were 3.8% (n=378), 7.7% (n=315), and 17.1% (n=1113), respectively.

Another important factor for clinical pregnancy after IUI was found to be duration of infertility. Nuojua-Huttunen *et al.* reported significantly different pregnancy rates according to whether the length of infertility was below or above six years [17]. Similarly the present authors also found that duration of infertility, independently from the drug used for ovulation induction, significantly influenced the pregnancy rate. Women who became pregnant had significantly shorter infertility duration than women who did not (4.8 *vs* 3.2 years, $p = 0.01$).

In this study BMI and type of infertility (primer or seconder) did not appear to affect pregnancy rates, and Dodson and Legros did not find any difference, although they observed that the dose of gonadotropin had to be increased for stimulation in obese women [18].

Sperm parameters may also play an important role in the success of IUI. Sakhel *et al.* obtained a pregnancy rate per cycle of 30.3% with more than five million spermatozoa/ml *vs* 18.8% with less than five million ($p = 0.1$) Belaisch-Allart *et al.* obtained a pregnancy rate per cycle of 12.5% with less than ten million spermatozoa/ml and 17% with more than 20 million. This difference was not statistically significant but illustrates a relationship between number of spermatozoa and the pregnancy rate [19]. In the present study, sperm count was higher in the pregnant group but this was not statistically significant (35.9 *vs* 31.7 million/ml) Sperm motility and morphology were not found to be correlated with pregnancy. A possible explanation for sperm motility and morphology not being a predictive factor of the pregnancy outcome may be because the majority of men in the present study couples had total motile sperm count above threshold.

Goverde *et al.* stated that the woman's age is the most important factor influencing the likelihood of pregnancy, whatever treatment is chosen (IUI or IVF) [20]. In contrast, Brezechffa *et al.* reported that the age of women under 40 years had no influence on the pregnancy rate after stimulation with clomiphene citrate and hMG [21]. Similarly the present authors found that patients who became pregnant after IUI were younger, but this did not reach statistical significance (28.5 *vs* 29.7, respectively). It may be because most of the patients were younger than 40 years.

Silverberg *et al.* [22] analyzed IUI cycles after ovulation induction with human menopausal gonadotropins and found that ovulation success was higher in follicles larger than 20 mm on the day of hCG administration, although there was no relationship between the size of the leading follicle and cycle outcome. Also, Iberico *et al.* [8] found higher pregnancy rates when leading follicle was larger

than 20 mm, but this finding was not statistically significant. Similarly the present authors also did not find a relation for pregnancy rates for the leading follicle size.

In conclusion the present authors found that shorter duration of infertility is significantly associated with higher pregnancy rates. Also, drug used for ovulation induction and drug used for triggering ovulation significantly affects the pregnancy rates after IUI. Although the present authors analysed patients for ten years, retrospectively, a larger sample size may help in formulating better predictive parameters for IUI success. This is the limitation of this study, but all IUI procedures have been administered in a uniform manner by a unique team at a tertiary center. Since IUI represents a cost-effective and safe treatment of subfertility, it may enable the early identification of couples who would probably benefit from in vitro fertilization.

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