

Predictive factors for pregnancy outcome following controlled ovarian stimulation and intrauterine insemination

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Abstract

Objectives: To establish predictive factors for positive pregnancy outcome in cases of controlled ovarian stimulation and intrauterine insemination.

Methods: The retrospective study was conducted at Kanuni Sultan Suleyman Training and Research Hospital and comprised subjects having undergone ovulation induction cycles and intrauterine insemination between June 2010 and June 2015. Data was analysed in terms of various parameters affecting clinical pregnancy rates. SPSS 23 was used for statistical analysis.

Results: There were 475 patients having undergone a total of 923 cycles. Pregnancy was established in 133(28%) patients. Univariate analysis of biological/clinical variables revealed the presence of secondary infertility, high endometrial thickness, antral follicle number, post wash total motile sperm count and midluteal progesterone levels following intrauterine insemination to be associated with positive pregnancy outcomes ($p < 0.05$ each). Multiple logistic regression analysis was performed to establish factors that affected the pregnancy rate. The aetiology and type of infertility and high midluteal progesterone levels following intrauterine insemination were found to be statistically significant predictors of pregnancy ($p < 0.05$ each).

Conclusion: The best chance of pregnancy was found in cases with anovulatory infertility, a history of prior pregnancy, and high midluteal progesterone levels following treatment with gonadotrophins and intrauterine insemination.

Keywords: Predictors, Ovarian stimulation, Intrauterine insemination. (JPMA 67: 422; 2017)

Introduction

Infertility is one of the major public health problems affecting 15% of the patients and is defined as the inability to conceive after unprotected intercourse for 12 months.¹ Intrauterine insemination (IUI) is a commonly performed and efficient treatment modality for selected patient populations and is most effective when combined with controlled ovarian stimulation with gonadotropins.

IUI and ovulation induction with gonadotropins is currently offered to couples with mild to moderate male factor, unexplained infertility and anovulatory women who have failed to conceive with clomiphene citrate treatment. Through controlled ovarian stimulation, a larger number of oocytes are made available for fertilisation. IUI allows the introduction into the uterine cavity of a higher concentration of spermatozoa free of leucocytes, infectious agents or reactive oxygen species, all of which are factors thought to negatively affect the fertilisation process. Furthermore, cervical factor is eliminated and sperm motility is enhanced after the

sperm washing procedure in preparation for IUI.

A mean clinical pregnancy rate of 17.1% and live birth rate of 11.4% per cycle have been reported in literature following treatment of subfertile patients with gonadotropin stimulation and IUI.^{2,3} Various determinants of pregnancy such as the maternal age, aetiology and duration of infertility, endometrial thickness and number of preovulatory follicles have been reported, but the definitive determinants of success and the magnitude to which each factor contributes to positive pregnancy outcomes are still not unequivocal.²⁻⁴

The current study was planned to analyse IUI data obtained from controlled ovarian stimulation cycles with gonadotropins and establish the prognostic factors for positive pregnancy outcome.

Subjects and Method

The retrospective study was conducted at Kanuni Sultan Suleyman Training and Research Hospital and comprised subjects having undergone ovulation induction cycles and IUI between June 2010 and June 2015. Couples diagnosed with unexplained, anovulatory, tubal factor, ovarian or male-factor infertility and endometriosis were included.

For each couple, the demographic characteristics were

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recorded. These included female and male age, body mass index (BMI), parity, duration, type (primary or secondary) and aetiology of infertility, cycle day 3 serum follicle stimulating hormone (FSH) and estradiol (E2) levels, antral follicle counts, the size of the largest dominant follicle, number of dominant follicles and the endometrial thickness at the time of human chorionic gonadotropin (hCG) injection, midluteal progesterone levels after IUI, pre- and post-wash total motile sperm count (TMSC), treatment protocol and IUI outcome.

Male-factor infertility was considered in men with spermogram findings of TMSC <15 million/ml, normal morphology <4% and progressive motility <32%.

Anovulatory infertility was considered in patients with polycystic ovary syndrome (PCOS) diagnosed according to the Rotterdam criteria,⁵ women with World Health Organisation (WHO) Class 1 anovulation and in those with a midluteal progesterone level less than 10ng/ml.

Unexplained infertility was diagnosed when hysterosalpingographic bilateral tubal patency, ovulation and normal sperm parameters were demonstrated in the fertility workup of patients.

Patients with unilateral tubal patency on hysterosalpingogram were considered to have tubal factor infertility.

Patients with ultrasonographic findings consistent with endometrioma or laparoscopic evidence of stage 1 or 2 endometriosis were classified in the endometriosis group.

Patients with FSH levels above 10 IU/l were considered to have a poor ovarian reserve (POR).

Because the Turkish Ministry of Health provides funding for in vitro fertilisation (IVF) in male patients with TMSC <5 million/ml, they were referred directly to IVF without undergoing IUI treatment. Cycles in which 3 or more dominant follicles were found to develop were cancelled to avoid multiple pregnancies. Patients with a BMI >30kg/m² were referred to a dietitian and were denied

treatment until adequate weight loss and relative health gain was achieved.

Patients with an ovulation underwent ovulation induction using the low-dose step-up protocol⁶ with recombinant FSH (Gonal-F, Serono). The remaining patients received urinary FSH with the step-up protocol (Fostimon, IBSA). The starting FSH dose (37.5-150IU/day) was determined according to the age, BMI and hormonal profile of patients. Ovulation was triggered with 250 micrograms of recombinant hCG (Ovitrelle, Ares Serono) or 10,000 IU of urinary hCG (Choriomon, IBSA) when at least one dominant follicle of ≥ 17 mm was detected by ultrasonography. IUI was performed with a soft catheter 36 hours after hCG triggering. Patients were kept in a recumbent position for 15 minutes following the procedure. For luteal phase support 800 mg of vaginal micronised progesterone was administered for 2 weeks. Serum progesterone levels were obtained on the 8th day, and beta hCG levels on the 12th day following the triggering of ovulation. A clinical pregnancy was defined as the presence of a foetal heart beat on transvaginal ultrasonography performed 2-3 weeks after a positive pregnancy test.

Semen samples were obtained from male partners following a 3-day abstinence period and processed in the laboratory. Semen samples were prepared with the swim-up technique 2 hours before the IUI procedure.⁷ Semen analyses were performed using the WHO 2010 criteria.⁸

Statistical analysis was performed using SPSS 23. Results were expressed as mean $\pm$ standard deviation (SD). For scale and ordinal variables, Mann Whitney-U test was used. The categorical variables were evaluated by chi square test. $P \leq 0.05$ was considered statistically significant.

Logistic regression analysis was performed to determine the correlation between various clinical variables and pregnancy outcome.

Results

There were 475 patients having undergone a total of 923

Table-1: Clinical characteristics.

Clinical Parameters		Pregnant group (n=133)	Non-pregnant group (n=790)	p
Female age (years)		28.38 $\pm$ 4.54	28.85 $\pm$ 4.34	0.306
Male age (years)		31.2 $\pm$ 4.57	31.69 $\pm$ 4.24	0.202
BMI		24.35 $\pm$ 3.38	24.42 $\pm$ 3.18	0.828
Primary/Secondary Infertility (%)	Primary(n=748)	72.2%	82.5%	0.005
	Secondary(n=175)	27.8%	17.5%	
Infertility duration (years)		3.76 $\pm$ 2.65	4.32 $\pm$ 3.14	0.071

BMI: Body mass index; POR: Poor ovarian reserve.

Mann Whitney- U test was used for all variables except primary/secondary infertility. Primary/secondary infertility was evaluated by Chi-square test.

Table-2: Comparison of hormonal, ultrasonographic and spermiogram parameters.

	Pregnant group (n=133)	Nonpregnant group (n=790)	p
Basal FSH	6.67±2.31	6.92±1.99	0.168
Basal E2	53.75±35.88	52.03±33.29	0.736
Antral Follicle count	8.93±4.23	8.41±3.33	0.391
Endometrial thickness	8.24±2.94	7.6±3.27	0.049
Progesteron levels following IUI	31.47±12.01	25.99±10.85	0.000
Initial TPMSC (x106)	82.62 ±121.92	287.50±3414.87	0.101
Postwash TPMSC (x106)	27.95±32.11	22.12±23.11	0.002
DF diameter (%)	17.33±1.65	17.35±1.70	0.889
Follicle number >15mm (%)	1.13±0.43	1.13±0.375	0.755

FSH: Follicle stimulating hormone; E2: Estradiol; IUI: Intrauterine insemination; TPMSC: Total progressive motile sperm count; DF: Dominant follicle
Mann Whitney- U test was used for all variables.

Table-3: Predictive factors of pregnancy according to the results of multivariate analysis.

Factors	OR	95%CI	P value
Unexplained Infertility	1.12	0.42-3.01	0.817
Anovulatory infertility	0.388	0.179-0.839	0.016
Infertility duration	0.64	0.39-1.04	0.041
Antral follicle count	1.02	1.00-1.05	0.105
Endometrial thickness	1.114	1.030-1.206	0.007
Progesteron levels following IUI	1.027	1.005-1.051	0.018
Postwash TPMSC	1.001	1.001-1.001	0.047

CI: confidence interval; OR: Odds ratio; TPMSC: Total progressive motile sperm count.

cycles. Pregnancy was established in 133(28%) patients, which meant treatment cycle success of 133(14.4%). The mean number of treatment cycles per couple was 1.94 ± 0.79 . The mean duration of infertility was 3.76 ± 2.65 in the pregnant group and 4.32 ± 3.14 in the non-pregnant group (overall range: 1.18-7.4 years) ($p=0.071$). Mean maternal age was 28.7 ± 4.36 years (range: 19-39 years) and mean BMI was 24.4 ± 3.21 kg/m² (range: 19-30 kg/m²) (Table-1).

The pregnancy rates among 133 patients who got pregnant according to the aetiology of infertility were 57.1% for unexplained infertility (n=76), 25.6% for anovulatory infertility (n=34), 7.5% for tubal factor (n=10), 2.3% for WHO Class1 (n=3), 4.5% for male factor (n=6), 1.5% for endometriosis (n=2) and 1.5% for POR (n=2).

Hormonal, ultrasonographic and spermiogram parameters between the pregnant and non-pregnant groups were also compared (Table 2).

Univariate analysis of biological/clinical variables revealed the presence of secondary infertility, high endometrial thickness, antral follicle number, post-wash TMSC and midluteal progesterone levels following IUI to be associated with positive pregnancy outcomes ($p<0.05$

each). There were no significant differences in the maternal or paternal ages, BMI, size of dominant follicles (DF), number of follicles larger than 15mm on the day of ovulation triggering, stimulation protocol, starting FSH dose, Day 3 FSH and estradiol (E2) levels, duration of infertility and pre-wash TMSC between the positive and negative pregnancy groups ($p>0.05$ each).

Multiple logistic regression analysis was performed to establish factors that affect pregnancy rates. Presence of anovulatory infertility, secondary infertility, duration of infertility, endometrial thickness, post-wash TMSC and higher midluteal progesterone levels following IUI were statistically significant predictors of pregnancy ($p<0.05$ each; Table-3).

Discussion

The results of the current study demonstrate that the aetiology, type of infertility, midluteal phase progesterone levels, endometrial thickness and post-wash TMSC are predictors of pregnancy in gonadotropin-stimulated IUI cycles.

Anovulatory and unexplained infertility have been reported in the literature to have more favourable outcomes after IUI when compared with other aetiologies of infertility.^{4,9-12} In the present study, anovulatory infertility was found to be a predictor of pregnancy, whereas unexplained infertility was not. IUI and ovarian stimulation with gonadotropins is offered to patients with PCOS who are resistant to or have failed to achieve pregnancy with clomiphene citrate (CC), and cumulative live birth rates up to 71% are reported to be achieved in patients with PCOS.¹³ Since one of the primary modes of action of IUI and gonadotropin stimulation is to induce ovulation, it is logical to expect a higher likelihood of pregnancy in patients with ovulatory problems relative to those with other causes of infertility. Unexplained infertility on the other hand is

a diagnosis of exclusion and a specific cause such as gamete or implantation abnormality which cannot be identified with existing tests are likely to be the underlying reason for infertility. IUI and gonadotropin stimulation therefore may not be an optimal treatment strategy directed at the cause of infertility, yielding lower pregnancy rates.

While several studies have shown secondary infertility to have a positive influence on pregnancy outcomes¹⁴ after IUI and ovarian stimulation, others have failed to demonstrate such a relationship.^{4,12} The presence of a prior history of pregnancy was found to be a predictor of pregnancy in the present study; a factor associated with increased chances of success in IVF cycles as well.¹⁵

High midluteal progesterone levels following IUI was the third factor found to be a predictor of pregnancy in the present study. Higher progesterone levels may be an indicator of ensured ovulation or increased bioavailability of micronised progesterone administered for luteal support. Thus, higher progesterone levels may serve to prevent luteal phase deficiency, leading to better endometrial receptivity and higher pregnancy rates.

The number of mature follicles and size of the biggest mature follicle were not predictors of pregnancy in the present study. Although the presence of three or more follicles on the day of ovulation trigger has been associated with higher pregnancy rates than monofollicular development in several studies,^{4,11} but this could not be demonstrated in the present study, since those cycles with 3 or more mature follicles were cancelled to avoid multiple pregnancies according to the treatment protocol used in our institution. Ghosh et al. reported higher pregnancy rates when the dominant follicle measured more than 20mm as opposed to less than 20mm.¹⁶ However, the size of the biggest mature follicle was not a predictor of pregnancy in the present study.

Regarding semen parameters, the post-wash total motile count has been proposed as a test to determine couples who would benefit from IUI,¹⁷ but a cut-off point above which a higher likelihood of pregnancy can be expected has not been agreed upon. TMSC thresholds ranging from 1million/ml to 10 million/ml have been suggested by different authors in distinguishing patients who should be referred to IVF or receive IUI treatment.^{14,18} In the present study, only patients with TMSC more than 5 million received IUI and gonadotropin stimulation due to the regulations set by

the Turkish Ministry of Health. A higher post-wash TMSC was associated with a higher possibility of pregnancy and it was found to be a positive predictor of pregnancy.

Ovarian reserve is an important indicator of treatment response and may be determined by hormonal assays on the third day of the menstrual cycle or the antral follicle count (AFC). In the present study, cycle day 3 E2 and FSH levels were similar in pregnant and non-pregnant patients in accordance with Merviel et al.'s findings, but a higher AFC was found in pregnant patients. This may be explained by the fact that AFCs are considered to be superior to day 3 FSH levels as indicators of ovarian reserve.¹⁹ Furthermore, increased AFCs may be linked with PCOS and anovulatory infertility; a factor shown to be predictor of IUI success relative to other aetiologies of infertility in the present study.

In the present study, a sufficient endometrial thickness before IUI has been shown to be an important determinant of pregnancy, which is in accordance with a number of studies.^{14,20} Pregnancy rates have been shown to increase parallel with increasing endometrial thicknesses up to 10mm, reaching a plateau after this measurement. Wolff et al. failed to find a negative influence of endometrial thickness ≥ 14 mm on pregnancy rates for IUI cycles. They also reported clinical pregnancies in endometrial thicknesses between 4-7mm.

The duration of pregnancy had an effect on pregnancy outcome in the present study. Similarly, several studies demonstrated that the longer the duration of infertility, the lower the chances of a successful pregnancy.^{3,4} Indeed, Nuojua-Huttunen et al. found decreased pregnancy rates in couples with an infertility period of 6 years or more. IVF is generally offered to couples with an infertility duration longer than 4 years.²¹

Age-related decline in fertility is a well-known phenomenon and is linked to progressive follicular depletion and loss of oocyte quality. This decline in fertility is believed to become evident around 35 years of age and accelerate greatly after 40.²² Thus, female age has been found to be one of the strongest predictors of pregnancy success in many reports.^{12,21,23,24} However, this was not the case with the present study. Inclusion of only female patients below the age of 40, and a low mean age of the patient population in the present study may be the reason why such a relation between maternal age and pregnancy rates could not be demonstrated. Others have also failed to show a

negative influence of female age on pregnancy rates in IUI cycles in women under 40 years of age, indicating that IUI can be offered to patients at least until this age.^{12,23,25,26}

Merviel and Dodson showed that BMI does not influence pregnancy rates in IUI cycles, but the dose of gonadotropin required to stimulate the ovaries increases parallel with BMI.^{21,27} A relationship between BMI and IUI success was also not demonstrated in the present study in which the mean BMI of the study population was 24kg/m².

One of the limitations of this study is that the majority of patients in the study population had unexplained and anovulatory infertility, with smaller number of patients with tubal, mixed, or male-factor infertility. Also, only clinical pregnancy rates were recorded whereas the main outcome measure of infertility treatment happens to be live birth rates.

Despite the retrospective nature of the study, the findings may help in the identification of couples with good prognostic factors who would benefit from treatment with IUI and gonadotropins.

Conclusion

The variations in the predictors of pregnancy in IUI cycles in literature are most probably due to the heterogenous nature of study populations and the lack of prospective randomised trials. According to our results, the best chances of pregnancy were achieved in those with anovulatory infertility, a history of prior pregnancy, post-wash TMSC, infertility duration, endometrial thickness and high midluteal progesterone levels following IUI.

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Conflict of Interest: None.

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