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ORIGINAL RESEARCH

Medicine Science International Medical Journal

Medicine Science 2018;7(4):785-9

# The prognostic factors for pregnancy after gonadotropin-induced controlled ovarian stimulation therapy with intrauterine insemination cycles

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Received 12 April 2018; Accepted 19 April 2018
Available online 25.04.2018 with doi: 10.5455/medscience.2018.07.8784



**Abstract**

To identify the predictive determinants for pregnancy in patients who underwent controlled ovarian stimulation (COS) /intrauterine insemination (IUI). A total 458 gonadotropin-induced controlled ovarian stimulation and intrauterine insemination cycles in 361 couples using were studied between February 2014 and January 2018. The main outcome was clinical pregnancy rate, which has been analyzed according to baseline clinical characteristics (women age, length of infertility, day 3. follicle stimulating hormone, estradiol level) and variables related to intrauterine insemination cycle (number of preovulatory follicles, endometrial thickness), and sperm parameters (sperm concentration, sperm motility, sperm morphology and total motile sperm count (TMSC). The overall clinical pregnancy rate was 11.6% (53/458) per cycle. Clinical pregnancy rate per cycle was 12.0% (43/361) in the first cycle; 10.3% (9/87) in the second cycle, and 10% (1/10) in the third cycle. Among the predictive factors evaluated, more than 25x106 TMSC was also good predictor for clinical pregnancy. The TMSC in ejaculate proved to be a useful predictor of the chance for pregnancy after IUI treatment.

**Keywords:** Intrauterine insemination, ovarian stimulation, predictive factors, TMSC

## Introduction

Around 10-15 % of couples are infertile. Intrauterine insemination (IUI). is a simple and first line treatment for infertile couples with unexplained infertility, cervical factors–related infertility, ejaculatory abnormalities, and male subfertility [1]. The pregnancy rate per IUI cycle changed from 3% to 65% [2,3]. These huge variances in pregnancy rate may be due to patients' selection criteria, the incidence of several infertility factors, different ovarian stimulation protocols, and different sperm parameters, preparation techniques [4].

In the literature, many topics have been described as influencing pregnancy rates after IUI treatment, such as the female age, the length of infertility, type of infertility, number of mature follicles, estradiol (E2) level on the day of hCG application, and the nature of catheter used [5,]). In addition to, there was a significant difference in pregnancy rate in relation to stimulation protocols combined with IUI. A meta-analysis involving 556 women demonstrated that pregnancy rates were higher in women with gonadotropins than oral agents such as clomiphene citrate (OR: 1.8: 95 CI: 1.2-2.7) [2].

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The objective of this study was to identify prognostic determinants for achieving a pregnancy in couples undergoing the IUI cycles with controlled ovarian stimulation (COH) using gonadotropins.

## Material and Method

### Subjects

We retrieved the data from gonadotropin and IUI treatment cycles that conducted at the Division of Reproductive Endocrinology and Infertility, School of Medicine, Inonu University, between February 24, 2014, and January 31, 2018.

During this period, 482 IUI treatment cycles were started. Of these, 24 IUI cycles were withdrawn because of polyfollicular development (8 cycles), premature luteinizing hormone (LH) peak (3 cycles), drug insensitivity/drug administration error (3 cycles), or for additional causes (10 cycles). In the 458 remaining IUI cycles, 87 patients had encountered 2 IUI treatment cycles, and 10 patients had encountered 3 IUI treatment cycles.

The study participants had infertility which is defined as at least 12 months of intercourse without contraception. All couples had encountered an infertility assessment consisting of comprehensive couples medical story, serum hormone evaluation on the second or the third day of the menstrual cycle [Follicle stimulating hormone (FSH), Luteinizing hormone (LH), Estradiol (E2),

Thyroid-stimulating hormone (TSH), and Prolactin (PRL)], baseline vaginal pelvic ultrasonography and semen examination. Gynaecological examinations were performed for all patients. Tubal patency was confirmed by hysterosalpingography or laparoscopy. In addition, at least two sample analyzed according to World Health Organization 2010 standards [7]. Total motile sperm count (TMSC) was calculated by multiplying the volume of the ejaculate in millimeters by sperm concentration and the proportion of fast forward progressive and slow progressive motile sperms divided by 100%.

The study was accepted by the Malatya Ethical Review Board and was designed and conducted in accordance with the Declaration of Helsinki.

**Clinical and Laboratory Procedures**

All IUI cycles were accompanied by COH with gonadotropins. The management was started on the 2 or 3 day of the menstrual cycle. These women received ovarian stimulation with human menopausal gonadotropins (Menogon, Ferring, Switzerland) or recombinant FSH (Gonal F, Merck, Germany). The initial dose of gonadotropin (37.5–75 IU) relied on the patient's age, day-3 FSH and E2 level, and antral follicle count. Patients were monitored with the usual hormonal serum hormone (LH and E2) level and through vaginal ultrasound examination for follicle number, size, and endometrial thickness. If the vaginal ultrasound showed an enough number of developed follicles of at least 17- 18 mm, the final oocyte maturation is achieved by the injection of 250 µg of recombinant human chorionic gonadotropin (hCG) (Ovitrelle Merck, Germany). Approximately, 34–36 hours after the hCG injection, we performed insemination. In cycles with a spontaneous LH surge, IUI was performed 24 hours after the surge. If more than two leading follicles (>17-18 mm) were present in the day of trigger, insemination was cancelled.

Semen samples were collected after 72 hours of abstinence. After the first assessment, discontinuous Percoll centrifugation methods with gradients of 80% and 40% was performed [8]. Semen examples were evaluated according to the 2010 World Health Organization standards [7]. Prepared sperm inseminated with a soft catheter (Laboratoire C.C.D., Paris, France) in the procedure. A serum sample for quantitate β-hCG measurement was taken on 14 days after insemination. If β-hCG was positive, a transvaginal ultrasound was performed 21 days after pregnancy test. The clinical pregnancy rate defined as the presence of a gestational sac with a fetal heartbeat detected by ultrasound. Biochemical pregnancy loss and tubal pregnancy were noted, but both of them excluded from the analysis.

**Statistical Analysis**

Data were stored and analyzed by using the Statistical Package for Social Science Software for Windows, release 11.0 (SPSS, Inc; Chicago, IL, USA). The chi-square or Fisher's exact tests were used for categorical variables. Parameters with a normal distribution were demonstrated as mean ± standard deviation (SD), and parameters with an abnormal distribution were demonstrated as median and interquartile range (IQR). To compare variables between the pregnant and non-pregnant groups, student's t-test was used for parametric data and the Mann-Whitney U test was used for non-parametric data. A p-value less than 0.05 was considered statistically significant.

**Results**

Four hundred fifty-eight (458) IUI cycles in 361 couples were analyzed. The mean women age was 29.06 ±4.4 years(y) and the mean age of men was 32.52± 4.2 y. The mean period of marriage was 4.87 ± 3.1y and the mean age of period of infertility was 3.53± 2.1 y. A majority of total subjects (73%) had primary infertility, and 27% of subjects had secondary infertility. The median serum basal FSH, LH, E2, TSH and PRL levels were 6.3 (IQR: 5.2-7.6) IU /l; 5.2 (IQR: 3.7-7.4) IU /l; 46(IQR: 34-69) pg /ml, 12.9 mIU /l (IQR: 9.05-18.2), and 1.7 ( IQR: 1.2-2.5) ng/ml, respectively.

The median whole gonadotropin dose used per cycles was 600 (IQR: 412.5 -900) IU. On the day of hCG, the mean number of follicles measuring >14 mm diameter was 1.4 ±0.8 and the mean endometrial thickness was 9.9± 5.2 mm. A basal median sperm concentrations was 43 (IQR:28-58) million/ml, and median ratio of motility was 50 (IQR: 45-52)% , median morphology according to Kruger criteria was 2(2-3)%, and TMSC were 36 (IQR: 21-59) millions.

The overall pregnancy rate was 13.1 % (60/458). After the exclusion of 5 biochemical pregnancy losses, and 1 anembryonic gestation, and 1 ectopic pregnancy, the clinical pregnancy rate was 11.6% (53/458).

The clinical pregnancy rate per cycle was 12.0% (43/361) in the first cycle; 10.3% (9/87) in the second cycle, and 10% (1/10) in the third cycle.

The clinical characteristics and smoking habits of the patients are showed in Table 1. There were no significant difference between the groups in respect to the age of couples, duration of infertility, previous live birth history, basal serum FSH, LH, and E2 concentrations, and smoking habits.

**Table 1.** Sociodemographic and clinical characteristics among groups

| Factors | Clinical pregnant group (n= 53) | Non-pregnant group (n= 398) | p value |
|---|---|---|---|
| Women age (y) | 29.3±4.6 | 29.0±4.3 | 0.58 |
| Men age (y) | 32.6±4.5 | 32.5±4.1 | 0.72 |
| Length of marriage (y) | 4.75± 3.0 | 4.86± 3.1 | 0.8 |
| Length of infertility (y) | 3.38±1.8 | 3.55± 2.1 | 0.57 |
| Primer /Secondary infertility | | | 0.79 |
| Primer | 38 (71.7) | 292 (73.51) | |
| Secondary | 15 (28.3) | 106 (26.5) | |
| Previous live birth | | | 0.86 |
| Yes | 7 (13.2%) | 56 (14.1) | |
| No | 46 ( 86.8) | 342 (85.9) | |
| Basal serum FSH(mIU/ml) | 6.3 (5.37- 7.56) | 6.4 (5.2- 7.6) | 0.69 |
| Basal serum LH(mIU/ml) | 5.4 (3.5- 9.24) | 5.2 (3.8-7.2) | 0.32 |
| Basal serum E2(pg/ml) | 42.7 (29.5-71.5) | 47.0 (35-70.2) | 0.41 |
| Serum Prolactin(ng/ml) | 13.1 (9.25-19.24) | 13.0 (9.1-18.2) | 0.83 |
| Serum TSH(mIU/ml) | 2.0 (1.32-2.75) | 1.7 (1.1-2.47) | 0.55 |
| Smoking | 6 (12.3%) | 36 (10.8) | 0.58 |

The variables related to treatment with controlled ovulation induction and sperm parameters of the groups group are showed in Table 2. Both the number of pre-ovulatory follicle and the

endometrial thickness was not the related to clinical pregnancy rate. The clinical pregnancy rate per cycle was 10.7% for one pre-ovulatory follicle development, whereas the pregnancy rate was 13.9% for two or more pre-ovulatory follicle development. Although no pregnancies were achieved with a thickness below 7 mm, the endometrial thickness was not a predictive factor of pregnancy.

**Table 2.** Factors related to treatment with controlled ovulation induction and sperm parameters among groups

| Factors | Clinical pregnant group (n= 53) | Non-pregnant group (n= 398) | p value |
|---|---|---|---|
| Number of cycles | | | 0.68 |
| 1 | 43 (81.1) | 313 (78.6) | |
| ≥2 | 10 (18.9) | 85 (21.4) | |
| Number of follicle >14mm* | | | 0.33 |
| 1 | 34 (64.2) | 281(70.6) | |
| ≥ 2 | 19 (35.9) | 117 (29.4) | |
| Endometrial thickness* | | | 0.14 |
| <7mm | 0 (0) | 18 (4.5) | |
| ≥7 mm | 53 (100%) | 380 (95.5) | |
| Sperm concentration (million/ml) | | | 1.00 |
| <15 | 2 (3.8) | 17 (4.3) | |
| ≥ 15 | 51(96.2) | 381 (95.7) | |
| Sperm motility (%) | | | 0.16 |
| <40 | 1 (1.9) | 32 (8.0) | |
| ≥ 40 | 52 (98.2) | 366 (92.0) | |
| Sperm progressive motility (%) | | | 0.68 |
| <32 | 20 (37.7) | 162 (40.7) | |
| ≥ 32 | 33(62.3) | 236 (59.3) | |
| Sperm morphology | | | 0.43 |
| 0-1 | 15 (28.3) | 93 (23.4) | |
| ≥2 | 38 (71.7) | 305 (76.6) | |
| TMSC (million) # | | | |
| <25 | 11(20.8) | 137 (34.5) | 0.04 |
| ≥25 | 42 (79.2) | 261(65.5) | |

*On the day hCG # TMSC: Total motile sperm count

In this study, sperm concentration, motility, and morphology did not help to predict IUI success. But among the predictive factors evaluated, the TMSC more than 25x106 is also good predictor factor for clinical pregnancy (p=0.04). The clinical pregnancy rate per cycle reduced from 11.6 to 8.5 if TMSC lower than 25 million.

## Discussion

In this retrospective study, we reported an overall clinical pregnancy rate 11.6% (53/458). Our results are within the range of previous studies [9,10]. In the present study, the clinical pregnancy rate per cycle was 12.0 % (43/361) in the first cycle; 10.3% (9/87) in the second cycle, and 10% (1/10) in the third cycle. Some studies demonstrated that the clinical pregnancy rate was significantly higher in the first IUI cycle [6,11], whereas other studies have described constant pregnancy rates for the first three to seven IUI cycles [12,13]. Eventually, most pregnancy after IUI took place within the first three treatment cycles, favoring maximum of three IUI cycles before IVF.

Variables influencing the outcome of COH/IUI

### Age

In this study, we did not find any association between woman's age and IUI success, which is in agreements with the results of earlier results [14,15]. This is evidently due to patient's selection critaeria, because we did not recommended to older women than 38 years in vitro fertilization. A research by Brzechffa et al. [16] reported that, the age of female under 40 had no influence on the pregnancy after IUI. Similarly, Wainer et al. [15] showed that the pregnancy rate per cycle were similar between 25 and 40 years. In contrast, Bronte et al. [17] showed an age-related difference in gestation rate: 18.9% until age 26; 13.9% between 26-30; 12.4% between 31-35, 11.1% between 36-40; 4.7 between 41-45, and 0.5% over age 45 . Lastly, all these results showed that IUI is a poor treatment choice for women over age 40 years.

### Duration of infertility

In this study there was no significant decrease in clinical pregnancy rate with an increasing period of infertility, as also reported formerly in some investigation [18,19].This is evidently due to patient's selection criteria because we recommended to couples with at longer than 5 years duration of infertility in vitro fertilization. In contrast that some studies demonstrated that a significant decrease in pregnancy rate with increasing period of infertility [6,11,20]. Finally, IUI cannot be advised to patients when the infertility period longer than 5 years.

### Basal hormone assays

There was no statistically significant difference in pregnancy rate according to FSH, and E2 levels. Likewise, Merviel et al. [10] did not find any significant differences in the pregnancy rate per couples: 9.4 IU/L when FSH baseline level and 80 pg/mL for the E2 baseline level.

### Smoking

In this study, smoking status did not appear to affect pregnancy rates. As an agreement, Merviel et al. [10] did not find any association between smoking habits and pregnancy rates after IUI. Although smoking can negatively influence a couple's fecundity, however the particular impact of these factors on IUI efficiency does not appear in the various reports.

### Endometrial thickness

In this study, endometrial thickness did not appear to affect pregnancy rates. Endometrial thickness has been associated with the success rate of assisted reproductive technology as well as IUI [20], but the results of the studies about the importance of endometrial thickness have been contradictory. Several studies reported significant associations between endometrial thickness and pregnancy rates [6]. In this study there did not achieve any pregnancy when the endometrial thickness was less than 7 mm, which is in agreement with the lower limits of endometrial width described in earlier studies [21].

### Number of leading follicles

In this study, the number of leading follicles were not a good prognostic factor for the pregnancy after IUI. This result is agreement with earlier studies [20]. On the contrary, some studies reported the number of follicles was a good prognostic factor for pregnancy after IUI. Nuojua- Huttunen et al. [6] reported that the maximum pregnancy rate (16.3%) was detected in cycles with three pre-ovulatory follicles, whereas the pregnancy rate was 5.7

in cycles with only one follicle.

**Male factor**

In this study, sperm concentration, motility, morphology did not help to predict IUI success. Only TMSC in ejaculate proved to be a valuable prognostic factor of the chance for pregnancy after IUI treatment.

Regarding of male factor, some studies did not found any statistically significant differences about semen parameters [10, 20]. With respect to sperm count, Sakhel et. al. [22] obtained 30.3% pregnancy rate per cycle by using more than 5 million spermatozoa/ml vs 18.8 with less than 5 million spermatozoa/ml (p=0.1). Belashi-Allart et al. 823] demonstrated that a pregnancy rate per cycle of 12.5% with less than 10 million spermatozoa/ml and 17% with more than 20 million/ml. Although these differences are not statistically significant, those two studies illustrate a direct relationship between spermatozoa and the pregnancy rate.

With respect to mobility, Belaish-Allart et al. [23] did not report any link between the proportion of motile spermatozoa and the pregnancy rate. In contrast, Sakhel et al. [22] described an rise in the pregnancy rate from 17.1% to 30.4% if the motility exceeded 20% (p=0.06). In a study by Merviel et al. [10] the pregnancy rate per couple decreased from 40.9 to 19.3 if 70% of the spermatozoa were immobile.

Focusing on morphology, Burr et al. [24] reported a decline in the pregnancy rate from 18.2 to 4.3% when the ratio of teratozoospermia reaches 90%. Belaish-Allart et al. [23] did not recommended IUI to male as teratozoospermia rate over 80%. In contrast, Karabinus et al. [25] did not report any differences among pregnancy rates under this threshold. Weiner et al. [26] reported the pregnancy rate not significantly influenced by teratozoospermia as long as more than 5x 106 motile spermatozoa/ml were existing for insemination.

Van Voorhis et al [18] reported that TMSC as the prognostic factor for clinical pregnancy after IUI. They found that pregnancy rates were very low in couples with the lowest average TMSC below 10x106 after IUI treatment (6.5 %), whereas pregnancy rates were improved and persistent above 10 million TMSC in ejaculate. However, Cohlen et al. showed that a pregnancy rate of 12% per cycle after IUI even if the average TMSC of men's below <10 million [27]. Surely, the threshold value of TMSC is not absolute. Miller et al [76] demonstrated a pregnancy rate 12.4 when TMSC is over 20x106 compared with 7.4% when it is between 10-20x106.

## Conclusion

In conclusion, the present study showed that the TMSC above 25x106 is also good predictor factor for clinical pregnancy. The TMSC in ejaculate proved to be a valuable clinical prognostic factor of the chance for pregnancy after IUI treatment.

**Competing interests**

*The authors declare that they have no competing interest*

**Financial Disclosure**

*The financial support for this study was provided by the investigators themselves.*

**Ethical approval:**

*Ethical approval was obtained from the hospital administration to use the patients' data.*

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