Is Anxiety an Effective Factor on the Success of Ovulation Induction/Intrauterine Insemination Cycle?

Kaygı Ovulasyon İndüksiyonu/İntrauterin İnseminasyon Siklus Başarısında Etkili Bir Faktör Müdür?

Kaygı ve Intrauterin Inseminasyon / Anxiety and Intrauterine Insemination

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Özet

Amaç: Ovulasyon indüksiyonu/intrauterin inseminasyon (OI/IUI) siklus başarısında kaygının etkisini araştırmayı amaçladık. Gereç ve Yöntem: Açıklanamayan infertilite nedeniyle rekombinant folikül stimule edici hormon ile birinci OI/IUI tedavisi uygulanan 150 infertil çift bu prospektif çalışmaya dahil edildi. Tedavi sonucuna göre katılımcılar gebelik var ya da gebelik yok diye iki gruba ayrıldılar. İki farklı durumdaki kaygı derecelerini ölçmek için tüm kadınlara Durumluluk ve Sürekli Kaygı Ölçeği Anketi (State-Trait Anxiety Inventory Scale) uygulandı: 1) menstruel siklusun üçüncü gününde ovulasyon indüksiyonuna başlamadan hemen önce sürekli kaygı dereceleri ölçüldü. 2) İnseminasyon günü işlemden önce durumluluk kaygı dereceleri ülçüldü. Çoklu regeresyon analizi ile değişik faktörlerin OI/IUI sonuçları üzerine etkileri değerlendirildi. Bulgular: İnseminasyon siklusları sonrasında 22 (14.7%) kadın gebe kaldı. Durumluluk kaygı, OI/IUI sonrası klinik gebelik oranlarını olumsuz etkilerken, sürekli kaygı inseminasyon sonuçlarını etkilemedi. Çoklu regeresyon analizinde kadın yaşı, menstruel siklusun 3. günündeki antral folikül sayısı, hCG uygulamasından önceki ≥16 mm folikül sayısı ve durumluluk kaygı derecesi, OI/IUI sonrası klinik gebelik sonuçları için etkili faktörler olarak bulundu. Tartışma: Bu çalışma durumluluk kaygının OI/IUI siklus başarısına etki edebileceğini göstermiştir. Bu yüzden bu tür tedavi protokolleri ile birlikte gerekli danışmanlık hastalara verilmelidir.

Anahtar Kelimeler

Kaygı; İnfertilite; İntrauterin İnseminasyon; Ovulasyon İndüksiyonu

Abstract

Aim: To evaluate the effect of anxiety on the success of ovulation induction/intrauterine insemination (OI/IUI) cycle. Material and Method: 150 unexplained infertile couples underwent first OI/IUI cycle with recombinant follicle stimulating hormone were enrolled in this prospective study. They were cathegorized, based on their intrauterine insemination results to positive and negative pregnancy groups. All of the women were asked to fill out State-Trait Anxiety Inventory Scale to measure the different type of anxiety levels at two times: 1) On the third day of menstruel cycle, before starting the OI, trait anxiety scores were calculated 2) On the insemination day, state anxiety scores were calculated prior to procedure. The effect of various contributing factors on OI/IUI outcomes were evaluated with multivariate logistic regression analysis. Results: After IUI cycles, 22 women (14.7%) became pregnant. State anxiety levels were inversely effective on clinical pregnancy rates of OI/IUI cycles. However, trait anxiety did not influenced the IUI success. In logistic regression model including covariates, it was found that woman's age, antral follicle count on the third day of menstruel cycle, number of ≥16 mm follicle before hCG administration and state anxiety scores were effective factors of clinical pregnancy rate in OI/IUI cycles. Discussion: This study suggests that state anxiety may have an effect on success of the OI/IUI cycle. Thus, OI with IUI treatment protocols should consider offering counselling interventions.

Keywords

Anxiety; Infertility; Intrauterine Insemination; Ovulation Induction

DOI: 10.4328/JCAM.3588 Received: 11.05.2015 Accepted: 20.06.2015 Printed: 01.12.2015 J Clin Anal Med 2015;6(suppl 6): 770-3
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Introduction

A combination of controlled ovulation induction (OI) with intrauterine insemination (IUI) remains an important therapeutic step in infertility, and is especially appropriate for cases with mild male factor infertility, anovulation, endometriosis with at least one patent tube, and unexplained infertility. OI/IUI is a widely used treatment modality of infertility due to its simplicity, easy management, low cost, and absence of potentially serious complications [1].

Infertility is a mental stress-inducing condition. This mental stress, particularly anxiety and depression, may be due to various factors, including uncertainty of the cause of infertility, financial stress, and pressure from others who know the couple [2]. And also women receiving medical treatment for infertility may have some psychiatric disorders with high prevalence. Chen et al. reported that in women who visited an assisted reproduction clinic for a new course of the treatment, 40.2% had a psychiatric disorder, with generalized anxiety disorder being the most frequent diagnosis (23.2%), followed by major depression (17.0%) [3]. But, it is unclear, whether the psychological stress and anxiety effect on treatment success and whether interventions to decrease stress and anxiety are beneficial.

The aim of this study is to describe anxiety levels during OI/IUI treatment at two time points and to assess if they are effective on treatment success.

Material and Method

This study was an observational prospective cohort study determining anxiety levels of infertile women undergoing OI with IUI treatment at Zekai Tahir Burak Woman's Health Research And Education Hospital between January-May 2014. A total of 150 women were recruited for this study who agreed to participate and signed a written informed consent form. This study was approved by Ethical Committe of hospital. Study procedures conformed to the Decleration of Helsinki for Medical Research involving Human Subjects. All women participated in the sudy met the following criteria: age <30 years; normal findings on hysterosalpingography; regular menstrual cycles with normal basal serum follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and thyroid stimulating hormone; and normal sperm parameters of husbands. Women with any kind of psychiatric disorder and antipsychotic drug use were exculeded.

The Turkish version of the self-administered Spielberger State-Trait Anxiety Inventory (STAI) questionnaire form was used to measure anxiety levels. Its use to assess anxiety status has been validated [4,5]. The STAI consists of two subscales. State Anxiety (STAI-S) is a measure of situational anxiety with subjects being asked to respond based on "how you feel right now". Trait Anxiety (STAI-T) is a measure of a general tendency to be anxious with subjects being asked to respond based on "how you generally feel". Each subscale consists of 20 items scored on a four- point Likert-type scale; thus the range of possible scores on each subscale is 20 (low anxiety) to 80 (high anxiety). The reliability coefficient (Cronbach's a), referring to a normative sample of men and women, is 0.91 for STAI-S and 0.90 for STAI-T. The test-retest reliability ranges from 0.92 (after 90 min) to 0.75 (after 118 days) for the STAI-T. The participants filled out STAI-T subscale on the third day of menstrual cycle, before the start of OI and STAI-S subscale on the insemination day immediately before the IUI.

All women in the study were treated by same senior physician with the same OI/IUI procedures. All IUI cycles were started on the third day of menstrual cycle, after basal ultrasound examination and hormonal assay. And all OI cycles were continued until ovulation. Recombinant FSH was used for OI. The starting dose of FSH was 75-150 IU according to the status of the patient, including age and hormonal status. All the IUI cycles were the first attempt using FSH after three times of unsuccessful IUI treatment with clomiphene citrate. Follicular development was monitored by vaginal ultrasound and serum estradiol levels, and the dose of FSH was adjusted accordingly every 1-3 days. When at least one follicle with diameter ≥18mm was observed, 10,000 IU of human chorionic gonadotropin (hCG) was given to induce ovulation. A single IUI was performed 36 hours after administration of hCG.

Semen was collected 2 hours prior to the insemination and after 72 hours of abstinence. Swim up method was used for sperm preparation. Biochemical pregnancy was initially detected 15-20 days after insemination. Ultrasound was performed at 6 weeks of gestation to confirm fetal viability. Clinical pregnancy was defined as the presence of a gestational sac confirmed by ultrasound scanning. Spontaneous abortion was defined as the loss of a pregnancy before the 12th week.

SPSS 17.0 (SPSS, Inc., Chicago, IL, USA) for Windows software was used for statistical analysis of the study data. Numeric variables were stated as mean±standard deviation (SD), and categorical variables were expressed as number and percentage. After descriptive tests, Kolmogorov-Smirnov test was used to determine the data distributions. Categorical variables were compared using a x2 test, and continuous variables were analyzed using Students' t-test.. The effects of factors correlated with clinical pregnancy rate after OI/IUI treatment were assessed using a multivariate logistic regression model. The p values less than 0.05 were considered statistically significant.

Results

Data were collected from 150 primary infertile couples. After OI/IUI cycles, 22 women (14.7%) became pregnant. Two of them resulted with first trimester abortions. Demographic and baseline characteristics of the couples were shown in Table 1. The mean age of women and their husbands in clinically positive pregnancy group were significantly smaller than in negative pregnancy group ($p<0.001$ and $p=0.001$ respectively). No significant differences were observed between groups with regard to educational levels, employement status, current smoking ratios, duration of infertility, body mass index (BMI), third day FSH and estradiol levels, semen characteristics, endometrial thickness on hCG day, duration of stimulation and total used gonadotropin dose. Pregnant women, had significantly higher number of antral follicle count on the third day of menstruel cycle and higher number of ≥16 mm-diameter follicle before hCG administration, compared to non-pregnant ones ($p<0.05$).

The results demonstrated that pregnant women were not significantly different from non-pregnant ones regarding their mean score for trait anxiety (38.82±3.78 and 37.58±4.25, respectively; $p=0.215$) . However, mean state anxiety score of

Table 1. Demographic and baseline characteristics of the couples

	Positive pregnancy (N=22)	Negative pregnancy (N=128)	p*
Woman's age (years)	22.86±1.49	26.76±4.13	<0.001
Infertility duration(years)	2.34±0.70	2.13±0.64	0.178
BMI(kg/m2)	24.90±2.02	24.05±2.50	0.148
Educational Level			
Elementary school	6 (27.3)	21 (16.4)	
Middle school	6 (27.3)	43 (33.6)	
High school	7 (31.3)	54 (42.2)	
University	3 (13.6)	10 (7.8)	0.442
Employed woman	8 (36.4)	57 (44.5)	0.475
Current smooking	4 (18.2)	19 (14.8)	0.688
FSH level (IU/L)	6.06±1.35	6.78±2.11	0.129
Estradiol level (pg/ml)	55.50±26.23	52.04±19.62	0.279
Number of antral follicle count	7.28±2.98	5.15±1.86	<0.001
Husband's age (year)	27.68±2.75	29.66±2.41	0.001
Semen volume (ml)	3.31±0.56	3.17±0.56	0.300
Sperm concentration (x 109/L)	63.05±8.69	64.08±6.25	0.523
Sperm motility (%)	55.50±5.17	53.96±5.30	0.221
No. of follicle (≥16 mm)	2.64±0.73	1.91±0.69	<0.001
Estradiol level on hCG day (pg/ml)	505.19±45.80	480.56±60.96	0.079
Endometrial thickness on hCG day (mm)	9.00±1.31	8.73±1.18	0.341
Duration of stimulation (day)	8.91±0.68	8.92±0.54	0.929
Gonadotropin dose (U/ml)	682.05±43.36	701.37±52.22	0.111
STAI-T score	38.82±3.78	37.58±4.25	0.215
STAI-S score	41.19±3.47	44.84±4.18	<0.001

Values are given as mean±standard deviation and number(percentage)
STAI-T: State Trait Anxiety Inventory-Trait; STAI-S: State Trait Anxiety Inventory-State; BMI:Body Mass Index, FSH: Follicle Stimulating Hormone
*p<0.05 is considered statistically significant

pregnant women were significantly lower than of non-pregnant women (41.19±3.47 and 44.84±4.18, respectively; p<0.001) (Table 1).

Analysis by logistic regression model showed that woman's age, total number of antral follicule count on the third day of menstruel cycle, ≥16mm in diameter follicule number and state anxiety level were the independent factors which affect the clinical pregnancy rate of OI/IUI treatment, significantly (Table 2).

Table 2. Multivariate logistic regression model to compare odds ratio of possible effective factors on success of OI/IUI treatment

	Wald	OR	95% CI for OR	p*
Woman's age	4.449	1.473	1.028-2.110	0.035
Infertility duration	0.897	2.332	0.404-13.460	0.344
BMI	2.632	0.625	0.354-1.103	0.105
FSH level	0.339	0.831	0.445-1.552	0.561
Antral follicle count	5.348	0.460	0.238-0.888	0.021
≥16mm follicle number	3.967	0.163	0.027-0.972	0.046
Husband's age	0.111	1.086	0.669-1.761	0.739
STAI-T score	2.014	0.680	0.399-1.158	0.156
STAI-S score	4.166	1.871	1,025-3.416	0.041

OR: Odds Ratio; CI: Confidence Interval; STAI-T: State Trait Anxiety Inventory-Trait; STAI-S: State Trait Anxiety Inventory-State; BMI:Body Mass Index, FSH: Follicle Stimulating Hormone
*p<0.05 is considered statistically significant

Discussion

IUI is often suggested as a first option treatment for infertile couples with unexplained infertility [1]. In literature, it is well established that using gonadotropins has the best treatment outcomes in controlled OI with IUI [6,7]. In our study, the pregnancy rate in OI/IUI cycles with gonadotropins was 14.6%, which was similar to two meta-analysis results reported by Hughes and Guzyck et al. [8,9].

We assessed the anxiety levels, as measured by STAI questionnaire at two time points in IUI cycle. We found STAI-Trait levels of women as 37.64±4.02 on the third day of menstruel cycle and STAI-State levels as 44.12±4.29 on the IUI day. In published reports, average STAI scores in women undergoing fertility treatment range from 33 to 50, reflecting in part the variation in mean scores among different countries as well as differences in population norms [10].

Results obtained from the logistic regression analysis showed that state anxiety was effective on pregnancy rate after IUI treatment. In other words, women who achieved pregnancy after an IUI cycle had lower anxiety score as measured by STAI-S. These findings are consistent with the findings of many previous studies [11-14], including invitro fertilization and intracytoplasmatic sperm injection treatment outcome. However, some other studies have reported no association between anxiety and reproductive outcomes [15,16].

The effects of stress and anxiety on infertility development are explained well by hypothalamic-pituitary-adrenal (HPA) axis related mechanism. Psychological factors activates the HPA axis, which is involved in the excretions of corticotrophic-releasing hormone, adrenocorticotrophic hormone and cortisol, respectively [17]. The literature suggests the mediation of the HPA axis on the down-regulation of the hypothalamic-pituitary-ovarian axis at all levels. The HPA activation in untreated women inhibits the GnRH pulse generator and consequently inhibits the secretion of gonadotropins (LH, FSH) and sex steroids [18]. However, in gonadotropin stimulated IUI and IVF, psychological effect is unlikely to occur through this pathway because of administration of gonadotropins exogenously. Thus, the state anxiety is probably effective in the implantation phase of the stimulated cycles [19].

In addition, we have also found three more factors that are statistically effective on pregnancy rate after OI/IUI cycle in our study. The woman's age is one of them, that seems to influence the outcome inversely. It is generally accepted that the woman's age is the most important factor influencing the likelihood of pregnancy and female fecundity following to IUI procedure, namely treatment success decreases as the woman becomes older [20,21]. Another factor found to be effective total antral follicle count on the third day of menstruel cycle. Similarly, Erdem et al. noted that lower antral follicle count on basal transvaginal ultrasonography was associated with lower clinical pregnancy and live birth rates in unexplained subfertile couples who were treated with controlled OI and IUI [22]. The number of ≥16 mm in diameter follicle before hCG administration was the last one that influenced the OI/IUI success, significantly. Mer-

viel et al. analyzed 1038 IUI cycles and reported that pregnancy rates were significantly influenced by the number of follicles >16mm and the estradiol levels on the day of hCG administration and also they found a string link between these two parameters and the rate of multiple pregnancies [23]. However, Noujua-Huttunen et al. did not find any link between the number of follicles and the multiple pregnancy rate, even though they also noted lower pregnancy rates with a single >16mm follicle than with three follicles [24].

This study has some limitations. Firstly, the sample size of the present study is relatively small and the sample of infertile women is drawn only from one public infertility clinic and not from many clinics, which may have introduced selection bias and may not provide to generalize the results to other populations from reproductive treatment clinics. Although we considered the effects of many possible confounding variables on the success of treatment, we did not controll lifestyle factors, such as caffeine, and alcohol intake and psychosocial factors, such as partner's stress and women's perception of stigma. Additionally, we did not evaluate anxiety levels at any time points subsequent to IUI procedure. Anxiety status following to procedure may also be effective on the success of treatment. Morover, we did not assess biochemical markers such as adrenalin, cortisol. Therefore, future studies investigating the association between anxiety and treatment outcomes should include all known aspects of anxiety, such as psychosocial aspects, lifestyle aspects, the autonomic nervous system and the endocrine system.

In conclusion, we demonstrated that state anxiety levels inversely influenced OI/IUI success. Therefore, women with fertility problems enrolling for IUI treatment should be evaluated for levels of anxiety and should be offered appropriate psychological counseling interventions, because reducing anxiety levels may be beneficial for IUI treatment outcomes. And also, younger woman age, greater number of antral follicle count on the third day of menstruel cycle and greater number of ≥16mm follicle before hCG administration was predictive factors for OI/IUI cycle success. Clinicians providing IUI for infertile couples should pay close attention to these factors.

Competing interests

The authors declare that they have no competing interests.

References

1. Veltman-Verhulst SM, Cohlen BJ, Hughes E, Heineman MJ. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev 2012;9:CD001838.
2. Ogawa M, Takamatsu K, Horiguchi F. Evaluation of factors associated with the anxiety and depression of female infertility patients. Biopsychosoc Med 2011;5:15.
3. Chen TH, Chang SP, Tsai CF, Juang KD. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod 2004;10:2313–8.
4. Spielberger CD. Manual for the State-Trait Anxiety Inventory. In. Palo Alto, CA: Consulting Psychologists Press, Inc. 1983.
5. Oner N, LeCompte A. Süreksiz durumluk/sürekli kaygı envanteri, 2nd edn. Boğaziçi Üniversitesi Yayınevi, Istanbul 1998.
6. Reindollar RH, Goldman MB. Gonadotropin therapy: a 20th century relic. Fertil Steril 2012;97:813-8.
7. Zeyneloglu HB, Arici A, Olive DL, Duleba AJ. Comparison of intrauterine insemination with timed intercourse in superovulated cycles with gonadotropins: a meta-analysis. Fertil Steril 1998;69:486–91.
8. Hughes EG. The effectiveness of ovulation induction and intra-uterine insemination in the treatment of persistent infertility: a meta-analysis. Hum Reprod 1997;12:1865–72.
9. Guzyck DS, Sullivan MW, Adamson GD, Cedars MI, Falk RJ, Peterson EP, et al. Efficacy of treatment for unexplained infertility. Fertil Steril 1998;70:207–13.
10. Verhaak CM, Smeenk JM, Evers AW, Kremer JA, Kraaimaat FW, Braat DD. Women's emotional adjustment to IVF: a systematic review of 25 years of research. Hum Reprod Update 2007;13:27-36.
11. Smeenk JM, Verhaak CM, Eugster A. van Minnen A, Zielhuis GA, Braat DD. The effect of anxiety and depression on the outcome of in vitro fertilization. Hum Reprod 2001;16:1420–3.
12. Eugster A, Vingerhoets AJ, van Heck GL, Merkus JM. The effect of episodic anxiety on in vitro fertilization and intracytoplasmatic sperm injection treatment outcome: A pilot study. J Psychosom Obstet Gynaecol 2004;25:57–65.
13. An Y, Sun Z, Li L, Zhang Y, Ji H. Relationship between psychological stress and reproductive outcome in women undergoing in vitro fertilization treatment: psychological and neurohormonal assessment. J Assist Reprod Genet 2013;30:35-41.
14. Gourounti K, Anagnostopoulos F, Vaslamatzis G. The relation of psychological stres to pregnancy outcome among women undergoing in-vitro fertilization and intracytoplasmic sperm injection. Women Health 2011;51:321-39.
15. Lintsen A, Verhaak CM, Eijkemans MJ, Smeenk JM, Braat DD. Anxiety and depression have no influence on the cancellation and pregnancy rates of a first IVF or ICSI treatment. Hum Reprod 2009;24:1092-8.
16. Hashemi S, Simbar M, Ramezani-Tehrani F, Shams J, Majd HA. Anxiety and success of in vitro fertilization. Eur J Obstet Gynecol Reprod Biol 2012;164:60-4.
17. Gold PW. The organization of the stress system and its dysregulation in depressive illness. Mol Psychiatry 2015;20:32-47.
18. Ferin M. Clinical review 105: Stress and the reproductive cycle. J Clin Endocrinol Metab 1999;84:1768-74.
19. Gallinelli A, Roncaglia R, Matteo ML, Ciaccio I, Volpe A, Facchinetti F. Immunological changes and stress are associated with different implantation rates in patients undergoing in vitro fertilization-embryo transfer. Fertil Steril 2001;76:85–91.
20. Jeon YE, Jung JA, Kim HY, Seo SK, Cho S, Choi YS, et al. Predictive factors for pregnancy during the first four intrauterine insemination cycles using gonadotropin. Gynecol Endocrinol 2013;29:834-8.
21. Speyer BE, Abramov B, Saab W, Doshi A, Sarna U, Harper JC, et al. Factors influencing the outcome of intrauterine insemination (IUI): age, clinical variables and significant thresholds. J Obstet Gynaecol 2013;33:697-700.
22. Erdem M, Erdem A, Guler I, Atmaca S. Role of antral follicle count in controlled ovarian hyperstimulation and intrauterin insemination cycles in patients with unexplained subfertility. Fertil Steril 2008;90:360-6.
23. Merviel P, Heraud MH, Grenier N, Lourdel E, Sanguinet P, Copin H. Predictive factors for pregnancy after intrauterine insemination (IUI): an analysisi of 1038 cycles and a review of the literature. Fertil Steril 2010;93:79-88.
24. Nuojua-Huttunen S, Tomas C, Bloigu R, Tuomivaara L, Martikainen H. Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome. Hum Reprod 1999;14:698–703.

How to cite this article:
Kokanalı D, Kokanalı MK, Eroğlu E, Yılmaz N. Is Anxiety an Effective Factor on the Success of Ovulation Induction/Intrauterine Insemination Cycle? J Clin Anal Med 2015;6(suppl 6): 770-3.