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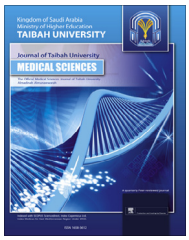

Clinical Study

# Impact of estradiol monitoring on the prediction of intrauterine insemination outcome

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**الملخص**

**أهداف البحث:** يهدف البحث لتقدير القيمة التنبئية لمستويات "الإستراديول" في نفس يوم حقن هرمون الغدد التناسلية المشيمي البشري على نسبة نجاح التلقيح داخل الرحم.

**طرق البحث:** شملت هذه الدراسة 206 دورة تلقيح داخل الرحم تمت في الفترة ما بين يونيو 2011م وأكتوبر 2012م. سبق جميع دورات التلقيح داخل الرحم تنشيط للمبيض بهرمون الغدد التناسلية المشيمي البشري بدءا من اليوم الثالث للدورة. كما تم إجراء تلقيح واحد داخل الرحم بعد إعطاء هرمون الغدد التناسلية المشيمي البشري بـ 24-36 ساعة. واستخدم تحليل الإنحدار اللوجستي الثنائي لتحديد المتغيرات لنجاح التلقيح داخل الرحم. جرى تقييم النتيجة الرئيسة لقياس معدل الحمل السريري في كل دورة وفقا لمستوى الإستراديول .

**النتائج:** بحسب LR+=2 و AUC =73,0 أظهر تحليل ROC أن مستوى الإستراديول 465 بج/مل للتنبؤ بالحمل مع حساسية 60% وخصوصية 66%. حدد تحليل الإنحدار اللوجستي الثنائي وجود مستويات الإستراديول أعلى من 465 بج/مل (قيمة P أصغر من 01,0، 95% نطاق الثقة =147,0 - 687,0) ومدة التحفيز (قيمة P أصغر من 01,0 ,95% CI) =201, 0 -705, 0 كمتغيرات أعطت دلالة إحصائية لنجاح التلقيح داخل الرحم .

**الاستنتاجات:** مستوى الإستراديول أكبر من 465 ب ج/مل في يوم حقن هرمون الغدد التناسلية المشيمي البشري قد يشير إلى نتائج متقدمة على التحفيز المعتدل للمبيض جنبا إلى جنب مع التلقيح.

**الكلمات المفتاحية:** مستوى الإستراديول; التلقيح داخل الرحم; النتائج; معدل الحمل

**Abstract**

**Objective:** To evaluate the predictive value of oestradiol levels on the day of human chorionic gonadotrophin (hCG) administration on intrauterine insemination success rate.

**Methods:** The present study included 206 intrauterine insemination (IUI) cycles performed between June 2011 and October 2012. All IUI cycles were preceded by ovarian stimulation with gonadotrophins starting on cycle day 3. A single IUI was performed 24–36 h after hCG administration. Binary logistic regression analysis was performed to define the covariates of IUI success. The main outcome measure, clinical pregnancy rate per cycle, was assessed according to the oestradiol level.

**Results:** With LR + = 2 and AUC = 0.73, ROC analysis revealed out the oestradiol level as 465 pg/mL to predict the pregnancy with 60% sensitivity and 66% specificity. Binary logistic regression analysis identified the presence of oestradiol levels higher than 465 pg/mL ($p < 0.01$, 95%

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CI = 0.147–0.687) and stimulation duration ($p < 0.01$, 95% CI = 0.201–0.705) as the covariates approached statistical significance for IUI success.

**Conclusions:** Oestradiol level >465 pg/mL on the day of hCG administration might point out advanced outcome on mild ovarian stimulation combined with insemination.

**Keywords:** Intrauterine insemination; Oestradiol level; Outcome; Pregnancy rate



## Introduction

Intrauterine insemination (IUI) is widely used to treat unexplained infertility and male subfertility. It is generally considered to be an intermediate step before assisted reproductive techniques such as in vitro fertilization with or without intracytoplasmic sperm injection.[1] The success rate of IUI is still a subject of controversy, with a 10–20% clinical pregnancy rate (CPR) expected per cycle.[2,3] IUI combined with controlled ovarian stimulation may increase the cumulative pregnancy rate,[4] and the low CPRs seen are often attributed to the use of mild stimulation protocols for a monofollicular response.[5] Aggressive protocols with higher doses of gonadotrophins improve pregnancy rates by increasing the number of preovulatory follicles and the rate of multiple pregnancy.[6] The aim of our study was to determine a cut-off value for the oestradiol level that predicts the insemination outcome after mild ovarian stimulation.

## Materials and Methods

The population studied consisted of 206 women who underwent ovulation induction with IUI between June 2011 and October 2012. The inclusion criteria were failure to conceive for ⩾12 months of unprotected intercourse, age <38 years, basal follicle-stimulating hormone (FSH) level <12 IU/l and total motile sperm count of the partner >5 million. The exclusion criteria were ovarian cysts >15 mm on a baseline transvaginal ultrasound scan, severe endometriosis (stage III or IV according to the revised American Fertility Society staging), the total number of motile sperm <5 million, any contraindication for one of the ovarian stimulation drugs and multiple pregnancy.

All the couples had undergone a standard infertility evaluation that included medical history, physical examination, assessment of tubal patency by either hysterosalpingography or laparoscopy, basal FSH, luteinizing hormone, oestradiol, thyroid-stimulating hormone, prolactin evaluation on cycle day 3 and a semen analysis. Abnormal semen results were confirmed by a second analysis ⩾3 weeks apart. Semen samples with a concentration of >20 million/ml, progressive motility >50% and normal morphology >14% were considered normal.[7,8] The motility categories were classified as grade A (rapid linear with sluggish progressive motility), grade B (nonprogressive motility) and grade C (immotility). Semen analyses that failed to meet these criteria but with a total motile sperm count of >5 million were included. Couples were considered eligible if the woman had at least one patent fallopian tube and a documented normal endometrial cavity.

A transvaginal ultrasound scan was performed on cycle day 3. On the same day, ovarian stimulation was performed with recombinant FSH (rFSH; Gonal-F, Merck Serono, Istanbul, Turkey; or Puregon, MSD, Istanbul, Turkey) at a starting dose of 75 IU/day. If the patient's body mass index (BMI) was ⩾25 kg/m$^2$, the starting dose of rFSH was increased to 100 IU/day. The ovarian response and endometrial thickness were monitored by transvaginal ultrasonography first on day 7 of stimulation and then on alternate days; the rFSH dose was adjusted according to the ovarian response. When the average diameter of the leading follicle reached ⩾16 mm, 250 μg of recombinant human chorionic gonadotropin (hCG, Ovitrelle, Merck Serono, Istanbul, Turkey) was administered, and endometrial thickness and oestradiol levels were evaluated.

A single IUI was performed 24–36 h after hCG injection. The semen samples used for insemination were processed within 1 h of ejaculation by density gradient centrifugation, followed by washing with culture medium. The women rested for 15 min after IUI. Luteal phase support was given to all women with 90 mg daily of vaginal micronized 8% progesterone gel. When there were four or more follicles with a diameter ⩾16 mm or a serum oestradiol level >1500 pg/ml, hCG administration was stopped, and regular coitus was forbidden to avoid multiple pregnancy.

### *Statistical analysis*

Statistical analysis was performed with SPSS version 16.0. The main outcome measure was CPR per cycle. Clinical pregnancy was defined as the evidence of pregnancy by ultrasound examination of the gestational sac at weeks 5–7. To predict the outcome, female age, duration of infertility, baseline FSH level, baseline luteinizing hormone level, baseline oestradiol level, total rFSH dose, stimulation duration and total motile sperm count were included in the calculations. Descriptive statistics were presented as percentages or the mean ± standard deviation. Differences between groups for categorical variables were analysed by the Chi-square test or Fisher's exact test, as appropriate, and comparisons of continuous variables between groups were analysed with the Student's $t$ test according to the results of normality tests. Binary logistic regression analysis was used to analyse oestradiol level on the day of hCG administration, dominant follicle count, duration of stimulation, total motile sperm count before and after washing, BMI, previous pelvic surgery and insemination time, in order to identify the covariates that were significantly associated with successful IUI. Receiver operating characteristic (ROC) analysis was performed to determine the area under the curve and the likelihood ratio that showed the oestradiol level predicted pregnancy. $P$ values <0.05 were considered statistically significant.

## Results

The overall CPR of the cohort was 16.8% per cycle. The demographic and clinical characteristics of the women are presented in Table 1 and the stimulation and insemination parameters of the couples in Table 2. With a likelihood ratio of 2 and an area