

Serum beta human chorionic gonadotropin levels at 16 days following embryo transfer in intra cytoplasmic sperm injection cycles to predict pregnancy outcome

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ABSTRACT

الأهداف: تحديد القيمة التنبؤية لبيتا موجهة الغدد التناسلية المشيمائية البشرية (B-hCG) في اليوم 16 بعد عملية زرع الجنين وذلك من أجل الكشف عن الحمل.

الطريقة: تم عمل هذه الدراسة الاسترجاعية في مركز فاطمة الزهراء لأمراض العقم والخصوبة بجامعة بابل للعلوم الصحية، بابل، إيران وذلك خلال الفترة من يناير 2008م إلى ديسمبر 2009م. شملت الدراسة 97 امرأة حامل ممن أجريت لهن عملية الحقن المجهري (ICSI)، وبعدها خضعن لاختبار قياس هرمون (B-hCG)، وقد تم تحديد العوامل التالية: نوع العقم، وأسبابه، ومدته، وعمر المريضة، ومعدل هرمون (B-hCG) في اليوم 16 بعد عملية زرع الجنين، وعدد الأجنة، بالإضافة إلى نتائج الحمل.

النتائج: بلغت نسبة الحمل العيوش 38.9% من النساء اللاتي ظهر فيهن هرمون (B-hCG) بمعدل أقل من 100 وحدة دولية/ لتر (العدد=18)، فيما وصلت هذه النسبة إلى 84.4% من النساء اللاتي ظهر فيهن هذا الهرمون بمعدل أكبر من أو يساوي 100 وحدة دولية/ لتر (العدد=79). ولقد كانت العلاقة بين ظهور (B-hCG) ونتائج الحمل واضحة ($p < 0.001$). بلغت القيمة القاطعة (cut-off value) لهرمون (B-hCG) والذي من شأنه الكشف عن الحمل العيوش 100 وحدة دولية/ لتر (درجة الحساسية - 91%، درجة الدقة - 48%، نسبة النتائج الإيجابية - 85%، ونسبة النتائج السلبية - 61%)، فيما وصل معدل (B-hCG) في الحمل المتعدد إلى أكبر من أو يساوي 200 وحدة دولية/ لتر مع درجة الحساسية - 88%، ودرجة الدقة - 45%، ونسبة النتائج الإيجابية - 37%، ونسبة النتائج السلبية - 91%.

خاتمة: يمكن الاستعانة بمعدل هرمون (B-hCG) في اليوم 16 بعد عملية زرع الجنين من أجل الكشف عن نتائج الحمل وذلك في عمليات الحقن المجهري.

Objectives: To determine the prognostic value of beta human chorionic gonadotropin (β -hCG) concentration on the sixteenth day after embryo transfer to predict pregnancy outcome.

Methods: In this retrospective cohort study, β -hCG levels were measured in 97 pregnant women that underwent intra-cytoplasmic sperm injection (ICSI) in Fatemeh-Zahra Infertility and Reproductive Health Research Center, Babol University of Medical Sciences, Babol, Iran from January 2008 to December 2009. Type, duration, causes of infertility, and age of patients, β -hCG levels on the sixteenth day after embryo transfer, the number of embryos, and pregnancy outcome were assessed.

Results: Incidence of viable pregnancies in β -hCG levels < 100 IU/L ($n=18$) was 38.9%, and in β -hCG levels ≥ 100 IU/L ($n=79$) was 84.4%. Correlation of β -hCG with pregnancy outcome was significant ($p < 0.001$). Cut-off value of β -hCG to predict viable pregnancy was 100 IU/L (sensitivity - 91%, specificity - 48%, PPV - 85%, and NPV - 61%). The β -hCG levels ≥ 200 IU/L with a sensitivity of 88%, specificity of 45%, PPV - 37%, and NPV = 91% had predicted twin pregnancy.

Conclusion: Serum β -hCG level on the sixteenth day after embryo transfer can be useful to predict the pregnancy outcome in ICSI cycles.

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Assisted reproductive technology (ART) was initiated in humans in the mid 1970's following the birth of Louise Brown in 1978.¹ The ART has been performed in many medical centers worldwide. The early diagnosis of pregnancy and its predictive outcome is a reasonable concern for every infertile couple exposed to pregnancy.² Pregnancies that occurred after assisted conception and embryo transfer are at increased risk for an adverse outcome compared with women who conceive naturally. Multiple gestations also occur more frequently. Therefore, it is necessary for markers that precisely diagnose the pregnancy, and predict its outcome as early as possible, allowing for modification of monitoring and its treatment. Sonographic evaluation is part of the routine follow-up after assisted conception, but a gestational sac is not reliably visible before 33-37 days after ovulation induction. There is an ongoing effort to look into endocrine markers that can earlier detect the establishment of pregnancy and predict its outcome.³ Researchers are trying to discover markers or hormones, which can diagnose pregnancy in earlier stages. In addition, some placental hormones have been proposed as useful diagnostic markers for pregnancy. Human chorionic gonadotropin (hCG) is the first detectable marker, and it is used as the main marker for the diagnosis of pregnancy following ART.⁴ The hCG is a glycoprotein with lipid structure. Its best known biologic function is the maintenance of the corpus luteum of pregnancy. It has been hypothesized that hCG may act to promote uterine vascular vasodilatation and myometrial smooth muscle relaxation. Some investigators also showed that beta-hCG (β -hCG) levels can be elevated in pre-eclamptic women at term pregnancy.⁵ At day 16 following retrieval of oocyte, β -hCG can be measured serially in the laboratory. If the determination of β -hCG is carried out before this time, it may result in false positive, or false negative findings. Exogenous hCG can be detected up to 14 days after injection.^{1,4} Some studies for determining the prediction of pregnancy outcome by measuring markers including serum progesterone, interleukin-8, estradiol, inhibin, and specific glycoproteins of pregnancy have been carried out.^{3,6-8} However, the clinical role of these markers has not been well understood.^{9,10} A positive correlation has been observed between early serum β -hCG levels, and pregnancy outcome after in vitro fertilization (IVF), or intra-cytoplasmic sperm injection (ICSI) treatment cycles.^{11,12} A single, inexpensive, and reliable laboratory test, which can predict pregnancy outcome is of high importance for both the patient and the medical team. The purpose of this study was to determine the predictive value of serum β -hCG measurement on day 16 after embryo transfer in ICSI treatment cycles for pregnancy outcome.

Methods. This was a retrospective cohort study, in which 97 infertile females who were treated by ICSI were included. These patients were referred to Fatemeh-Zahra Infertility and Reproductive Health Research Center, Babol University of Medical Sciences, Babol, Iran from January 2008 to December 2009. The ethics committee of the university approved the study. The inclusion criteria were female, age 20-35 years, with body mass index of 20-25 kg/m², duration of infertility more than 2 years, a normal menstrual cycle, and a normal day 3 hormonal assays. We excluded women with endocrine abnormalities. Five ml blood sample was obtained from each patient. All of the serum samples were kept in a refrigerator, and then tested for β -hCG by radioimmunoassay (manufacturer, Yavarantebjam, Iran). Functional sensitivity of the assay was 4.0 IU/L. The antibodies used in the immunoassay were highly specific for β -hCG. Cross reactivities less than 1% were obtained with several related molecules. Following screening by vaginal ultrasound on day one of the menstrual cycle, patients underwent long standard gonadotropin releasing hormone (GnRH) agonist protocol.¹³ From the third day of the menstrual cycle, high dose oral contraceptive tablet was initiated for patients, and continued for 21 days. Then, ovarian stimulation protocol for preparation of follicles was carried out by GnRH agonist (Superfact, Aventis Pharma Deutshlan, Frankfurt, Germany) in a single daily subcutaneous dose of 0.5 mg. From the third day of the next menstrual cycle, human menopausal gonadotropin (HMG) injection (IBSA, Switzerland) was initiated, and Superfact was reduced to 0.25 mg/day. Monitoring of follicles by transvaginal sonography (TVS) was carried out. When at least 3 follicles had a diameter exceeding 18 mm, a 10,000 IU units of hCG (Daropakshsh Pharmaceutical Industries, Tabriz, Iran) was administered. Cycle would be cancelled if the ovarian response was poor with <3 follicle at day 8 of the cycle.¹⁴ Aspiration of oocytes was carried out in the operation room under general anesthesia, 34-36 hours after administration of hCG. Oocytes were fertilized in the laboratory by ICSI method, and embryo transfer was performed 2 days after oocyte retrieval. The embryo transfer was carried out using Friedman catheter (Solco Basle (UK) Ltd, High Wycombe, UK) through the cervix. After placement of speculum in lithotomy position and washing the vagina, the catheter was passed through the cervical canal, and under the guide of abdominal ultrasound, transfer of 2 embryos into the uterus was accomplished. For supporting the luteal phase, Cyclogest suppository (Actavis, Barnstaple, UK) 400 mg daily was applied. The blood samples of patients 16 days after embryo transfer were collected to measure the concentration of β -hCG by radioimmunoassay.

Patients whose β -hCG concentration was more than 25 IU/L were entered to the study.¹⁵ A checklist was designed and the following variables were gathered from the patients: age, type of infertility (primary or secondary), duration of infertility, factor of infertility (male or female), β -hCG level on day 16 post embryo transfer, number of embryos (singleton, twin pregnancy), and outcome of pregnancy. The patients were followed-up until the twentieth weeks of gestation. Outcomes of pregnancies were divided as viable and non-viable pregnancy. Viable pregnancy was defined as one resulting in delivery of at least one live fetus at ≥ 20 week's gestation. Non-viable pregnancies constituted biochemical pregnancies (a temporary rise of serum β -hCG without signs of intrauterine pregnancy in TVS), ectopic pregnancy (diagnosed in TVS), miscarriages (cessation of development of intrauterine pregnancy observed in TVS), and pregnancies with hydatidiform mole (a pathologic-anatomic diagnosis).¹⁶

For statistical analyses, descriptive indices such as frequency (percentage), mean and standard deviation (\pm SD) were used. For categorical variables, the chi-square test or Fisher's exact test, and for continuous variables the t-test was applied. A $p < 0.05$ was considered statistically significant. Outcome measures of this study were sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Receiver operating characteristic (ROC) curve was used for general evaluation of β -hCG level.¹⁷ All analyses were performed using the Statistical Package for Social Sciences version 13.0 for Windows (SPSS Inc, Chicago, IL, USA). Informed consent was obtained from all participants prior to enrollment. The study protocol was in conformity with the ethical guidelines of the 1975 Declaration of Helsinki.¹⁸

Results. The mean \pm SD age of patients was 27.85 ± 5.92 years. The mean \pm SD duration of infertility was 6.7 ± 5.02 years. Eighty-two (84.5%) infertilities were primary. Male factor infertility constituted 58 (59.8%) cases of subjects. With respect to pregnancy outcome, 23 cases (23.7%) of miscarriages occurred. There was no ectopic pregnancy, hydatidiform mole, and biochemical pregnancy. In Table 1, type of infertility and its factor, number of fetuses, and outcome of pregnancies are presented. There was a significant correlation between pregnancy outcome and β -hCG concentration ($p < 0.001$). A level of β -hCG ≥ 100 IU/L predicted ongoing pregnancy with a sensitivity of 91% (95% confidence interval [CI]: 84-97), specificity of 48% (95% CI: 27-68), PPV - 85% (95% CI: 77-93), and NPV - 61% (95% CI: 39-84). According to the ROC curve presented in Figure 1, this level of β -hCG concentration was the most suitable cut-off point in order to determine

and predict viable pregnancy. Using the ROC curve, the ability of serum β -hCG concentration on day 16 after embryo transfer was relatively high in differentiating viable pregnancy versus pregnancy failure (Figure 1, area under the ROC curve: 0.649, 95% CI=0.494-0.804, $p = 0.032$). The risk ratio of miscarriage among patients with β -hCG levels < 100 IU/L was 4.023 times (95% CI: 2.83-27.14) greater than those with β -hCG levels ≥ 100 IU/L. Eighteen (18.6%) individuals had β -hCG level < 100 IU/L (first group), and 79 (81.4%) cases had β -hCG ≥ 100 IU/L (second group). In the first group, 61.1% had non-viable pregnancy and 38.9% had viable pregnancy. In the second group, viable pregnancy rate was 15.2%, and non-viable pregnancy rate was 84.4%. The mean \pm SD of β -hCG in singleton pregnancy was 253.79 ± 229.86 IU/L, and twin pregnancy was 435 ± 364.03 IU/L. There was a significant correlation between β -hCG level and twin pregnancy ($p = 0.024$).

Table 1 - Frequency of infertility type, factor, number of fetuses, and pregnancy outcome.

Variables	Frequency	(%)
<i>Infertility type</i>		
Primary	82	(84.5)
Secondary	15	(15.5)
<i>Infertility factor</i>		
Male	58	(59.8)
Female	29	(29.9)
Male/Female	10	(10.3)
<i>Number of fetus</i>		
Singleton	71	(73.2)
Twin	26	(28.8)
<i>Pregnancy outcome</i>		
Miscarriage	23	(22.7)
Viable pregnancy	77	(76.3)
Biochemical/molar/ectopic pregnancy	0	(0.0)

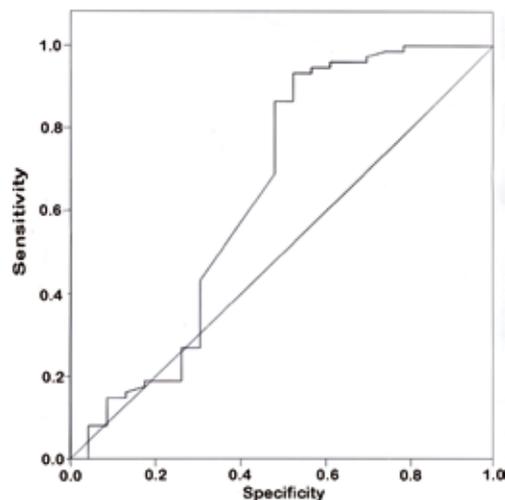


Figure 1 - Receiver operating characteristic curve for predicting viable pregnancy using serum beta human chorionic gonadotropin concentration on day 16 after embryo transfer.

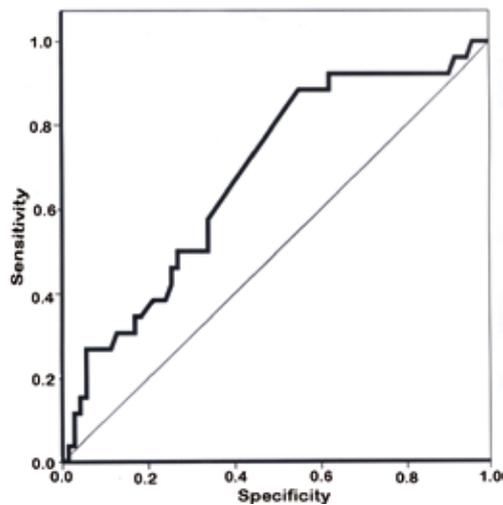


Figure 2 - Receiver operating characteristic curve for predicting the probability of twin pregnancy according to beta human chorionic gonadotropin level.

Using the ROC curve, β -hCG level of ≥ 200 IU/L with a sensitivity of 88% (95% CI: 76-100), and specificity of 45% (95% CI: 33-57), PPV=37% (95% CI: 25-49), NPV=91% (95% CI: 82-100) predicted the probability of twin pregnancies (Figure 2, area under the ROC curve = 0.683, 95% CI: 0.566-0.800, $p=0.006$). No significant relationship was found between the concentration of β -hCG and age, duration, and factor of infertility. In addition, the relationship between the type of infertility (primary or secondary) and the pregnancy outcome was not statistically significant ($p=0.182$). Women who had a viable pregnancy were significantly younger (26.89 ± 5.19 years) than those who lost their pregnancy (30.91 ± 7.12 years), ($p=0.018$). No significant relationship was found between age of partners and β -hCG level ($r=0.118$, $p=0.251$).

Discussion. In this study, the best cut-off β -hCG value for prediction of the viable pregnancy was equal or more than 100 IU/LI. We measured β -hCG level 16 days after embryo transfer as previous studies^{1,4} showed that determination of hCG before this time may result in false positive or false negative findings. False positive finding may be due to intramuscular administration of hCG for stimulation of ovulation. In a study by Kumbak et al,¹⁹ pregnancies following ART were evaluated. It was revealed that in case of embryo transfer 3 days after oocyte retrieval, β -hCG = 98 IU/l with a sensitivity of 89%, and a specificity of 69% predicted viable pregnancy. For embryo transfers carried out 5 days after oocyte retrieval, β -hCG = 257 IU/l with a sensitivity of 78% and specificity of 81% predicted the likelihood of a viable pregnancy.¹⁹ In Porat et al's study,¹¹ β -hCG levels more than 150 IU/l on day 13 after embryo transfer

were considerably associated with successful pregnancy. In Homan et al's study,²⁰ serum β -hCG level on day 16 after ovulation was measured, and had shown that in a β -hCG levels between 25 and 50 IU/l the probability of a successful pregnancy is 35%, whereas in levels of >500 IU/l the likelihood increases to 95%. They concluded that a single β -hCG level on day 16 after ovulation provides a useful predictor of pregnancy outcome.²⁰ In Urbansek et al's study,²¹ β -hCG = 50 IU/l on day 11 after embryo transfer with a sensitivity of 75% and specificity of 81% was introduced as the cut-off point for predicting pregnancy outcome.

In Chen et al's study,¹² serum β -hCG concentration of 150 IU/l on day 15 after embryo transfer with a sensitivity of 71%, specificity of 77%, PPV of 89%, and NPV of 51% predicted a viable pregnancy efficiently. According to Poikkeus et al's study,¹⁶ the median hCG concentration was 126 IU/L in viable pregnancies, and 31 IU/L in non-viable pregnancies ($p<0.0001$). The median hCG concentration in twin pregnancies was almost double than that in singleton pregnancies (201 IU/L versus 115 IU /L, $p<0.0001$).¹⁶

The discrepancy in suggested cut-off point levels in different studies can be attributed to the difference in time of measuring β -hCG. However, a significant relationship between serum β -hCG level and pregnancy outcome has been reported, and introduced β -hCG as a factor for predicting pregnancy outcome. According to the results of the current study, a significant relationship was observed between serum β -hCG level and singleton or twin pregnancies, and β -hCG ≥ 200 IU/L with a sensitivity of 88% and specificity of 45% predicted twin pregnancy. Based on Urbansek et al's reports,²¹ a cut-off value of β -hCG level >135 IU/l on day 11 after embryo transfer with a sensitivity of 80% and a specificity of 88% predicted ongoing multiple gestation. Some researchers have pointed out to 2 linked hCG measurements to increase predictive accuracy of pregnancy outcome rather than one measurement. In a study conducted by Sugantha et al²² they reported that with β -hCG levels of <50 IU/l on day 14 and <200 IU/l on day 21 after embryo transfer, the probability of birth was 0%, abortion - 72%, and ectopic pregnancy - 28%. With β -hCG levels of >50 IU/l on day 14 and >1000 IU/l on day 21, the probability of birth was 90%, abortion - 8%, and ectopic pregnancy - 1%. Most multiple pregnancy occurred in this group. Contrary to these reports, there is evidence showing that a single serum hCG measurement on day 14 or 15 after oocyte retrieval, or ovulation is sufficient to differentiate viable pregnancies from non-viable ones accurately.²³ It has been shown that with β -hCG levels <300 IU/l on day 14 after embryo transfer, the rate of a multiple pregnancy

was 9%. With β -hCG levels between 300 and 600 IU/l this rate increased to 40%, and with β -hCG more than 600 IU/l, the rate of multiple pregnancy was 100%.²⁴

According to the study of Almog et al,²⁵ the β -hCG level was higher in twin viable pregnancy. In our study, there was no significant relationship between β -hCG level and age, duration, and etiology of infertility. In Homan et al's study,²⁰ age and progesterone had minor effects in the prediction of pregnancy outcome. Poikkeus et al¹⁶ found a relationship between the factor of infertility and successful viable pregnancy. The lowest hCG concentrations (median 88 IU/L) were observed in cases with both male factor infertility and ICSI treatment.¹⁶

In recent years, hyperglycosylated hCG has been the focus of some researchers. Measurement of this factor in early stages of pregnancy may provide useful information regarding the clinical outcome of pregnancy. In a study on 87 IVF patients,²⁶ this marker was measured in 3 weeks following embryo transfer. It decreased significantly in biochemical pregnancy compared to early pregnancy loss and ongoing pregnancy. This marker discriminated early pregnancy loss from ongoing pregnancy efficiently. In Porat et al's study,¹¹ early low serum β -hCG level was a good predictor for poor pregnancy outcome. Although we did not find a significant relationship between age and β -hCG concentration, it was revealed that with increasing age, the rate of pregnancy failure increased.¹¹ The practice of early pregnancy detection using β -hCG in fertility centers can be extended to predict the probability of a normal pregnancy, as well as the probability of that normal pregnancy being a single or a multiple pregnancy. Patients can be counseled appropriately, and therefore prepared earlier both mentally and emotionally.²

In conclusion, this study shows that a single measurement of β -hCG on day 16 after embryo transfer would help physicians in subsequent medical managements and follow-ups. It would also be useful in the determination of pregnancy outcome, prediction of viable or non-viable pregnancy, prediction of singleton and twin pregnancies irrespective to factors like age, factor of infertility, and its duration. Little sample size in subgroups of infertility factors could be our study limitation. As a result of this study, we believe that the assay of hCG 16 days after embryo transfer is useful for predictive information concerning pregnancy outcome that should be helpful for the staff and infertility patients. A well-designed study in the future comparing various days after embryo transfer to predict pregnancy is suggested.

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Related topics

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