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Nomogram to predict ongoing pregnancy using age of women and serum biomarkers after in vitro fertilization cycles

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ABSTRACT

Objective: To develop a nomogram for prediction of ongoing pregnancy after in vitro fertilization (IVF)-embryo transfer (ET) using age of women and serum biomarkers.
Study design: Prospective longitudinal study of 103 patients undergoing IVF-ET at a university-based hospital. Serum HCG and progesterone levels were measured at the time of the pregnancy test (14 days after oocyte retrieval) and pregnancy outcomes were followed. The main outcome was ongoing pregnancy prediction.
Results: For the prediction of ongoing pregnancy, a combination of serum HCG, progesterone and age of the woman shows the best predictive accuracy (AUC 0.912 [95% CI 0.815–1.000], sensitivity 89.3%, specificity 80.0%, positive predictive value 89.3%, negative predictive value 80.0%). On the basis of these variables, we developed a nomogram to predict ongoing pregnancy.
Conclusion: A nomogram could help to predict ongoing pregnancy after IVF-ET. The nomogram needs further validation to improve individualized prediction of ongoing pregnancy.

1. Introduction

Pregnancies achieved by in vitro fertilization (IVF) and embryo transfer (ET) are at increased risk of adverse outcomes compared with natural pregnancies [1]. Early pregnancy losses such as biochemical pregnancies, abortions and ectopic pregnancies are common during the first trimester. Thus, the prediction of ongoing pregnancy, especially at the time of pregnancy testing, is of interest to clinicians and infertile couples undergoing IVF-ET.

In practice, the initial establishment of pregnancy after ET is assessed by measuring serum human chorionic gonadotropin (HCG) concentration which is a reliable marker to forecast pregnancy outcome toward the end of the second week after ET. HCG is a glycoprotein composed of two dissimilar subunits, the alpha and beta subunits, non-covalently linked by disulfide bonds [2]. Unique biologic activity as well as specificity in immunoassays is attributed to the molecular and carbohydrate differences in the beta subunit. It can be detected in maternal blood with the current assay approximately 8–12 days after conception [3,4]. Over 100 immunoassays are available for quantifying HCG-related molecules in serum or urine. Each assay measures non-nicked HCG (intact dimers) and the other HCG-related molecules such as nicked HCG, free beta subunit, etc. according to the type of capture antibody. This is the source of interassay discordance in HCG determinations [5]. Numerous studies have revealed the efficiency of serum HCG in predicting pregnancy outcomes [6–10]. However, its cut-off values with positive predictive value (PPV) and negative predictive value (NPV) vary among studies. Thus, studies still have been going on to forecast pregnancy outcome more correctly at the earliest stage.

In the previous study from our center [11], we assessed the prognostic value of serum HCG, progesterone and inhibin A levels measured at 11 days post-ET in predicting pregnancy outcome. To predict ongoing pregnancy, serum HCG was the most reliable prognostic factor (area under the curve [AUC] = 0.909), but serum progesterone alone (AUC = 0.606) was reliable not in women undergoing IVF-ET. Nevertheless, we hypothesized that progesterone has some role in discriminating pregnancy outcome in IVF patients because progesterone is produced by the corpus luteum in response to HCG and plays a crucial role in pregnancy maintenance, and thus serum HCG level combined with progesterone may improve the predictive accuracy.

In general, nomograms can quantify a risk by combining several prognostic factors in some diseases. Since a nomogram could facilitate estimation of an individualized probability, it can be applied to predict the IVF pregnancy rate. Ballester et al. [12]

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developed the nomogram to predict the individualized clinical pregnancy rate in patients with and without deep infiltrating endometriosis based on criteria before the IVF procedure. An individualized probability of ongoing pregnancy at the time of the pregnancy test would also give great help in IVF practitioners and infertile couples. To the best of our knowledge, however, a nomogram to predict ongoing pregnancy after IVF-ET has not been developed so far.

The aim of the present study was to develop a nomogram for prediction of ongoing pregnancy after IVF-ET using age of women and serum biomarkers. We also evaluated the role of serum progesterone for prediction of pregnancy outcomes in women undergoing IVF and considered the optimal progesterone for luteal support.

2. Materials and methods

2.1. Patients

We performed a prospective longitudinal study including 103 infertile women undergoing IVF-ET from April 2011 to December 2012. The basic human IVF protocol was performed similar to the previous report from our center [11]. All patients received progesterone (50 mg/day intramuscularly, Watson Pharmaceuticals, Morristown, NJ, USA) from the day of oocyte pick-up (OPU) to the 6th or 7th week of gestation as the luteal support. Serum HCG and progesterone levels were measured at the time of the pregnancy test (exactly 14 days post-OPU) and pregnancy outcomes were followed. When the pregnancy test was performed on a different day, it was excluded because HCG and/or progesterone concentrations during early pregnancy change rapidly and consistently. Finally, 86 cycles of day 3 ET and 17 cycles of day 5 ET were included. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital [B-1302/192-106].

2.2. Hormone assays

Serum HCG level was measured with a chemiluminescent microparticle immunoassay (Architect i2000, Abbott Laboratories, AbbottPark, IL, USA). It detects nicked and non-nicked HCG and free beta subunit. The measuring range for HCG was 0–15,000 mIU/mL. Samples with HCG concentration >15,000 mIU/mL were diluted using normal saline and multiplication was performed by the dilution factor. The intra- and inter-assay coefficient of variation (CV) was 1.2–4.7% and 1.6–4.9%, respectively.

Serum progesterone level was measured using an electrochemiluminescence immunoassay (Elecsys Progesterone II; Hitachi High-technologies, Tokyo, Japan). The measuring range for progesterone was 0.03–60 ng/mL. Samples with progesterone concentration >60 ng/mL were diluted (1:10) using Elecsys Diluent Estradiol/Progesterone, and multiplication was performed by the dilution factor. The intra- and inter-assay CV was 1.5–2.7% and 4.1–5.5%, respectively.

2.3. Pregnancy outcome

When the HCG level was above 10 IU/L, repeated measure was performed. Further classifications of pregnancy outcomes were as follows: biochemical pregnancy was defined if the HCG level was above 10 IU/L at the time of pregnancy test and its value increased first but after that it dropped and there was no sign of clinical pregnancy; clinical pregnancy was confirmed by the presence of a gestational sac, with or without a fetal heartbeat on ultrasound examination, and clinical abortion was defined by pregnancy failure after confirming the gestational sac. Ongoing pregnancy was defined as progression beyond 12 weeks' gestation.

2.4. Statistical analysis and construction of the nomogram

All statistical analyses were performed using SPSS version 18 (SPSS, Chicago, IL), and R software version 2.14.2 (http://www.r-project.org). Statistical significance was set as p-value < 0.05. The one-way analysis of variance test was used for the comparison of continuous variables between groups. Simple and multiple logistic regression analyses were performed to test the association between ongoing pregnancy and age, serum HCG and progesterone levels, respectively, and to assess the joint effect of variables. To assess the predictive accuracy and estimate the sensitivity and specificity values for each, and combinations of the variables, receiver-operating characteristic (ROC) curves were generated. On the basis of these predictive factors, a nomogram was constructed to predict ongoing pregnancy.

3. Results

The initial serum HCG titer was elevated in 43 women, but 8 women ended up with a biochemical pregnancy. Intrauterine pregnancy was identified in 33 women. Among them, five women experienced spontaneous miscarriage; 20 women had singletons, and 8 had twins. Two women were diagnosed as having ectopic pregnancies and underwent surgery.

The age of the women was similar in the different pregnancy groups, but women in the ongoing pregnancy group tended to be younger than other groups. The mean HCG level was similar in the clinical abortion, ectopic pregnancy and singleton pregnancy groups but it was two-fold higher in the multiple pregnancy group. Progesterone level was similar between the clinical abortion and ongoing pregnancy groups but in the ectopic pregnancy group, progesterone level tended to be higher than the other groups (Table 1).

We divided arbitrarily the serum levels of HCG and progesterone to make relatively similar numbers of cases included in each interval as shown in Table 2. The probability of ongoing pregnancy tended to increase with increasing HCG levels. Interestingly, in

Table 1
Age of woman and serum concentration of HCG and progesterone measured at post ovum pick up 14 days according to the pregnancy outcome.

Pregnancy outcomes	No.	Age (years)	HCG (IU/L)	Progesterone (ng/mL)
Non-pregnancy	60	36.3 ± 4.0	1.3 ± 0.9a	26.9 ± 11.1a
Chemical pregnancy	8	36.1 ± 4.6	50.2 ± 29.1a,b	26.4 ± 10.2a
Clinical abortion	5	37.4 ± 5.3	134.7 ± 49.2b,c	82.8 ± 46.5a,b
Ectopic pregnancy	2	39.0 ± 1.4	128.1 ± 41.0b,c	115.5 ± 57.5b
Ongoing pregnancy (singleton)	20	34.2 ± 2.8	180.5 ± 104.2c	71.9 ± 58.1a,b
Ongoing pregnancy (multifetal)	8	34.0 ± 3.6	365.2 ± 134.1d	96.0 ± 43.7b
p-Value by ANOVA test		0.152	0.000	0.000

Mean ± SD. Different letters means a statistical significance within same column ($p < 0.05$) by the post hoc Scheffe test.