Received: 8 June 2023 | Revised: 9 March 2024 | Accepted: 13 March 2024

DOI: 10.1002/hsr2.2015

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Levels of serum β-human chorionic gonadotropin after embryo transfer and subsequent miscarriage, pre-eclampsia, and intrauterine growth restriction

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Abstract

Background: This study aimed to examine maternal serum concentration of β-human chorionic gonadotropin (β-hCG) on Day 16 after embryo transfer and risk of miscarriage, pre-eclampsia, and intrauterine growth restriction (IUGR).

Methods: In this study, we evaluated 125 pregnancies following in vitro fertilization (IVF). β-hCG concentrations were measured on the morning of Day 16 after embryo transfer. Baseline characteristics of the study participants were also recorded.

Results: Concentrations of β-hCG on Day 16 after embryo transfer were inversely associated with the higher risk of miscarriage ($p < 0.001$), but did not with pre-eclampsia and IUGR ($p > 0.05$). Spearman's correlation coefficient showed a reverse and significant association between β-hCG and higher risk of miscarriage ($\sigma = 0.531$ and $p < 0.001$). There was a significant association between frozen embryo transfer and the risk of IUGR and pre-eclampsia ($p = 0.005$ and $p = 0.023$, respectively).

Conclusions: Maternal serum concentrations of β-hCG on Day 16 after IVF/embryo transfer were associated with the higher risk of miscarriage, but not pre-eclampsia and IUGR.

KEYWORDS

embryo transfer, IUGR, IVF, miscarriage, pre-eclampsia, β-hCG

1 | INTRODUCTION

In the absence of pathologic abnormalities, human chorionic gonadotropin (hCG) is secreted in large amounts only during pregnancy. The serum β-HCG level is secreted by chorionic cells and increases over time after embryo implantation. It has been demonstrated that there is an association between the serum β-HCG levels after embryo transplantations and early pregnancy outcomes.[1,2] hCG is one of the first molecular signals sent out by the pre-implanting embryo to modulate the endometrium for the implantation process.[3] Secretion of the hormone starts at the blastocyst stage[4] and its detection in the maternal serum 10 days

after fertilization. The abnormally high or low levels of hCG hormone could be associated with adverse pregnancy outcomes. However, in the absence of chromosomal or structural anomalies in fetus, there are conflicting data regarding an association between abnormal free β-hCG levels and pregnancy outcomes.[5]

The clinical presentation of pre-eclampsia is highly variable, but hypertension and proteinuria are usually seen. The placental or maternal causes of pre-eclampsia vary among patients. Abnormal placentation in early pregnancy may involve the pathogenesis of pre-eclampsia. hCG regulates placental development and angiogenesis and it has been reported that high total hCG concentration in early pregnancy is associated with an increased risk of pre-eclampsia.[6] Disorders of placental development cause pre-eclampsia and fetal growth restriction which have some shared mechanistic features. Initiation of these disorders is often rooted in impaired development of maternal–placental blood supply.[7]

It has been reported that low β-hCG concentrations in very early pregnancy were associated with an increased risk of spontaneous miscarriage among patients undergoing in vitro fertilization (IVF).[8] Krantz et al. reported a significant association between low β-hCG levels and IUGR,[9] while the other study has not demonstrated such associations.[10] In women undergoing IVF, it has been reported that low serum hCG concentrations in very early pregnancy are associated with an increased risk of severe pre-eclampsia.[11]

The relationship between elevated β-hCG and adverse pregnancy outcomes is still controversial. A low β-hCG level implies poor placental development. Although it is well known that low serum β-hCG in early pregnancy is related to poor outcomes, there is no widely accepted method of using β-hCG levels to predict successful pregnancy outcomes.[12] Therefore, in this study, we examined maternal serum concentration of β-hCG on Day 16 after embryo transfer and risk of miscarriage, pre-eclampsia, and IUGR in the subsequent pregnancy.

2 | MATERIALS AND METHODS

2.1 | Study population

In this cross-sectional study, we evaluated 125 pregnancies following IVF at the infertility clinic of Al-Zahra Hospital, Rasht, Iran, between May and October 2021. We included pregnancies after fresh or frozen embryos transfer of intracytoplasmic sperm injection (ICSI) cycles. Women under the age of 42 were included in the study. Exclusion criteria included IVF failure, twin pregnancies, and cycles using donor oocytes. Approval was obtained from the Ethics Committee of Guilan University of Medical Sciences (Approval ID: IR.GUMS.REC.1400.041). All participants signed an informed consent form before including in the study.

2.2 | IVF protocol

From Day 20 of the previous menstrual cycle, 2 mg of estradiol was started every 12 h and on the second day of the menstrual cycle, ultrasound was performed and in the absence of follicles of ≥10 mm, ovarian stimulation by recombinant follicle stimulating hormone (FSH) (Cinnal-F, Cinnagen)/human menopausal gonadotropin (PD HOMOG, Pooyesh Darou) has been done. The ovarian response to stimulation was assessed by ultrasound. The first ultrasound was performed 5–6 days after ovarian stimulation and if there was a 13–14 mm follicle, the GnRH antagonist (0.25 mg Cetrotide, Merck) was administrated to prevent luteinizing hormone (LH) surge. After observing at least two 18 mm follicles, ovarian stimulation was stopped and 10,000 units of hCG were injected. Then 36–40 h after hCG administration, ovarian follicles were obtained under general anesthesia using vaginal ultrasound guidance. After oocyte denudation and ICSI by an embryologist, 1–3 embryos (based on the number of available embryos and the patient's age) were transferred to the patient by fresh or frozen cycle.

2.3 | β-hCG measurements and data collection

β-hCG concentrations were measured in fresh serum samples drawn on the morning of Day 16 after cleavage stage (6–8 cells Day 3 embryo) embryo transfer at the clinical laboratory of Al-Zahra hospital, Rasht, Iran. β-hCG measurements were done using an ELISA (enzyme-linked immunosorbent assay) test kit (Padtan Elm) according to the manufacturer's instructions. β-hCG concentrations were measured on the morning of Day 16 after embryo transfer because Day 16 was the day that majority of patients were available.

Baseline characteristics of the study participants, including age, BMI, duration of infertility, gravidity, anti-Müllerian hormone, FSH, number of IVF cycles, and number of embryos, were recorded. Miscarriage was considered as the loss of a fetus from the uterus before the 20th week of gestation. IUGR is diagnosed when ultrasound-estimated fetal weight is below the 10th percentile for gestational age.[13] The diagnosis of pre-eclampsia was based on the development of hypertension (blood pressure ≥140 mmHg) and proteinuria (protein dip stick ≥1+ or ≥0.3 g/24 h) after 20 weeks of pregnancy.

2.4 | Statistical analysis

Statistical analysis was done using Statistical Package for the Social Sciences for Windows (SPSS, version 22.0) software. The normal distribution of quantitative variables was assessed by the Kolmogorov–Smirnov test. Mean and the standard deviation were used to present quantitative variables with normal distribution and was also defined based on numbers and percentages. Mann–Whitney test was used to compare β-hCG concentrations between patients with miscarriage, IUGR, and pre-eclampsia and patients who did not experience these complications. The Spearman's correlation coefficient test was used to measure the

correlation between concentrations of β-hCG and risk of miscarriage, IUGR, and pre-eclampsia. The significance level of the tests was considered $p < 0.05$.

The association between type of embryo transfer (fresh or frozen embryo transfer) in patients with miscarriage, IUGR, and pre-eclampsia is presented in Table 4. There was no association between type of embryo transfer and risk of miscarriage ($p = 0.72$). However, there was a significant association between frozen embryo transfer and the risk of IUGR and pre-eclampsia ($p = 0.005$ and $p = 0.023$, respectively).

3 | RESULTS

Baseline characteristics of the study participants are presented in Table 1. The mean age of the study population was 32.28 ± 5.14. Among 125 patients with successful pregnancy after embryo transfer, 59 (47.2%) had miscarriages, 6 (4.8%) IUGR, and 12 (9.6%) were complicated by pre-eclampsia. Concentrations of β-hCG on Day 16 after embryo transfer were inversely associated with the risk of miscarriage ($p < 0.001$, Table 2). Mean concentrations of β-hCG in patients who experienced miscarriage were significantly lower than those who did not experience miscarriage (204.28 ± 235.28 and 525.83 ± 510.42 IU/L, respectively). However, concentrations of β-hCG on Day 16 after embryo transfer were not significantly different between patients who experienced IUGR and pre-eclampsia, and those who did not ($p > 0.05$).

Spearman's correlation analysis was used to measure the correlation between concentrations of β-hCG and risk of miscarriage, IUGR, and pre-eclampsia (Table 3). Spearman's correlation coefficient showed a reverse and significant association between β-hCG and risk of miscarriage ($\sigma = 0.531$ and $p < 0/001$). However, there was no association between concentrations of β-hCG and risk of IUGR, and pre-eclampsia ($\sigma = -0.74$ and $p = 0.414$; $\sigma = -0.72$ and $p = 0.426$, respectively).

The association between type of embryo transfer (fresh or frozen embryo transfer) in patients with miscarriage, IUGR, and pre-eclampsia is presented in Table 4. There was no association between type of embryo transfer and risk of miscarriage ($p = 0.72$). However, there was a significant association between frozen embryo transfer and the risk of IUGR and pre-eclampsia ($p = 0.005$ and $p = 0.023$, respectively).

TABLE 3 Spearman's correlation coefficient between β-hCG and miscarriage, IUGR, and pre-eclampsia.

	β-hCG	
	σ	p
Miscarriage	0.531	<0.001*
IUGR	−0.074	0.414
Pre-eclampsia	−0.072	0.426

Abbreviations: IUGR, intrauterine growth restriction; β-hCG, β-human chorionic gonadotropin.

*Correlation is significant at the 0.01 level (2-tailed).

TABLE 1 Basic characteristics of the study population.

	Age (year)	BMI (kg/m^2)	Duration of infertility	Gravidity	AMH (ng/ml)	FSH (IU/ML)	Number of IVF cycles	Number of embryos
Mean	32.28	27.07	5.70	1.40	4.52	7.02	1.90	3.64
SD	5.142	3.66	4.31	0.623	4.08	3.60	1.09	2.15
Minimum	19.00	18.60	1.00	1.00	0.09	1.20	1.00	1.00
Maximum	42.00	42.00	20.00	4.00	17.70	28.00	5.00	15.00

Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; FSH, follicle stimulating hormone; IVF, in vitro fertilization; SD, Std. deviation.

TABLE 2 Mann Whitney test for β-hCG level in patients with abortion, IUGR, and pre-eclampsia.

	Yes					No					
	N (%)	Mean	Min	Max	SD	N (%)	Mean	Min	Max	SD	p value [a]
Miscarriage	59 (47.2%)	204.28	23.00	1077.00	235.28	66 (52.8%)	525.83	29.84	3700.00	510.42	<0.001*
IUGR	6 (4.8%)	461.00	87.00	1086.00	389.45	119 (95.2%)	369.68	23.00	3700.00	437.25	0.412
Pre-eclampsia	12 (9.6%)	425.07	29.84	1086.00	330.16	113 (90.4%)	368.64	23.00	3700.00	444.53	0.423

Abbreviations: IUGR, intrauterine growth restriction; β-hCG, β-human chorionic gonadotropin.

[a]Mean diff (Mann Whitney).

*p value < 0.05.

TABLE 4 Type of embryo transfer in patients with miscarriage, IUGR and pre-eclampsia.

			Type of transfer		
			FET	Fresh	*p* value
Miscarriage	Yes	Count	25	34	0.72
		% within group	45.5%	48.6%	
	No	Count	30	36	
		% within group	54.5%	51.4%	
IUGR	Yes	Count	6	0	0.005*
		% within group	10.9%	0.0%	
	No	Count	49	70	
		% within group	89.1%	100.0%	
Preeclampsia	Yes	Count	9	3	0.023
		% within group	16.4%	4.3%	
	No	Count	46	67	
		% within group	83.6%	95.7%	

Abbreviation: FET, frozen embryo transfer; Fresh, fresh embryo transfer; IUGR, intrauterine growth restriction.

*p value < 0.05.

4 | DISCUSSION

In this study, follow-up of pregnancies after IVF/embryo transfer showed that maternal serum concentrations of β-hCG on Day 16 after embryo transfer were associated with the risk of miscarriage, but not pre-eclampsia and IUGR. The Spearman's correlation coefficient showed a reverse and significant association between very early pregnancy β-hCG concentrations and risk of miscarriage.

It has been suggested that low hCG concentrations in the late first trimester may be associated with pre-eclampsia risk.[14] Asvold et al., for the first time, demonstrated that low hCG concentrations in very early pregnancy may be associated with subsequent risk of pre-eclampsia after embryo transfer.[11] hCG concentrations in the initial stages of pregnancy are maybe associated with the trophoblastic cells' function. Assessing β-hCG concentrations during the initial phase of placental development is possible only in pregnancy after IVF/embryo transfer, because in spontaneous pregnancies it is difficult to measure β-hCG in a large number of women on a specified day shortly after conception.

In previous studies, it has been reported that low β-hCG concentrations are associated with pregnancy loss.[15,16] The proposed underlying mechanisms are impaired placental development[17] and delayed implantation.[18] Our study findings showed a significant association between very early pregnancy β-hCG concentrations and risk of miscarriage. Therefore, low β-hCG concentrations could be a sign of impaired placental development and one of the causes of subsequent pregnancy loss. Kutluer et al. reported that early pregnancy losses are related to insufficient angiogenesis, and maternal serum alpha-higheroprotein and β-hCG can be used as markers of angiogenesis in the first trimester.[19] Defective vascular development underlies many early pregnancy losses.[20,21] hCG stimulates vascular endothelial growth factor (VEGF) via the LH receptor, and together they play roles in peri-trophoblastic angiogenesis.[21]

Fetal growth restriction (FGR), also known as IUGR, is a pathological state and a symptom of an underlying disorder inhibiting the growth potential of the fetus. Proper development of the placenta is fundamental for utero-placental circulation. Idiopathic low pregnancy-associated plasma protein-A (PAPP-A) or hCG levels have been correlated with an increased predisposition to placenta-related pathologies.[22] In our study of pregnancies after IVF/embryo transfer showed that maternal serum concentrations of β-hCG on Day 16 after the embryo transfer are not associated with the risk of subsequent IUGR. These results maybe because of the small study population, and additional studies are needed to explore such association.

Type of embryo transfer method may affect pregnancy outcomes in IVF/ICSI cycles. In addition to higher pregnancy rates,[23] frozen embryo transfer (FET) has been found to be associated with a lower risk of preterm delivery, low birth weight, and small for gestational age fetuses.[24] In the present study, there was a significant association between FET and the risk of IUGR and pre-eclampsia. Our findings are in accordance with previous studies that reported the risk of pre-eclampsia increased with FET.[24–26] Recent evidence suggests that the absence of the corpus luteum in FET cycles could be at least partly responsible for the increased risk of pre-eclampsia. The corpus luteum produces not only estradiol and progesterone but also vasoactive products, such as relaxin and vascular endothelial growth factor, which are hypothesized to be important for initial placentation.[27] On the other hand, in contrast to our findings, it has been reported no difference in the prevalence of fetal anomalies or IUGR between ET and FET groups.[28] Therefore, further studies with a larger sample size are needed to evaluate the association between IUGR and pre-eclampsia and the type of embryo transfer.

The first limitation of this study is the relatively small sample size. The second limitation was that a single marker of β-hCG concentrations in very early pregnancy may not be enough tool for the prediction of pregnancy outcomes. Third, the rate of pregnancy complications is slightly higher in IVF patients than in the general population, and the findings of this study cannot be generalized to the whole population.

5 | CONCLUSIONS

In conclusion, if markers such as maternal serum hCG can predict the future of pregnancy in the very early stages, the clinical management of patients after IVF/embryo transfer can be improved. However, in the present study, maternal serum concentrations of β-hCG on Day 16 after IVF/embryo transfer were associated with the higher risk of miscarriage, but not pre-eclampsia and IUGR. These results maybe

because of the small study population, and additional studies are needed to explore such association.

AUTHOR CONTRIBUTIONS

Roya Kabodmehri: Writing—original draft. **Nasrin Ghanami Gashti**: Resources; software. **Ziba Zahiri Sorouri**: Resources. **Seyedeh Hajar Sharami**: Methodology. **Forozan Milani**: Funding acquisition. **Marziyeh Hasanpour**: Software. **Habib Eslami-Kenarsari**: Formal analysis. **Zahra Rafiei Sorouri**: Conceptualization.

ACKNOWLEDGMENTS

The authors would like to thank the members of the Reproductive Health Research Center of Guilan University of Medical Sciences for their constant support. This study is financially supported by the Vice-Chancellorship of Research and Technology, Guilan University of Medical Sciences, Rasht, Iran.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Supporting data are available in Department of Obstetrics & Gynecology, Al-Zahra Hospital, School of Medicine, Reproductive Health Research Center, Guilan University of Medical Sciences, Rasht, Iran.

ETHICS STATEMENT

Ethical approval was obtained from the ethics committee of Guilan University of Medical Sciences (Approval ID: IR.GUMS.-REC.1400.041). Informed consent was taken from all participants. All stages of this research have been performed according to the Helsinki declaration. All procedures of the study were explained clearly to the participants who had the eligible inclusion criteria. Moreover, all participants voluntarily filled out the written informed consent form before they joined the study and they were free to decide whether or not to attend or withdraw at any time and for any reason without changing the medical care.

TRANSPARENCY STATEMENT

The lead author Zahra Rafiei Sorouri affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Kabodmehri R, Ghanami Gashti N, Zahiri Sorouri Z, et al. Levels of serum β-human chorionic gonadotropin after embryo transfer and subsequent miscarriage, pre-eclampsia, and intrauterine growth restriction. *Health Sci Rep*. 2024;7:e2015. doi:10.1002/hsr2.2015