10.5005/jp-journals-10016-1042

RESEARCH ARTICLE

First Postembryo Transfer Beta-hCG Level and Pregnancy Outcome in an Assisted Reproductive Technology Program

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ABSTRACT

Aim: To evaluate the prognostic value of first postembryo transfer beta human chorionic gonadotropin (hCG) levels in pregnancy outcome in an assisted reproductive technology (ART) program.

Subjects: Seventy-one women with an initial beta-hCG value of greater than 5 mIU/ml postembryo transfer in the ART program were taken in to the study. The beta-hCG test was done 14 days after embryo transfer. The period of study was from January 2008 to August 2010.

Observations: A significant correlation was found in beta-hCG values between viable and nonviable pregnancies. In women who had a day 2 embryo transfer the mean beta-hCG value was 608 ± 580 mIU/ml, in comparison to women who had a day 5 transfer 1,527 ± 2,024 mIU/ml, and this was statistically significant.

Women who had a single embryo transfer had a mean beta-hCG level of 168 mIU/ml, two embryos 464 mIU/ml and three embryos 612 mIU /ml.

Mean beta-hCG value was highest in women who developed gestational diabetes [2,074 mIU/ml] women with pregnancy-induced hypertension (PIH) had a mean beta-hCG value of 674 mIU/ml, and with antepartum hemorrhage the value was lower 220 mIU/ml.

Conclusion: To summarize, beta-hCG level is an useful marker for prognosticating early pregnancy well being, for predicting multiple pregnancies. When interpreting the first beta-hCG level uniformly after 2 weeks of embryo transfer, day of transfer of embryos should be taken into account. The number of embryos transferred does not alter the beta-hCG level significantly. Beta-hCG level implications in pregnancy complications, like gestational diabetes (GDM), PIH, APH, require further research and would be a useful tool for early screening and surveillance of pregnancy.

Keywords: Beta-hCG, Maternal, Fetal, Pregnancy, Ectopic, Perinatal, Ultrasonograph.

How to cite this article: Jayachandran KD, Natarajan P, Pandiyan R. First Postembryo Transfer Beta-hCG Level and Pregnancy Outcome in an Assisted Reproductive Technology Program. Int J Infertility Fetal Med 2012;3(2): 57-62.

Source of support: Nil

Conflict of interest: None declared

Date of Received: 28-06-12
Date of Acceptance: 19-07-12
Date of Publication: May 2012

INTRODUCTION

Early prediction of outcome is important in pregnancies following assisted reproductive technologies (ART). Pregnancies achieved by *in vitro* fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) are at higher risk for obstetrical and perinatal complications than spontaneous pregnancies.[1]

Women undergoing ART should be informed about the increased rate of obstetrical interventions, such as induced labor and elective cesarean delivery.[2]

A significant risk of ART is multiple pregnancies.[3] Risks of multiple pregnancies include higher rates of perinatal mortality, preterm birth, low birth weight, gestational hypertension, placental abruption and placenta previa, multi-fetal reduction. Infertile couples need to be informed of the increased risks of multifetal pregnancies.

Markers have been sought to distinguish between viable and nonviable pregnancies[4] before verification by transvaginal ultrasound. After implantation, currently human chorionic gonadotropin (hCG) is the first trophoblast signal detected in maternal blood and is used as a diagnostic marker of pregnancy.[5] It gives the clinician an idea about the nature of pregnancy much before the confirmation by ultrasound. Its use as a prognostic marker of pregnancy would be a useful tool in ART pregnancies, for adequate planning and preparation.[6]

OBJECTIVE OF THE STUDY

To evaluate the prognostic value of first postembryo transfer beta-hCG levels in pregnancy outcome in an ART program.

SUBJECTS

Seventy-one women with an initial beta-hCG value of greater than 5 mIU/ml postembryo transfer in the ART program were taken into the study. The beta-hCG test was done 14 days after embryo transfer. The period of study was from January 2008 to August 2010. The study was done in the Reproductive Medicine Department of Chettinad Hospital.

METHODOLOGY

Short protocol was followed for downregulation in this group. Ovulation trigger was given with 10,000 IU of hCG.

Luteal phase was supported with vaginal progesterone only. Beta-hCG testing was done uniformly 2 weeks after embryo transfer in this group.

Serum testing was done by ELISA hCG microplate technique with both neat and diluted sample of the serum, in the biochemistry department.[7]

REVIEW OF LITERATURE

Biological Tests

The first practical biological test for pregnancy was the Aschheim-Zondek test, published in 1928.[6] Urine was injected into immature female mice and a positive result was indicated by corpus luteum development in the ovaries. This took 4 to 5 days to perform. In the 1960s, it was learned that antibodies to hCG could be produced by injecting the hCG molecule into animals. This was the basis for developing immunologic pregnancy tests using antigen antibody reactions.

Human chorionic gonadotropin (hCG) monitoring is useful to assess the viability of pregnancy before the fetal heart is seen by the ultrasound. It also has an useful role in prediction and follow-up of an ectopic pregnancy.[7] Pregnancies that will miscarry and ectopic pregnancies are likely to show lower levels and slower rises of hCG.

Investigator Shirley A Fong et al[8] reported that the beta-hCG levels were highly significant for distinguishing viable pregnancies from those that did not sustain a fetal heart beat through the first trimester. Other than for the diagnosis of pregnancy, hCG is also often monitored over time for reasons, such as monitoring after a miscarriage, monitoring an ectopic pregnancy and after molar pregnancy.[9]

Implantation happens as early as 6 days after fertilization (usually about 9 days after ovulation). hCG is usually found in sufficient levels as early as 2 to 3 days after implantation. With regular laboratory hCG tests, blood hCG can be found 8 to 9 days after fertilization.[10]

The predictive value of early hCG secretion for pregnancy outcome is illustrated by the association between delayed implantation and subsequent pregnancy loss.[10] Moreover, a single hCG measurement on day 14 after embryo transfer[1] may identify those pregnancies likely to proceed to term.

The reason for the gender-related difference in maternal serum hCG has remained elusive since Brody and Carstrom first described this phenomenon in 1965.[11] It has been suggested that the gender-related differences in hCG result from differential activity of the fetal hypothalamic–hypophyseal–gonadal axis, thereby influencing fetal levels of pregnanediol, progesterone, androgens, testosterone or estradiol, which in turn affect hCG production or utilization.[12] Alternatively, it has been proposed that the gender-related difference in hCG is mediated by the sex chromosomes of the trophoblast, whereby some genes on the X chromosome that escape inactivation may be over-expressed by the placenta in the presence of a female fetus.[13]

With the widespread utilization of second-trimester biochemical screening for Down's syndrome, the same gender-related difference was also demonstrated in the second trimester in most studies.[14] Two studies found that maternal serum free β-hCG is also significantly higher in the late first trimester (10-14 weeks gestation) in women carrying female fetuses.[15]

Decreased free beta-hCG is more predictive of hypertensive disorders of pregnancy. Maternal serum free beta-hCG levels were lower in pregnancies complicated by pre-eclampsia than in normotensive ones. Free beta-hCG was found to be an independent predictor of gestational hypertension and pre-eclampsia.[16] The marker was not associated with preterm delivery. There was a significant positive correlation between birth weight and PAPP-A, but not free beta-hCG levels.[17]

RESULTS

Study Group Final Outcome

The final outcome was observed in the group of 71 women (Table 1).

There is a statistically significant difference between biochemical and multiple pregnancy beta-hCG levels (Table 2 and Fig. 1).

Mean beta-hCG level was lower in early day 2, 3 transfers compared to day 5, 6 transfers in the entire group (Table 3 and Figs 2A and B). But when analyzed in individual group of singleton and twins, it was not statistically significant.[21]

DISCUSSION

Early detection of pregnancy is important for the patient as well as the medical team. Confirmation of pregnancy can relieve anxiety but at the same time can alert health care providers of high-risk conditions, such as early loss, ectopic pregnancy and multiple gestations.[18]

It has been suggested that there is an increased risk of ectopic pregnancy, multiple gestations and pregnancy wastage following IVF in comparison to the normal population.[19] Effective clinical management requires a method to predict pregnancy outcome as early as possible.[20] The object of our study was to measure serum quantitative

hCG levels 14 days after embryo transfer and to determine the relationship with pregnancy outcome (see Table 1).[19]

Mean beta-hCG levels in biochemical pregnancies was less than 100 mIU/ml, which was statistically significant compared to other outcomes. The prognosis of a pregnancy is guarded, if the value is less than 100 mIU/ml. Multiple pregnancies had a higher mean value of above 1,000 mIU/ml (see Table 2).

When the initial Beta-hCG level was between 300 and 500 mIU/ml, 70% of women had singleton pregnancies and 30% of women had multiple pregnancies. With beta-hCG levels more than 500 mIU/ml, there was no miscarriage observed. Predominantly multiple pregnancies (83.5%) were seen, when the initial beta-hCG level was above 1,000 mIU/ml.[20]

The number of embryos transferred did not alter beta-hCG levels significantly in this study.

Although the mean beta-hCG value was higher in women who had female fetuses compared to males, it was not statistically significant in our study (Table 4). Various other studies had quoted a higher value in woman with female fetus. Fetal gender has been shown to have a significant influence on maternal serum levels of hCG.

Table 1: Final outcome of pregnancy in the study group

S. no.	*Details*	*Number of women (71)*
1	Biochemical	9
2	Ectopic	4
3	Miscarriage	7
4	Singleton	21
5	Twins	13
6	Triplets	1
7	Ongoing pregnancy	10

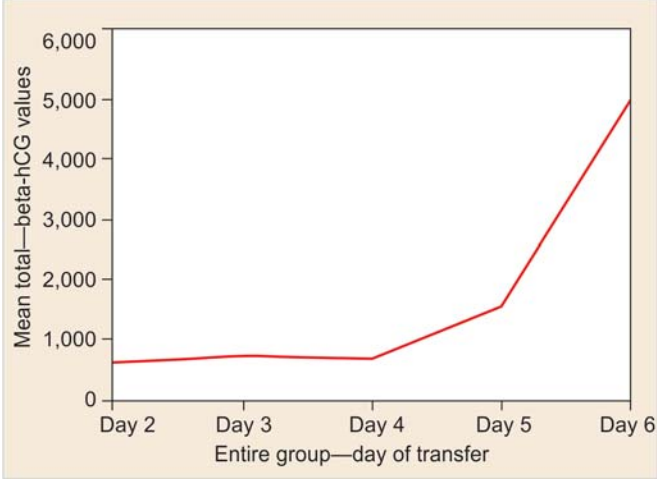


Fig. 1: Statistical analysis between biochemical and multiple pregnancy beta-hCG levels

It was initially demonstrated that third trimester serum hCG is higher in women carrying a female fetus than in those with a male.[11,12]

These findings may have implications not only on evaluating risks of Down syndrome (women carrying female fetuses had a higher risk for Down syndrome), but also on timing of a pregnancy test. If women carrying a male fetus have lower hCG levels then it may be possible that their first positive urine pregnancy test could be delayed because of the male gender.[15]

There was no significant difference noted in beta-hCG values in relation to pregnancy duration or birth weight.[22] The time of delivery is influenced by various other factors, like an elective cesarean decided by the obstetrician.

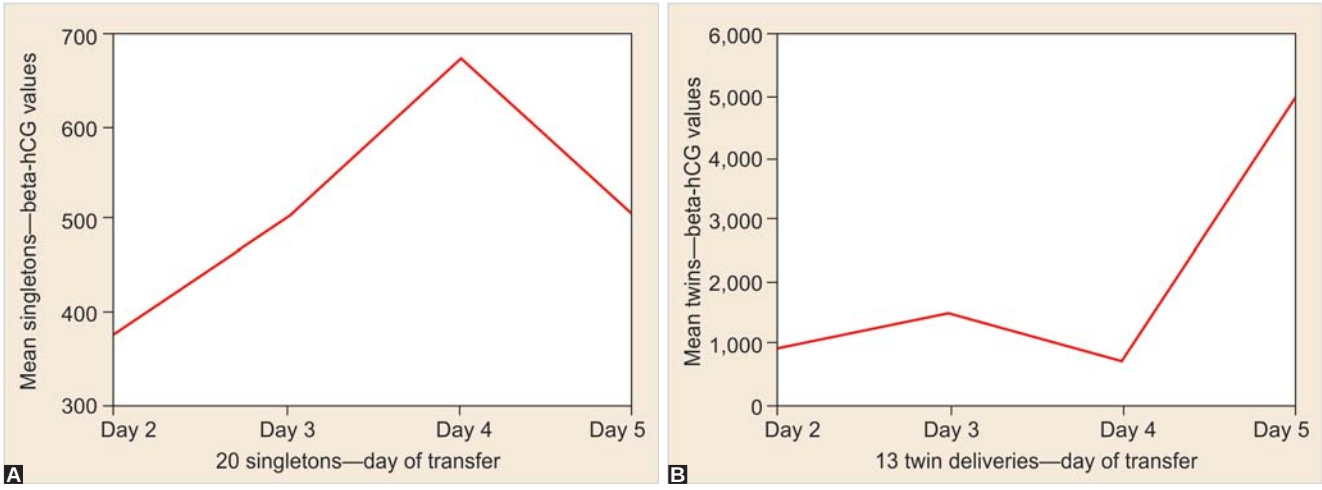
The mean beta-hCG values were high in women who had gestational diabetes (2,074 mIU/ml) (Fig. 3). But, it was not statistically significant due to the small number of

Table 2: Statistical analysis of beta-hCG with the final pregnancy outcome

Group—beta-hCG values	*Mean*	*SD*	*SE*	*N*	*ANOVA*	
					F-value	*Sig.*
Biochemical	69	51	17	9	–	–
Miscarriage	413	585	221	7	–	–
Ectopic	105	119	60	4	–	–
Singleton	523	345	77	20	4.188	0.001
Twins-to-singleton	1394	1558	589	7	–	–
Twins	1979	2101	583	13	–	–
Triplets	1557	979	400	6	–	–

Table 3: Statistical analysis of beta-hCG levels according to day of transfer

Total—beta-hCG values	*Entire group—day of transfer*					*F-value*	*Sig.*
	Day 2	*Day 3*	*Day 4*	*Day 5*	*Day 6*		
Mean	608	709	682	1527	4905	–	–
SD	580	943	441	2024	4809	5.979	0.000
SE	290	159	139	477	2776	–	–
N	4	35	10	18	3	–	–



Figs 2A and B: Statistical analysis of beta-hCG levels according to day of embryo transfer: (A) In 20 singleton deliveries, (B) in 13 twin deliveries

Table 4: Beta-hCG levels correlation with gender of the child after delivery

Beta-hCG values	*Gender*		*t*	*Sig.*
	Male	*Female*		
Mean	454	570		
SD	236	405	0.727	0.477
SE	83	117		
N	8	12		

Beta-hCG levels in both sex in 20 singleton deliveries (statistical analysis)

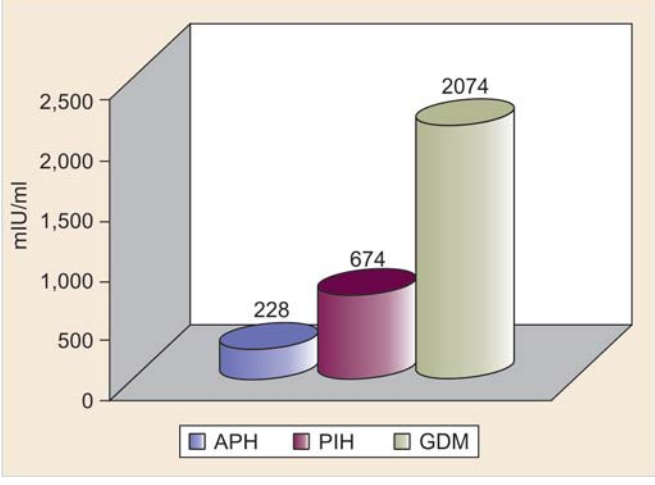


Fig. 3: Beta-hCG levels and pregnancy complications

women. This could help in early screening and detection in women with high-risk for GDM.

The hyperplacentation observed in diabetic women could attribute for the high beta-hCG values and defective placentation for lower values in women with antepartum hemorrhage and in PIH.

ANALYSIS OF DATA AND SUMMARY

A significant correlation was found in beta-hCG values between viable and nonviable pregnancies (Table 5).

Mean Beta-hCG Levels According to Gender of the Fetus

- Male—454 mIU/ml (8/20 singleton deliveries)
- Female—570 mIU/ml (12/20 singleton deliveries)

Interpretation with Duration of Pregnancy

- <37 weeks—518 mIU/ml
- >37 weeks—527 mIU/ml

Correlation with Birth Weight

- <2.5 kg—560 mIU/ml
- 2.5-3 kg—396 mIU/ml
- >3 kg—700 mIU/ml

Correlation with Pregnancy Complications

- APH—220 mIU/ml
- PIH—674 mIU/ml
- GDM—2074 mIU/ml

To summarize, beta-hCG level is an useful marker for prognosticating early pregnancy loss, for predicting multiple pregnancies.[23] When interpreting the first beta-hCG level uniformly after 2 weeks of embryo transfer, day of transfer of embryos should be taken into account[24] (Table 6). The number of embryos transferred does not alter the beta-hCG level (Table 7).

Duration of pregnancy and birth weight are influenced by other factors, like an elective cesarean decided by the obstetrician. So beta-hCG level may not be predictive of these factors.

Beta-hCG level implications in pregnancy complications like GDM, PIH, APH requires further research and would be a useful tool for early screening and surveillance of pregnancy.[25,26]

Table 5: Mean beta-hCG values and pregnancy status at 6 weeks

Value (mIU/ml)	*Biochemical*	*Miscarriage*	*Ectopic*	*Singleton*	*Twins*	*Triplets*
<100	64%	9%	18%	9%	–	–
100-200	27.2%	18.2%	9.1%	36.4%	9.1%	–
200-300	–	43%	14%	14%	29%	–
300-500	–	–	–	70%	10%	20%
500-1000	–	–	–	63.6%	36.4%	–
1,000-2,000	–	–	–	16.5%	67%	16.5%
>2,000	–	–	–	33.3%	44.4%	22.3%

Table 6: Beta-hCG levels *vs* day of transfer

Day of transfer	*Entire group*	*Singleton*	*Twins*
2	604 mIU/ml	381 mIU/ml	732 mIU/ml
3	709 mIU/ml	503 mIU/ml	1,503 mIU/ml
4	682 mIU/ml	676 mIU/ml	726 mIU/ml
5	1,527 mIU/ml	507 mIU/ml	4,954 mIU/ml
6	4,905 mIU/ml	–	–

Table 7: Number of embryos transferred and beta-hCG levels in singleton deliveries and twins

No. of embryos	*Singleton*	*Twins*
3	612 mIU/ml	1,118 mIU/ml
2	464 mIU/ml	2,750 mIU/ml
1	168 mIU/ml	–

CONCLUSION

- Beta-hCG values has a significant predictability for biochemical and multiple pregnancies with statistical significance.
- Significant variation in beta-hCG levels was observed between day 2 and day 6 transfer.
- Mean beta-hCG levels was higher in women who had female fetuses compared to males. But this was not statistically significant due to the small number in our study.
- Beta-hCG levels are not influenced by the number of embryos transferred in our study.
- Beta-hCG levels is not predictive of birth weight and gestational age of the fetus in our study.
- Further studies are required to evaluate the predictability of beta-hCG in pregnancy complications, like gestational diabetes, antepartum hemorrhage, PIH.

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