

“Correlation of Serial Beta Hcg Titre And Ca125 Estimation In Predicting Early Pregnancy Failure

¹Dr. Aruna Bhattacharya , ²Dr.sumit Ranjan Pramanik , ³Dr. Rama Saha ,
⁴Dr.Bhaswati das , ⁵Oishee Maya Sen

¹Assistant Professor,department of Biochemistry, Institute of Postgraduate Medical Education & Research, Kolkata, West Bengal, India

Institute of Postgraduate Medical Education & Research, Kolkata, West Bengal, India

²Associate Professor,department of Obstetrics & gynaecology, Institute of Postgraduate Medical Education & Research, Kolkata, West Bengal, India.

³Associate Professor,department of Pathology, Institute of Postgraduate Medical Education & Research, Kolkata, West Bengal, India.

⁴MD PGT 3RD Yerar,department of Biochemistry,IPGME Institute of Postgraduate Medical Education & Research, Kolkata, West Bengal, India

⁵Phd Scholar , Department Of Biochemistry,Ipgmer ,Kolkata-20

ABSTRACT

OBJECTIVE : To assess the diagnostic value of maternal CA 125 in patients with first trimester pregnancy and to evaluate the prognostic significance of CA 125 versus β -hCG in early pregnancies with intact fetal heartbeat, complicated by vaginal bleeding.

STUDY DESIGN

SETTING : The study was conducted at Dept. of O&G and Biochemistry of institute of post graduate medical education & research,Kolkata.Control patients were 30 pregnant women who had normal pregnancy without complications.Fifty patients with vaginal bleeding during gestational weeks 6-12 all of whom having demonstrable foetal heart beat were studied.17 patients finally aborted whereas the reminder 33 had normal pregnancy continued till term.

Measurement of serum CA 125 &Beta HCG were carried out at department of Biochemistry, IPGME&R.

MAIN OUTCOME MEASURE: 2 sequential measurements of serum CA125 and beta HCG performed within a 5-7 days interval were related to the outcome of pregnancy as indicated by changes of the ultrasound presentation,miscarriage etc.

RESULTS Initial CA 125 levels did not differ significantly between both groups of patients with 33/50 non-aborters and 17/50 aborters showing concentrations below 60 IU/ml. After 48-72 hrs, CA 125 in all patients who eventually aborted remained high or increased whereas non-aborters all had constantly low or declining CA 125 measures. β -hCG increased in all non-aborters and also in aborters during the 2-3 day interval.

CONCLUSION: Sequential determinations of maternal CA 125 measurements appear to be a highly sensitive prognostic marker in patients with viable pregnancy at risk for abortion whereas serum beta hcg did not show any significant change during that period.

KEYWORDS: Cancer Antigen -125(CA-125), , Beta subunit of Human Chorionic Gonadotropin (β -HCG), Bleeding P/V, Normal intrauterine pregnancy.

I. INTRODUCTION

Spontaneous abortion is one of the most common complications of pregnancy.CA125 is used as a predictive marker for spontaneous abortion or subsequent outcome of pregnancy.This antigen is a cell surface high molecular weight glycoprotein.During pregnancy ,CA125 was presented in tissues derived from embryonic coelomic epithelium¹. Throughout gestation, significant levels were seen in the decidua and chorion which is the main source.²CA125 had been found in high concentration in human amniotic fluid and the amnion was a major

source of it.³ During pregnancy, disruption of the epithelial basement membrane of the foetal membrane or disruption of the decidua could theoretically lead to a rise in the maternal CA125 level; this increase may be a predictor of subsequent spontaneous abortion of the foetus⁴.

This study was initiated to investigate a rise in the level of CA125 in serum that might predict spontaneous abortion or ongoing pregnancy in pregnant women with vaginal bleeding in first trimester and compare it with normal pregnant women. Also, serial beta hcg was measured to note if there is significant change in the levels along with miscarriage. Study on women with bleeding p/v reported that women older than 34 years had an odds ratio of 2.3 for miscarriage (Falco et al., 1996)⁵. Some women who bleed in early pregnancy, approximately half of them, will abort (Weiss et al., 2004)⁶. Occasionally, bleeding may persist for weeks, and then it becomes essential to decide whether there is any possibility of continuation of the pregnancy or not. The diagnosis of spontaneous abortion currently depends on a combination of ultrasonography and hormonal methods including serum human chorionic gonadotropin (HCG), urine HCG (Gerhavad and Runnebaum 1984⁷; Zeimet et al., 1998⁸; Osmanagaoglu et al., 2010⁹).

Another parameter that could be used as a predictive marker for a spontaneous abortion or subsequent outcome of pregnancy is Cancer Antigen-125 (CA-125). This antigen is a cell surface high molecular weight glycoprotein. It is a mucin like coelomic antigen, which is detected in 80% of non-mucus epithelial carcinomas of ovary. This antigen is secreted from normal tissues, such as coelomic epithelium, amnion and their derivatives including respiratory system, mesenteric organs and epithelium of female genital system (Berek 2002¹⁰). An increased CA-125 level is due to genital or non-genital origins. Nongenital causes include hepatic diseases, peritonitis, renal failure, breast, colon and lung cancer, and tuberculosis. Genital causes include pelvic inflammatory diseases, endometriosis, adenomyosis, leiomyoma, ectopic pregnancy, endometrial and ovarian cancer. Serum CA-125 levels are increased in early pregnancy and immediately after birth (Cunningham 2005¹¹; Speroff and Fritz 2005¹²), implicating the disintegration of the maternal decidua (i.e., blastocyst implantation and placental separation) as a possible source of the tumor marker elevation (Ayaty et al., 2007)¹³. There is a cyclic change in the serum concentration of CA-125 in normal menstruating women.

The hormone *human chorionic gonadotropin* (hCG) is produced during pregnancy. It is made by cells that form the placenta, which nourishes the egg after it has been fertilized and becomes attached to the uterine wall. Levels can first be detected by a blood test about 11 days after conception and about 12 - 14 days after conception by a urine test. In general the hCG levels will double every 72 hours. The level will reach its peak in the first 8 - 11 weeks of pregnancy and then will decline and level off for the remainder of the pregnancy. In about 85% of normal pregnancies, the hCG level will double every 48 - 72 hours. As you get further along in pregnancy and the hCG level gets higher, the time it takes to double can increase to about every 96 hours. Caution must be used in making too much of hCG numbers. A normal pregnancy may have low hCG levels and result in a perfectly healthy baby. An hCG level of less than 5mIU/ml is considered negative for pregnancy, and anything above 25mIU/ml is considered positive for pregnancy. The hCG hormone is measured in milli-international units per milliliter (mIU/ml). A transvaginal ultrasound should be able to show at least a gestational sac once the hCG levels have reached between 1,000 - 2,000mIU/ml. Because levels can differentiate so much and conception dating can be wrong, a diagnosis should not be made by ultrasound findings until the hCG level has reached at least 2,000. A single hCG reading is not enough information for most diagnoses. When there is a question regarding the health of the pregnancy, multiple testings of hCG done a couple of days apart give a more accurate assessment of the situation. Average values at 6 weeks LMP: 1,080 - 56,500 mIU/ml, 7 - 8 weeks LMP: 7, 650 - 229,000 mIU/ml, 9 - 12 weeks LMP: 25,700 - 288,000 mIU/ml, Non-pregnant females: <5.0 mIU/ml

These numbers are just a guideline - every woman's level of hCG can rise differently. It is not necessarily the level that matters but rather the change in the level. A low hCG level should be rechecked within 48-72 hours to see how the level is changing. A low hCG level could indicate: Miscalculation of pregnancy dating. Possible miscarriage or blighted ovum, ectopic pregnancy

A high level of hCG should be rechecked within 48-72 hours to evaluate changes in the level. A high hCG level can indicate miscalculation of pregnancy dating, molar pregnancy, multiple pregnancy. Most women can expect their levels to return to a non-pregnant range about 4 - 6 weeks after a pregnancy loss has occurred. This can be differentiated by how the loss occurred (spontaneous miscarriage, D & C procedure, abortion, natural delivery) and how high the levels were at the time of the loss. Health care providers usually will continue to test HCG levels after a pregnancy loss to ensure they return back to <5.0. Serial CA 125 levels may be helpful in determining early pregnancy loss. Schmidt and his colleagues¹⁴ found that patients who miscarried have increased or increasing levels of CA 125, whereas patients who did not miscarry have low or steeply declining

CA 125 levels. Transient elevation of the CA-125 level occurs in maternal serum during early pregnancy and just after delivery because of the destruction of decidual tissues may cause this transient elevation of CA-125 . Therefore

the elevated serum CA-125 levels in women with normal intrauterine pregnancies may be clinically useful in early pregnancy monitoring. This test is rather sensitive to differentiate the normal pregnancy and threatened abortion. There was not a significant correlation between CA-125 levels and gestational weeks (Yamane et al., 1989¹⁵). Consequently, an increase in serial CA-125 measurements in the follow-up of pregnancies with vaginal bleeding could be an early signal in determining the progression to the pregnancy loss. Although their sample size was small, Azogui and his colleagues ¹⁹also found that CA 125 levels are higher in women who eventually miscarry. Using a larger sample size but only using one measurement, however, Bonn and his colleagues ¹⁶found no differences in CA 125 levels in normal and abnormal pregnancies.

II. MATERIAL &METHODS

The study population comprised of 50 pregnant women who had vaginal bleeding in first trimester either ended with abortion confirmed by ultrasound and for some of them dilatation & curettage done some continued pregnancy without any untoward incident.. The women were recruited from gestational ages calculated according to the last menstrual period confirmed by ultrasound.The control group comprised 30 pregnant women who had normal pregnancy in first trimester and who had continued their pregnancy confirmed by antenatal care and follow-up.Maternal blood samples were taken in the first trimester and the serum was separated and measurement of serial beta HCG and CA125 was done in the department of Biochemistry, IPGME&R using ELISA method. Ethical clearance was taken from the ethical clearance committee of the institute before undergoing the study.

III. RESULTS

Initial CA 125 levels did not differ significantly between both groups of patients with 33/50 non-aborters and 17/50 aborters showing concentrations below 60 IU/ml. After 5–7 days, CA 125 in all patients who eventually aborted remained high or increased whereas non-aborters all had constantly low or declining CA 125 measures. β -HCG increased in all non-aborters and also in aborters during the 5–7 day interval In the seventeen patients who eventually aborted, the values of CA-125 were > 120 U/mL, whereas none of the successful pregnancies had a value > 91 U/mL. The mean values were 131 +/- 4.80 versus 35.95 +/- 22.1 U/mL for miscarriages and successful pregnancies, respectively. In normal pregnancies the respective value was 32.5 +/- 4.2 U/mL.Serum beta hcg measured had no correlation to the outcome of these pregnancies.50 pregnant women were recruited for this study.Their ages ranged from 16-33 years(mean 23 years,gravidity ranged from 1-33(mean2.48).No. of various abortions were 0-17(mean 0.54).All of them were nonsmokers and nonalcoholics.

Test

Table 1

Group I	End with abortion	n=17
Group II	Normal pregnancy	n=33

Table 2. Basal Level of CA-125 in the serum of pregnant women expressed as mean \pm standard

Group	Mean \pm SD	P-value
Group I	39.9 \pm 15.4	NS
Group II	28.03 \pm 4.5	NS

Table -3 CA-125 levels after an 5-7 days interval

Group	Mean \pm SD	P-value
Group I	139.9 \pm 5.4	Significant change
Group II	24.03 \pm 4.5	NS

Table-4
Maternal serum beta HCG levels between abortion group and normal pregnancy.

Group	Mean ±SD	P-value
Group I	1700.56±3.2	NS
Group II	1605.85±4.8	NS

IV. DISCUSSION

Serum CA-125 concentrations may be helpful as predictors and serve as a judge of good prognosis in threatened abortion indicators in association with other tests like ultrasonography. Some found that serum CA-125 levels are not predictive of spontaneous abortion in the first trimester and failed to discriminate among missed abortions, threatened abortions, and normal pregnancies (Mahdi 2010)¹⁷. An observation suggests CA-125 correlates less well with endometrial development in women suffering from recurrent miscarriage (Scrapellini et al., 1995)¹⁸. The concentration of CA-125 in the pregnant women who subsequently aborted were higher than those who did not, thus suggesting that serum CA-125 are not so important in maintaining successful pregnancy (Azogui et al., 1996)¹⁹. CA-125 may be useful in the assessment of endometrial development in recurrent miscarriage patients and this suggested the importance in preparing the endometrium for embryo implantation (Yu et al., 2008)²⁰. High level of serum CA-125 with high lactate dehydrogenase indicates more extensive trophoblastic tissue damage (Madendag et al., 2008)²¹. Some found that single serum CA-125 level determinations is valuable in women with imminent abortion presenting with abdominal pain, vaginal bleeding or both while others are in disagreement with this result (Fiegler et al., 2003)²². Possibly it may be attributed to the method of CA-125 measurement like the radioimmunoassay or the enzyme immune sorbent assay method.

The prognostic predictive value of maternal serum CA-125 measurement in threatened abortion can be useful to determine the extent of decidual destruction which is directly related to the outcome of pregnancy. So one can conclude a hypothesis of a tropho-decidual origin of this marker suggesting its possible usefulness in the prognostic evaluation of first trimester threatened abortion. To predict the outcome of patients with threatened abortion at an early stage of gestation is clinically important. Human chorionic gonadotropin is a glycoprotein produced by the trophoblasts of the developing placenta. It is detectable in maternal serum within a few days of implantation. An increasing doubling time is noted as pregnancy progresses. The average doubling time for HCG levels during the first 6 weeks from conception (8 weeks gestational age) is 1.94 days. This increases to an average of 4.75 days between 6 and 8 weeks from conception (8 to 10 weeks gestational age); HCG levels then begin to plateau, reaching an average peak of about 100 000 IU/L before declining and stabilizing at approximately 20 000 IU/L. This generally occurs at 10 to 14 weeks gestation, at which point HCG levels become less helpful in the evaluation of first-trimester bleeding.²³ Variation in serum HCG applies not only to serum levels, but to the rate of rise and the time to peak as well. At the end of 6 weeks from the last menstrual period, serum HCG has been shown to vary from 440 to 142 230 IU/L among women whose pregnancies resulted in normal term deliveries. Among women presenting with an initial HCG level lower than 5000 IU/L, a rise of as little as 53% over a 2-day period has been associated with normal pregnancy.

A slow rate of rise or a drop in HCG levels during the first 8 to 10 weeks of pregnancy represents death of trophoblastic tissue and can indicate ectopic or nonviable intrauterine pregnancy. Serial quantitative HCG values are, therefore, helpful in management of threatened early pregnancies. Correlation of HCG levels with transvaginal ultrasound scans contributes to management as well.^{24,25} Family physicians are generally familiar with the concept of a 2-day average doubling time for HCG values in a normal first-trimester pregnancy. A 2-day doubling time is a dependable marker up to 8 weeks gestational age, normal HCG activity is less clearly defined beyond that point, and the usually accepted doubling times might not apply.²⁶ Because there are few recent guidelines and reviews in the literature specifically addressing use of HCG levels in the evaluation of possible first-trimester pregnancy loss, family physicians might find themselves at a disadvantage when confronted with this issue.

V. CONCLUSION

The literature points to wide variability in HCG levels at any given point during pregnancy.^{27,28} When HCG levels plateau prematurely or fail to rise as expected, we consider that the pregnancy might not be viable. Normal HCG values vary up to 20 times between different pregnancies and an HCG that does not double every two to three days does not necessarily indicate a problem with the pregnancy. Some normal pregnancies will have quite low levels of HCG, and result in perfect babies.

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