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Role of Tumor Marker CA-125 in the Detection of Spontaneous Abortion

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1. Introduction

Spontaneous abortion represents a common pregnancy adverse outcome and is a serious emotional burden for women. Loss of pregnancy is a distressing problem for both the patient and physician.

The clinical diagnosis of threatened abortion is presumed when any bloody vaginal discharge or bleeding appears during the first trimester of pregnancy. A prospective study on women with threatened abortion reported that women older than 34 years had an odds ratio of 2.3 for miscarriage (Falco et al., 1996). Some women who bleed in early pregnancy, approximately half of them, will abort (Weiss et al., 2004). 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 nine hormonal methods including serum human chorionic gonadotropin (HCG), estradiol (E2), estrone, estriol, progesterone, human placental lactogen, cortisol, urine HCG and urine estrogen (Gerhavd and Runnebaum 1984; Zeimet et al., 1998; Osmanagaoglu et al., 2010). 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 2002). An increased CA-125 level is due to genital or non-genital origins. Non-genital causes include hepatic diseases, peritonitis, renal failure, breast, colon and lung cancer, and tuberculosis. Genital causes include: pelvic inflammatory diseases, endometriosis, adenomyosis, leiomioma, ectopic pregnancy, endometrial and ovarian cancer.

Serum CA-125 levels are increased in early pregnancy and immediately after birth (Cunningham 2005; Speroff and Fritz 2005), 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). There is a cyclic change in the serum concentration of CA-125 in normal menstruating women. It indicates that CA-125 was

produced from normal endometrium (Zeimet et al., 1993). Generation of potential immunogenic peptide (YTLDrDSLYV) derived from CA-125 that bind to human leukocyte antigen (HLA A2,1) leading to elicit peptide – specific human cytotoxic T lymphocytes that effectively kill ovarian tumors expressing CA-125 antigen (Kabawat et al., 1983; Bellon et al., 2009) .

Regarding the level of CA-125 in pregnancy, conflicting results have been reported. There is a positive correlation between CA-125 levels elevated 18-22 days after conception and spontaneous abortion, while repeated measurements at 6 weeks of gestation did not correlate with the outcome (Check et al., 1990). The distribution of CA-125 during pregnancy was highest in first trimester than second and third trimester (Brumsted et al., 1988). This may be due to the secretion of CA-125 and placenta protein 14 (PP14) by the glandular epithelium of the endometrium (Julkunen et al., 1986a; Julkunen et al., 1986b; Dalton et al.,1995; Dalton et al.,1998). Serum concentration of these parameters may increase during the first trimester of pregnancy as the concentration of progesterone rise to a maximum in the first trimester. These observations suggest that CA-125 is synthesized by normal endometrium in non pregnant female and by deciduas in pregnant women (Jacobs et al., 1988). Quirk et al. (1988) hypothesized that decidual CA-125 gains access to the maternal compartment via a "tubal reflux" resulting in subsequent absorption via the peritoneal lymphatics. They speculated further that the drop in maternal serum CA-125 might well be related to a functional obstruction of the tubes that occurs as pregnancy advances, with fusion of the decidua capsularis and the decidua parietalis.

The serum CA-125 level is higher in normal pregnancy compared to ectopic pregnancy 2-4 weeks after a missed menses due to impaired interaction between the fetal trophoblast and tubal mucosa (Niloff et al., 1984; Sadovsky et al., 1991; Predanic 2000). Increase in serum CA-125 levels was found in patients with vaginal bleeding and impending spontaneous abortion due to extensive decidual destruction and trophoblast separation from decidual cells (Kobayashi et al., 1993). Sequential determinations of maternal CA-125 measurements appear to be a highly sensitive prognostic marker in the patients with viable pregnancy at an abortion risk (Schmidt et al., 2001). 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 (Shin et al., 2003). 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., 1989). 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. It had been found that women with symptoms of imminent abortion, who have a CA-125 level of ≥43.IU/ml, should be considered at a greater risk of miscarriage (Fiegler et al., 2003; Sotiriadis et al., 2004) (Table-1).

Patients who eventually aborted had values of CA-125 more than 125 IU/ml while the control had a value not more than 93 IU/ml (Check et al., 1990; Ocer et al., 1992). In addition to that, an extremely high CA-125 level (over 2000 IU/mL) indicates a karyotype associated with fetal anomalies and CA-125 levels returned to normal after spontaneous abortion

eliminated the possibility that some other condition caused the marked increase (Munné et al., 1995). Although elevated CA-125 levels have been found previously in patients suffering from ovarian hyperstimulation syndrome and this merely reflect an increase in number of follicles (Bischof et al., 1989). Mordel et al. (1992) reported that CA-125 existed in significant amounts in the follicular fluid of periovulatory follicles of IVF and embryo transfer patients, but that there was no correlation between CA-125 concentrations and follicular fluid oestradiol, progesterone, testosterone, oocyte fertilization, embryo quality or pregnancy rates. It was stated that a possible ovarian tissue–blood barrier might preclude the passage of CA-125 from the follicular fluid to the serum (Fleuren et al., 1987). Endometrial receptivity is an important factor in IVF pregnancy success, and may be the origin of the changes in serum CA-125 that occur mostly from the endometrium. Bersinger et al. (1993) have investigated the considerable contribution of the endometrium to serum CA-125 concentrations and found that it reflects a favourable endometrium. The ability to predict the chances of pregnancy before embryo transfer might assist clinicians in deciding whether embryos have a greater chance of implantation if they are transferred in a subsequent cycle. It was noted that CA-125 concentrations on the day of oocyte retrieval were the best predictors of pregnancy, with concentrations >10 IU/ml having an accuracy of 86.6% for pregnancy. Thus, in intracytoplasmic sperm injection cycles, women with high serum CA-125 concentrations (>10 IU/ml) on the day of oocyte retrieval had very high pregnancy rates (Tavmergen et al., 2001) (Table 2).

Favorable prognostic factors	**Adverse prognostic factors**
History	
Advancing gestational age	Maternal age >34 years
	Increasing number of previous miscarriages
Sonography	
Fetal heart activity at presentation	Fetal bradycardia
	Discrepancy between gestational age and crown to rump length
	Empty gestational sac >15-17 mm
Maternal serum biochemistry	
Normal levels of these markers	Free β-hCG value of 20 ng/ml
	hCG increase <66% in 48 hrs
	Bioactive/immunoreactive ratio hCG <0.5
	Progesterone <45 nmol/l in 1st trimester
	Inhibin A <0.553 multiples of median
	CA-125 level ≥43.1 U/mL in 1st trimester

Table 1. Prognostic factors in cases of threatened abortion

Characteristic	Non-pregnant mean ± SEM	Pregnant mean ± SEM	P Values
No. of oocytes retrieved	7.58 ± 1.02	9.54 ± 0.92	NS
No. of mature oocytes	4.98 ± 0.58	6.43 ± 0.54	NS
Grade I embryo rates (%)	47.5	54.3	NS
No. of embryos transferred	3.0 ± 0.3	4.66 ± 0.3	<0.001
Peak oestradiol conc. (pg/ml)	1483.17 ± 129.9	2002.3 ± 114.8	0.004
Endometrial thickness (mm)	12.6 ± 0.38	13.45 ± 0.42	NS

NS: not significant (t test and x^2 test; $P > 0.05$).

Table 2. Value of serum CA-125 concentrations as predictors of pregnancy in assisted reproduction cycles

An observation suggests CA-125 correlates less well with endometrial development in women suffering from recurrent miscarriage (Scrapellini et al., 1995). 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). 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). High level of serum CA-125 with high lactate dehydrogenase indicates more extensive trophoblastic tissue damage (Madendag et al., 2008). 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). 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. CA-125 and hormones associated with pregnancy serum human chorionic gonadotropin beta-subunit, serum progesterone, serum cortisol, serum human placental lactogen, serum estrone, serum estradiol, serum estriol, urine human chorionic gonadotropin progesterone, inhibin A, and urine estrogen. 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 because others 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) (Table 3).

Test	Group I End with abortion n=42	Group II Normal pregnancy n=20
Serum Ca-125 Cut-off value up to 30 IU/ml	39.9±15.4	28.03±4.5
p-value	NS	NS

Table 3. Level of CA-125 in the serum of pregnant women expressed as mean ± standard error mean

The single measurement of free beta-hCG or progesterone levels can be useful in the prediction of first trimester spontaneous abortions, but using progesterone may be recommended since it has high availability and low cost.

As a conclusion, the measurement of serum CA-125 is not of value to predict the outcome of threatened abortion because it is secreted from different origins. There is no correlation between CA-125 level and outcome of pregnancy. CA-125 may have a predictive role in the successful outcome in ICSI cycles, but it has to be further investigated

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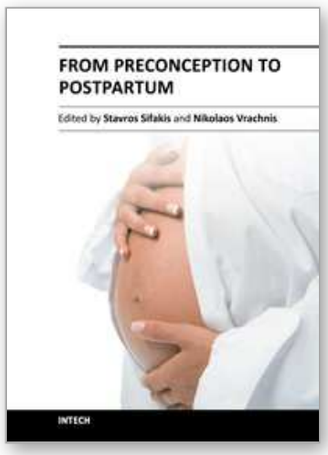

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