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Serum levels of CA 125 during the first trimester of normal outcome, ectopic and anembryonic pregnancies

I.J.Jacobs, T.N.Fay, J.Yovich[1], I.Stabile, C.Frost[2], J.Turner[3], D.H.Oram[4] and J.G.Grudzinskas[5]

Academic Unit of Obstetrics and Gynaecology, The London Hospital Medical College, London E1, UK, [1]PIVET Medical Centre, Perth, Western Australia, Australia, [2]Department of Environmental and Preventive Medicine, St Bartholomews Medical School, London, [3]Department of Medical Physics, The London Hospital, Whitechapel, London E1 and [4]Department of Obstetrics and Gynaecology, The London Hospital, Whitechapel, London E1 1BB, UK

[5]To whom correspondence should be addressed

Single serum samples were obtained during the first trimester of pregnancies with a retrospectively normal outcome (n = 150), ectopic pregnancies (n = 38) and anembryonic pregnancies (n = 78). Serial samples during the first trimester were also obtained from 43 women achieving pregnancy following successful treatment for infertility and with a retrospectively defined normal outcome. Significant variation in serum CA 125 levels in relation to gestational age was observed in pregnancies with a normal outcome (P < 0.0001). Peak serum CA 125 levels were observed at 6–7 weeks, the mean level at this gestation being 40.1 U/ml (range 31.7–50.7 U/ml) in the normal conception/normal outcome group and 36.5 U/ml (range 25.6–52.0 U/ml) in the assisted conception/normal outcome group. A rise and fall in serum CA 125 levels during the first trimester was observed in 42 of 43 assisted conceptions monitored serially, with peak levels ranging from 7 to 1398 U/ml (median 48.8 U/ml) occurring at 28–61 days (median 45 days) gestation. Mean serum CA 125 levels were higher in the anembryonic pregnancy group at 4–5 and 6–7 weeks gestation than in both normal pregnancy outcome groups (P < 0.01).

Key words: CA 125/pregnancy

Introduction

CA 125 is a tumor-associated antigen recognised by a monoclonal antibody OC 125 (Bast *et al.*, 1981, 1983). The highest serum levels of CA 125 are found in patients with ovarian cancer and it is of established value in monitoring the treatment of epithelial ovarian cancer. Elevated serum levels of CA 125 are also seen in women with other malignancies, benign conditions such as endometriosis and physiological states such as pregnancy and menstruation (Jacobs and Bast, 1989). The role of serum CA 125 estimation in screening for ovarian cancer and in the management of endometriosis is currently under investigation (Jacobs *et al.*, 1988a; Barbieri *et al.*, 1986; Kaupilla *et al.*, 1988; Patton *et al.*, 1986; Fedele *et al.*, 1988; Pittaway and Fayez, 1986).

The function of the glycoprotein expressing CA 125 remains unclear but the distribution of the antigen suggests that it may have a physiological role. We have previously reported the compartmental distribution of CA 125 in the reproductive tract of healthy pregnant and non-pregnant women (Jacobs *et al.*, 1988b) and, on the basis of our preliminary results, concluded that CA 125 is a product of normal endometrium and decidua. We describe here further clinical studies which were performed in order to observe the variation of serum CA 125 during early pregnancy and its complications.

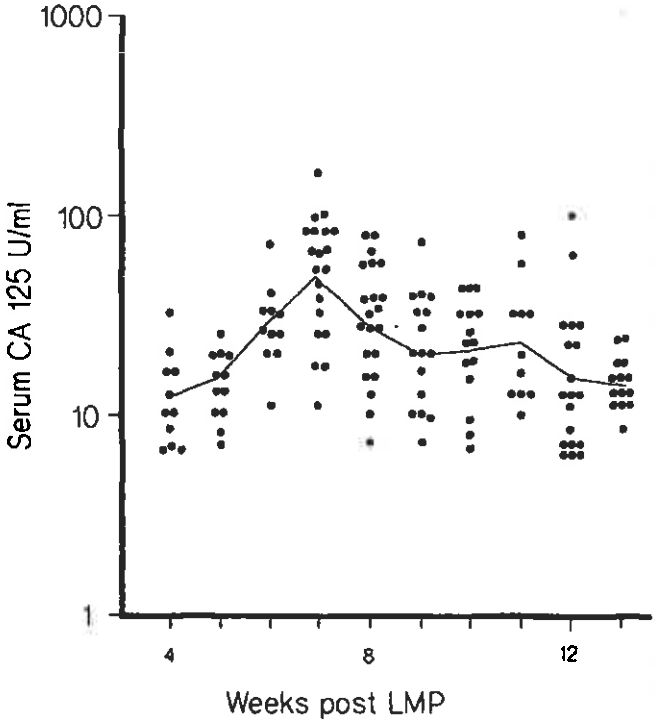

Fig. 1. Serum CA 125 levels during the first trimester of pregnancies (n = 150) achieved following natural conception and with a normal outcome. (Solid line = mean level. Dotted lines = ±2 SD from mean.)

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Materials and methods

Subjects and samples

Natural conception/normal outcome. Single serum samples were obtained from 149 women in the first trimester of pregnancy (4–13 weeks gestation) following natural conception and with a retrospectively defined normal outcome. Gestational age was calculated retrospectively from the first day of the last menstrual period or by ultrasound assessment of gestational age in the first trimester in women with irregular menstruation.

Assisted conception/normal outcome. Serum samples were obtained at approximately weekly intervals during the first trimester of pregnancy, from women achieving pregnancy following successful treatment for infertility at the PIVET Medical Centre, Perth, Western Australia. A total of 369 serum samples were obtained from 43 singleton pregnancies with a normal outcome. Ovulation was achieved spontaneously (n = 6) or induced with clomiphene citrate (n = 37). Fertilization was achieved by artificial insemination by husband or donor (n = 11), in-vitro fertilization (n = 8) or following intercourse (n = 24). A further 94 samples were obtained from seven twin and four triplet pregnancies achieved following ovulation induction with clomiphene and in-vitro fertilization. All conception cycles were monitored at regular intervals and the date of ovulation documented by ultrasound scanning or the identification of the LH surge. Gestational age is expressed as interval after the last menstrual period and calculated on the assumption that the date of ovulation was day 14 of the menstrual cycle, or by ultrasonic assessment of gestational age in the first trimester in women with irregular menstruation.

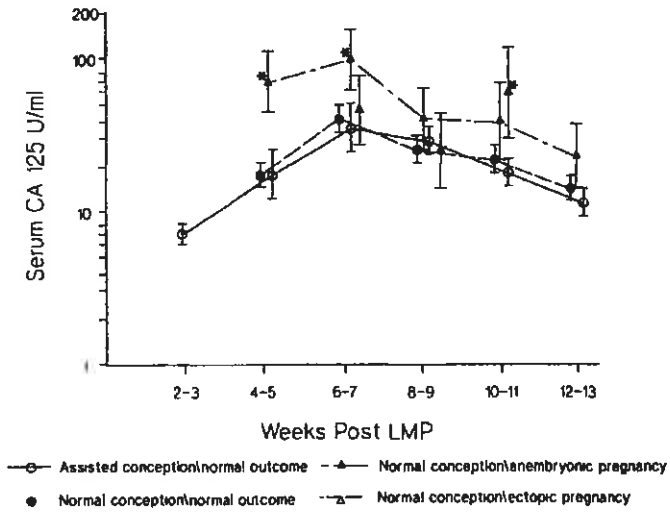

Fig. 2. Mean and 95% confidence limits around the mean for serum CA 125 at 2 weekly intervals during the first trimester of normal outcome (assisted and natural conception), anembryonic and ectopic pregnancies. (* = mean serum CA 125 levels significantly greater than pregnancies with a normal outcome.)

Natural conception/early pregnancy failure. Serum samples were obtained from patients with ectopic pregnancies (n = 38) and anembryonic pregnancies (n = 78) following natural conception. Gestational age was calculated retrospectively from the first day of the last menstrual period. Anembryonic pregnancy was defined as an empty gestational sac of volume greater than 2.5 ml, visualized by real time ultrasonography via the abdominal route. Serum HCG levels in these samples have been reported elsewhere (Stabile *et al.*, 1988; Grudzinskas *et al.*, 1989).

Radioimmunoassays

Venous blood was permitted to clot at room temperature, the serum separated by centrifugation, aliquoted and stored at −20°C until assayed. CA 125 activity was measured by radioimmunoassay (Abbott Laboratories, Chicago, USA). The detection limit of the assay was 7 U/ml. Serum HCG activity was measured by double antibody radioimmunoassay (Amersham

Table I. Mean log transformed CA 125 levels (and 95% confidence limits) by weeks gestation in normal outcome, ectopic and anembryonic pregnancies

Gestation (weeks)	Normal conception/ normal outcome	Assisted conception/ normal outcome	Normal conception/ ectopic pregnancy	Normal conception/ anembryonic pregnancy
4–5	13.3 (10.9–16.1)	18.3 (13.0–25.9)	—	72.6 (46.2–114.0)
6–7	40.1 (31.7–50.7)	36.5 25.6–52.0)	46.7 27.5–79.3)	99.1 64.0–153.5)
8–9	25.6 (20.5–31.9)	29.5 (23.2–37.5)	27.2 15.2–48.5)	40.8 (25.4–65.6)
10–11	21.7 (17.1–27.6)	16.9 (13.1–21.7)	63.1 (31.0–125.9)	39.1 (22.1–69.2)
12–13	14.3 (12.1–16.7)	11.7 (9.6–14.3)	—	22.8 (15.0–34.7)

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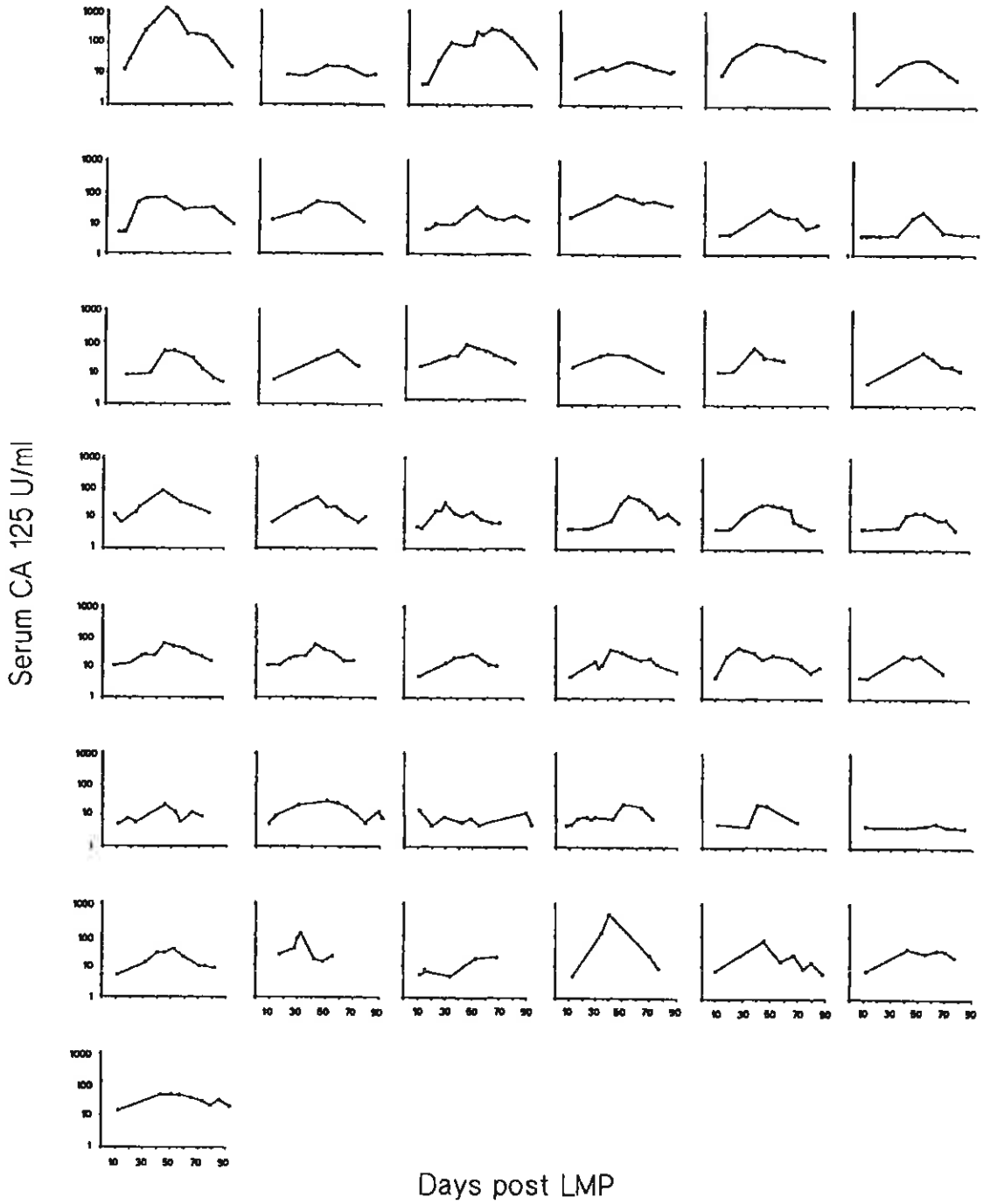

Fig. 3. Serial serum CA 125 levels during the first trimester of singleton pregnancies (n = 43) achieved following treatment at an infertility clinic and with a retrospectively normal outcome.

International, UK). The intra-assay and inter-assay coefficients of variation for both assays were <10%.

Statistical analysis

All data analysis was performed using log-transformed values for serum CA 125 and the Statistical Package for the Social Sciences. In groups (a) and (c), mean (±SE) of log CA 125 levels were calculated for gestational ages 2–3, 4–5, 6–7, 8–9, 10–11 and 12–13 weeks, and compared using analysis of variance. In group (b), for which serial samples were available, mean CA 125 for each patient in each time period was first

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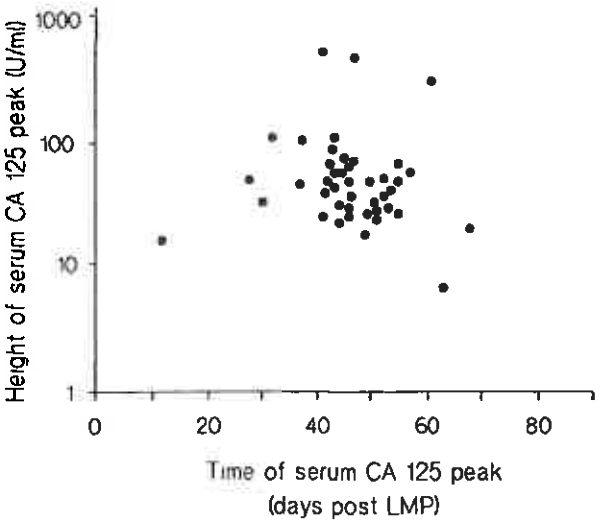

Fig. 4. Peaks serum CA 125 levels and gestational age at the time of peak levels in pregnancies (n = 43) achieved following treatment at an infertility clinic and with a retrospectively normal outcome.

computed and then a group mean (±SE) calculated for comparison with the results from groups (a) and (c).

Results

Normal pregnancy/normal outcome

Serum CA 125 levels in women in the 'natural conception/normal outcome' group, between 4 and 13 weeks post menstruation, are shown in Figure 1. High and low serum CA 125 levels were apparent during the first trimester of pregnancy and analysis of variance confirmed significant variation with gestational age ($P < 0.0001$), the mean log-transformed serum levels of CA 125 being highest at 6–7 weeks gestation, and were greater than at 4–5, 10–11 or 12–13 weeks gestation (Figure 2, Table I).

Assisted conception/normal outcome

Serial serum CA 125 levels for each singleton pregnancy monitored are shown in Figure 3. A rise in serum CA 125 levels to at least twice the non-pregnant level was observed in all but one of the 43 pregnancies. Peak serum CA 125 levels ranged from <7 to 1398.0 U/ml (median 48.8 U/ml) and occurred at 28–61 days gestation (median 45 days) (Figure 4). The pattern of mean log serum CA 125 levels by gestational age was not significantly different to that observed in group (a) (Figure 2, Table I). The distribution of serum HCG in these 43 singleton pregnancies is shown in Figure 5. Serial serum CA 125 levels for each multiple pregnancy monitored are shown in Figure 6.

Natural conception/early pregnancy failure

Figure 7 illustrates serum CA 125 levels in patients with ectopic and anembryonic pregnancies, superimposed on the range of serum CA 125 in the 'normal conception/normal outcome' pregnancies. Analysis of variance indicated significant variation in log serum CA 125 by week of gestation in patients with anembryonic pregnancies ($P = 0.0106$) but not in patients with ectopic pregnancies ($P = 0.17$). Significant differences were

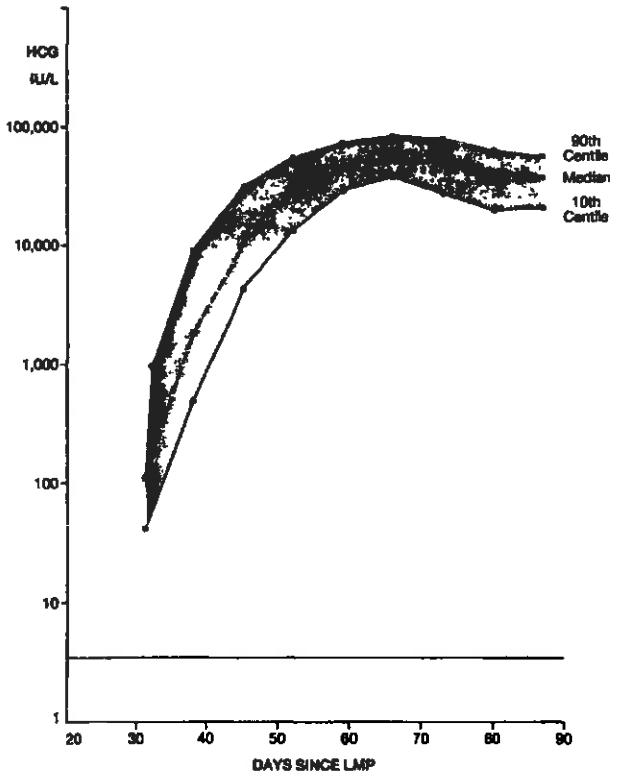

Fig. 5. Serum HCG levels during the first trimester of singleton pregnancies (n = 43) achieved following treatment of an infertility clinic and with a retrospectively normal outcome.

observed between serum CA 125 levels in the normal pregnancy outcome groups and both ectopic pregnancy ($P = 0.006$) and anembryonic pregnancy ($P < 0.001$) groups. Mean log-transformed CA 125 values were higher in the ectopic pregnancy group at 10–11 weeks gestation than in the groups with a normal pregnancy outcome (both assisted and natural conception) (Figure 7a, Table I). Mean log-transformed CA 125 values were higher in the anembryonic pregnancy group at 4–5 and 6–7 weeks than in the normal pregnancy outcome groups, (both assisted and natural conception), (Figure 7b, Table I). From 4–8 weeks gestation, 24 of 39 samples from anembryonic pregnancies were more than 2 SD above the mean for pregnancies with a normal outcome, whilst from 8–12 weeks, 35 of 39 were within 2 SD of the mean.

Discussion

We have demonstrated a consistent pattern of a rise and fall in serum CA 125 levels during the first trimester of pregnancies with a retrospectively-defined normal outcome. Our findings are in accord with earlier reports, in which elevations of serum CA 125 levels during the first trimester in comparison to the latter weeks of pregnancy or the non-pregnant state were observed (Seki *et al.*, 1986; Niloff *et al.*, 1984; Haga *et al.*, 1986; O'Brien *et al.*, 1986; Jacobs *et al.*, 1988b,c). With the exception of eight cases reported by Seki *et al.* (1986), these studies have been based on observations from single samples obtained more than 6 weeks

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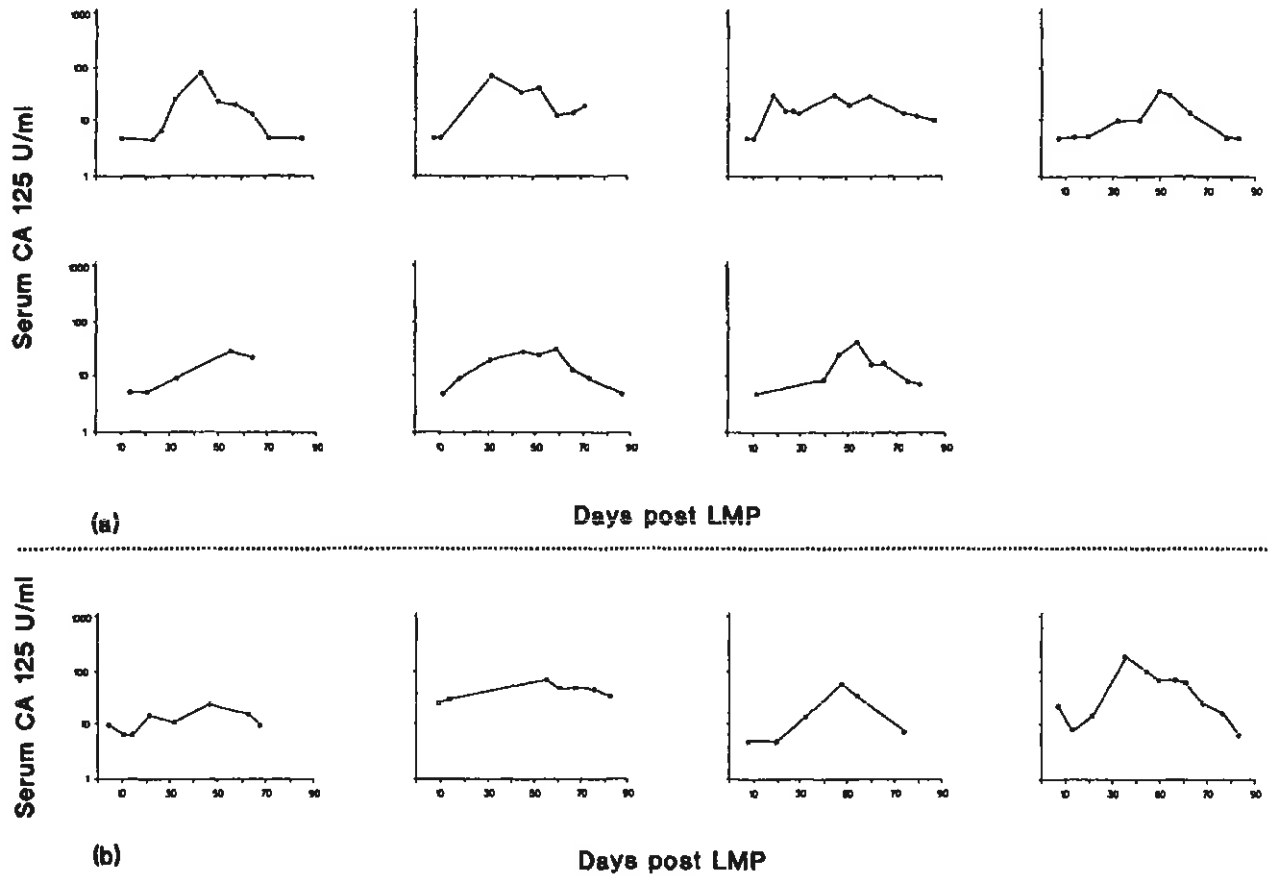

Fig. 6. Serial serum CA 125 levels during the first trimester of (a) twin (n = 7) and (b) triplet (n = 4) pregnancies achieved following treatment at an infertility clinic.

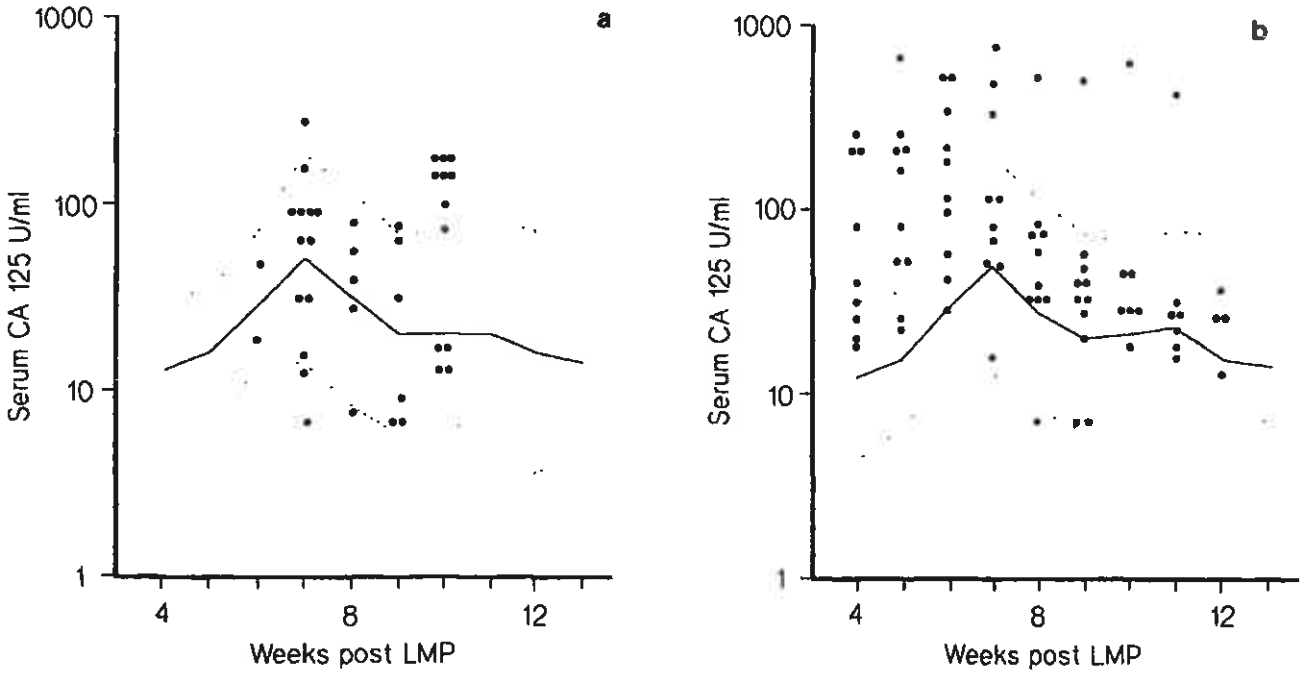

Fig. 7. Serum CA 125 levels during the first trimester of pregnancies achieved following natural conception and resulting in (a) ectopic pregnancies (n = 38) and (b) anembryonic pregnancies (n = 78). (Solid line = mean level for normal outcome pregnancies. Dotted lines = ± 2 SD from mean for normal outcome pregnancies.)

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after the last menstrual period. Consequently, high serum levels of CA 125 appeared to occur in a relatively small proportion of pregnancies. The findings reported here indicate that the elevation of serum CA 125 levels seen in the first trimester is usual in assisted conception pregnancies (Figure 3). Although serial samples were not obtained from 'natural conception/normal outcome' pregnancies it is likely that the same pattern occurs in these pregnancies given the similarity in mean levels of serum CA 125 during the first trimester in assisted conception and natural conception pregnancies (Figure 2).

The physiological basis for the elevation of serum CA 125 levels during the first trimester is unclear. We have previously reported high levels of CA 125 in aqueous extracts of first trimester decidua compared to non-pregnant endometrium or decidua obtained at term (Jacobs *et al.*, 1988b). The increase in serum levels may therefore simply represent diffusion of the CA 125 moiety down an increased tissue–blood concentration gradient. Quirk *et al.* (1987) have hypothesized that during early pregnancy, there is leakage of CA 125 from the gestation sac to the peritoneal cavity, via the Fallopian tubes, from where it is absorbed into the circulation. As the gestation sac enlarges, and the decidua capsularis fuses with the decidua parietalis, they suggest that this route of drainage is obstructed and hence serum CA 125 levels fall toward the end of the first trimester. However, such anatomical explanations do not account for the increased tissue production of CA 125 observed in early pregnancy. Evidence from three studies of CA 125 expression *in vitro* suggests that CA 125 production may be a regulated cellular process which can be modified by synthetic steroids and other drugs. Bischof *et al.* (1986) demonstrated inhibition by medroxyprogesterone of CA 125 production in monolayer culture of human endometrial stromal cells. This inhibition could be blocked by oestradiol or the progesterone antagonist RU486. Ishiwata *et al.* (1986) found that treatment of four ovarian cancer cell lines with the dibutyryl derivative of cyclic AMP stimulated CA 125 release. Most recently, Karlan *et al.* (1988) have demonstrated inhibition of release of CA 125 from OVCA 433 cells by treatment with dexamethasone. The inhibition was concentration-dependent and specific to glucocorticoids. These reports suggest that the observed rise in serum CA 125 levels may be related to the complex endocrinological events of early pregnancy.

This study was not designed to assess the diagnostic value of serum CA 125 measurement during early pregnancy, but has provided some information about two complications of early pregnancy. First, the elevation of serum CA 125 observed in assisted conception pregnancies was transient and variable in its timing, duration and magnitude (Figure 4). The 'normal range' for serum CA 125 is consequently wide. Secondly, although differences were observed between mean serum CA 125 levels in anembryonic and ectopic pregnancies compared to those with a normal outcome, there was considerable overlap in the range of values in the various groups. For these reasons, it is unlikely that serum CA 125 measurements during early pregnancy will be of clinical value.

The high levels of CA 125 observed in anembryonic pregnancies are intriguing and suggest that the presence of the fetus suppresses the release of CA 125 into the circulation. The rise in serum levels of CA 125 in ectopic pregnancies suggests that decidual trophoblast interaction is not essential for release of CA 125 into the maternal circulation. These observations are in contrast to serum levels of proteins of trophoblastic origin such as HCG PAPP-A and SP1 which are depressed in women with anembryonic pregnancies (Jacobs *et al.*, 1988c; Stabile *et al.*, 1989).

In summary, the observations described here suggest that elevation of serum CA 125 levels is a consistent feature of early pregnancy and not a phenomenon confined to a small proportion of pregnancies. Our preliminary results have revealed significant differences between the pattern of serum CA 125 in normal outcome and ectopic or anembryonic pregnancies. The function of the CA 125 moiety and its physiological significance remain unclear and are the subject of ongoing investigations.

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