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CA 125 in the management of endometriosis

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Summary

CA 125 is expressed by eutopic and ectopic endometrium. In women with advanced endometriosis, plasma concentrations are increased towards the end of the luteal phase and during menstruation but not during the follicular and early luteal phases. In women without endometriosis, such cyclic changes of CA 125 in plasma are not observed. In women with cystic ovarian endometriosis, plasma CA 125 concentrations are markedly elevated. Measurement of CA 125 in ovarian cyst fluid is the method of choice to differentiate a cystic corpus luteum from an ovarian endometriotic cyst, a frequent and difficult clinical problem. CA 125 can be used to diagnose deeply infiltrating endometriosis with a sensitivity of 36% and a specificity of 87%. These figures underestimate the clinical importance, since plasma CA 125 concentrations are mainly important for the diagnosis of deeply infiltrating endometriosis types II and III, which are the most severe forms and which are clinically easily missed. Because of the strong association of deep endometriosis and pelvic pain, the assay of CA 125 in plasma may be advocated in all women with unexplained pelvic pain as an aid in the diagnosis of deeply infiltrating endometriosis. Following surgical excision of endometriosis, CA 125 can be used to monitor the completeness of surgery.

CA 125; Tumor marker; Endometriosis

Introduction

CA 125 is a high molecular weight glycoprotein shown to be the tumor marker of choice for epithelial ovarian tumors [1]. CA 125 is expressed by epithelia derived from the coelomic epithelium. During the normal menstrual cycle, the eutopic endometrium is the major source of CA 125 production and secretion into the lumina of the glands and the blood vessels; during menstruation, very high levels of CA 125 are found in the menstrual discharge [2], and also the plasma concentrations are markedly increased most probably due to resorption by the damaged endometrial vascular bed [3,4]. In benign gynecologic pathologies, increased levels of CA 125 are found in women with endometriosis, in women with pelvic inflammatory disease and in women with fibroids. Plasma CA 125 levels also increase during early pregnancy [1].

In this paper, CA 125 concentrations will be reviewed in women with endometriosis in order to delineate the clinical usefulness of this tumor marker for the diagnosis and therapy monitoring of endometriosis.

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CA 125 in women with endometriosis

Plasma concentrations

Plasma concentrations of CA 125 are known to be elevated in women with endometriosis, especially in the more severe forms (revised American Fertility Society classification, classes III and IV). It has recently been demonstrated that increased concentrations are mainly found in women with cystic ovarian endometriosis and in women with deeply infiltrating endometriosis [5]. To understand this new observation, one should know that endometriotic cyst fluids contain very high concentrations of CA 125, and that deeply infiltrating endometriosis secretes CA 125 towards the bloodstream, whereas superficial endometriotic implants secrete mainly towards the peritoneal cavity from where CA 125 is only slowly resorbed because of its high molecular weight. Plasma CA 125 concentrations thus reflect, besides the endometrial production, the volume of the ovarian endometriotic cysts and the volume of the deeply infiltrating endometriotic nodules.

The hormonal regulation of CA 125 expression and secretion by the endometrium and endometriotic implants is still poorly understood. It has been suggested that estrogens alone stimulate expression, whereas progestogens would stimulate secretion. In order to understand the plasma CA 125 concentrations in endometriosis patients we probably should consider the local steroid hormone concentrations in the endometriotic lesions. Peritoneal implants are probably mainly influenced by the peritoneal fluid concentrations of 17β-estradiol and progesterone which are 10–100 times higher than in plasma, especially following ovulation. Moreover, 'elevated' peritoneal fluid progesterone concentrations are found throughout the menstrual cycle [6]. For ovarian endometriosis, the intra-ovarian concentrations of steroids should probably be taken into account and these are supposed to be even much higher.

The hormonal regulation of CA 125 expression and secretion should explain the slight midcycle increase of CA 125 concentration in normal women, and the progressive increase towards the end of the luteal phase in women with mild and moderate endometriosis. The intra-ovarian, peritoneal fluid and plasma steroid concentrations can also explain why women with cystic ovarian endometriosis and/or deeply infiltrating implants have constantly increased plasma concentrations of CA 125 throughout the menstrual cycle [5]. The marked menstrual increase of CA 125 concentration can probably be explained by resorption and pelvic peritoneal irritation as well as by local inflammatory reactions in and around endometriotic lesions.

Peritoneal fluid concentrations

As anticipated from the high levels of CA 125 in menstrual discharge and from pelvic irritation, the peritoneal fluid concentrations of CA 125 are highest during the early follicular phase and decrease progressively thereafter. In women with endometriosis, this early follicular increase is much more pronounced.

The measured concentrations are some 100 times higher than in plasma. This can probably be explained by local peritoneal production and slow resorption from the pouch of Douglas because of the high molecular weight of CA 125.

Menstrual discharge

CA 125 concentrations in menstrual discharge are very high and more increased in women with endometriosis [2].

CA 125 for diagnosis of endometriosis

Plasma concentrations in deeply infiltrating endometriosis

Although women with mild and moderate endometriosis have increased plasma CA 125 concentrations, especially during the late luteal phase and during menstruation, plasma CA 125 concentrations cannot yet be used clinically to diagnose early stages of endometriosis because of the overlap between concentrations of minimal, mild and moderate disease and those of women without endometriosis. It was recently shown, however, that the diagnostic accuracy can be much improved by repetitive sampling during menstrual and early follicular phase of the cycle. It was thus shown that the ratio of concentrations during menstrual and follicular phase is higher in women

with minimal and mild and in women with moderate disease as compared to control women. A ratio higher than 1.5 is suggested to be a sensitive indicator for endometriosis even in cases with minimal or mild disease. Further clinical evaluation of the usefulness of such a CA 125 ratio as a screening test for endometriosis will however be necessary.

Plasma CA 125 concentrations cannot be advocated as a single tool for diagnosis of ovarian endometriotic cysts since other diagnostic methods, such as ultrasonography are largely superior. For the differential diagnosis of ovarian endometriotic cysts, however, the increased concentrations of CA 125 in women with ovarian cystic endometriosis should be taken into consideration.

The most important application of plasma CA 125 concentrations known today is for the differential diagnosis of deeply infiltrating endometriosis. The published overall sensitivity of 36% and specificity of 87% underestimates the fact that CA 125 concentrations are probably mainly elevated in women with deeply infiltrating endometriosis types II (retraction) and III (adenomyosis externa) [7,8]. These subtypes of deep disease are less frequent than type I deep endometriosis, the latter representing a disease with less deeply infiltrating lesions [9]. Types II and III are the most severe forms of deep endometriosis and are strikingly most easily missed clinically and during laparoscopy. Since deeply infiltrating endometriosis is strongly associated with pelvic pain [9,10], plasma CA 125 concentrations may be used to screen for deep endometriosis in patients with chronic pelvic pain. A diagnosis of deeply infiltrating endometriosis is important since it will prompt to perform surgical (laparoscopic) exploration and excision of deep nodules. Elevated CA 125 levels may indicate the presence of deep disease and will

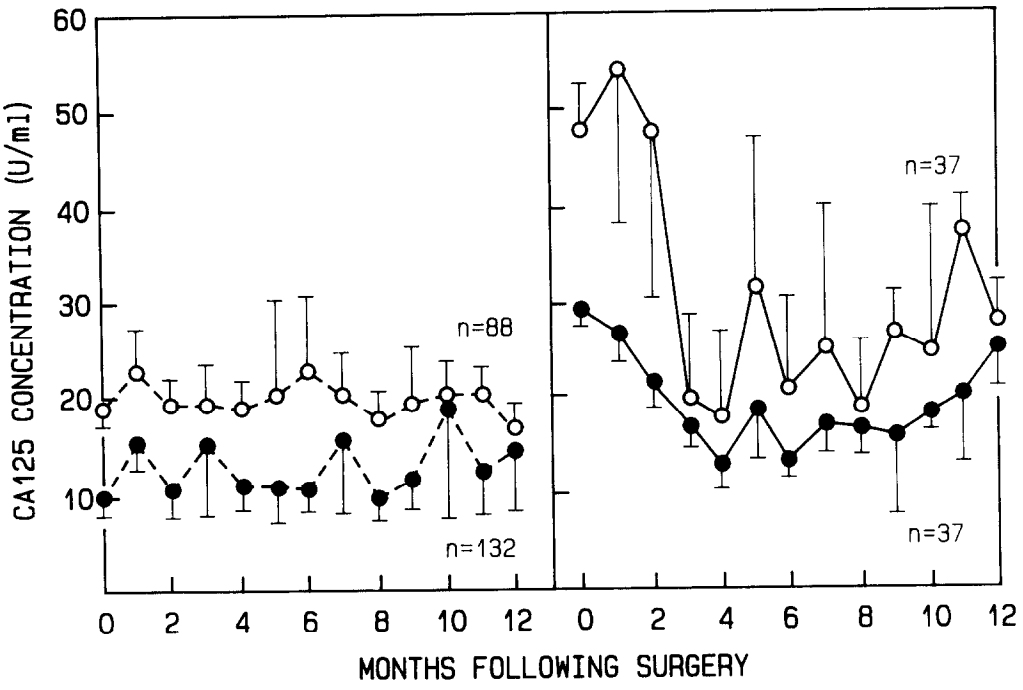

Fig. 1. Plasma CA 125 concentrations (means ± S.E.) before and following CO_2-laser endoscopic treatment of pelvic endometriosis. Women with plasma concentrations before surgery lower than 15 U/ml (left: ●), with plasma concentrations between 15 U/ml and 25 U/ml (left: ○), with plasma concentrations between 25 U/ml and 35 U/ml (right: ●), and with plasma concentrations greater than 35 U/ml (right: ○) are depicted separately (Koninckx et al., manuscript submitted).

prevent the diagnosis of infiltrating endometriosis being missed during subsequent surgery.

Cyst fluid concentrations

When dark brown 'chocolate' cyst fluid is aspirated, the diagnosis of an ovarian endometriotic cyst can reliably be made by CA 125 measurement in this fluid. Cyst fluid CA 125 concentrations higher than 10 000 U/ml alone or CA 125 levels between 1000 and 10 000 U/ml associated with low 17β-estradiol or low progesterone levels, indicate the presence of an ovarian endometriotic cyst, with a sensitivity of 100% and a specificity of 100% [11]. This is extremely important and useful to differentiate a cystic corpus luteum from an endometriotic cyst. Visual inspection of these ovarian cysts does not always allow accurate differential diagnosis. Indeed many excised so-called endometriotic cysts are shown to be cystic corpora lutea by pathology. The assay of CA 125 in cyst fluid would prevent unnecessary cystectomies for these misdiagnosed 'endometriotic' cysts. Also in IVF, 'chocolate-like' fluids are often aspirated during oocyte retrievals and it is important to know whether this reflects the presence of an old corpus luteum, a follicular cyst or an endometrioma [11].

CA 125 concentrations for the monitoring of treatment

CA 125 concentrations clearly decrease during medical treatment or after surgical excision of endometriotic implants [12,13].

From a recent prospective study of women following CO_2-laser excision of endometriotic implants the following conclusion can be drawn (Fig. 1). In women with normal pre-surgery levels of CA 125, the concentrations do not change after surgery. In women with elevated pre-surgical CA 125 concentrations, the plasma levels decrease rapidly to normal values. In some women in whom excision was impossible or in whom excision was documented to be incomplete, the CA 125 concentrations remained elevated throughout the follow-up period. CA 125 can thus be used to evaluate the quality or completeness of surgical excision of implants. This is extremely useful in patients with deeply infiltrating endometriosis with elevated levels of CA 125 before surgery. It is well known that deep excision of nodular infiltrating endometriotic implants is technically difficult and that complete excision is sometimes impossible. Future investigations will be necessary to ascertain the optimal sampling period during follow-up. Our data, however, strongly suggest that monitoring of the CA 125 concentrations after laser excision of implants should be postponed for at least 4 months after surgery. Furthermore, sampling should be done during comparable phases of the cycle, probably during menstruation.

The question whether CA 125 concentrations are useful to monitor disease recurrence or fertility outcome in infertile patients cannot yet be answered.

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