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A Decrease in Circulating Levels of Immunoreactive Insulin-like Growth Factor Binding Protein-1 (IGFBP-1) after Endometrial Ablation Using a Gynecologic Resectoscope

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Abstract

To determine how endometrium alone would contribute to maitaining the circulating levels of Insulin-like growth factor binding protein-1 in vivo, serum immunoreactive IGFBP-1 levels were measured in 19 patients undergoing endometrial ablation using gynecologic resectoscopy. After endometrial ablation there was a significant decrease in the mean levels of circulating IGFBP-1, which was not correlated with the menstrual cycle. This result indicates that the endometrium is one of the sources of the circulating IGFBP-1.

Key Words: Insulin-like growth factor binding protein-1, endometrial ablation

INTRODUCTION

Circulating and tissue insulin-like growth factor (IGF)-I and IGF-ll are associated with specific affinity binding proteins[1] which carry more than 99% of circulating IGFs.[2] The circulating insulin-like growth factor binding proteins (IGFBPs) are believed to prolong the half-life of the IGFs, as well as to regulate the endocrine effects of the growth factors.

The action of IGF-1 is modulated by binding proteins that either inhibit or potentiate the IGFs' action.[3,4] It has been suggested that most circulatory IGFBP-1 comes from the liver, but some also comes from ovarian follicles[5] and the uterus.[6] We tried to specify the source of IGFBP-1 in the human uterus. In our study, we evaluated the contribution of 'endometrium in vivo' to the circulating levels of IGFBP-1 and where there was any correlation between its levels and the phases of menstrual cycles after the isolated removal of endometrium.

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MATERIALS AND METHODS

Subjects

The study patients comprised 19 premenopausal women aged from 35 to 47 years, with irregular uterine bleeding requiring endometrial ablation. There were seven patients with uterine myoma, six with bloody dyscrasia, three with cystic endometrial hyperplasia and three with recurrent abnormal uterine bleeding refractory to repeated hormonal therapy and curettages. Among the patients with hemorrhagic disorders, three had idiopathic thrombocytopenic purpura and three had aplastic anemia. The types of myoma were intramural in three cases and submucosal in four cases (two sessile and two pedunculated). None of the patients had been treated with any hormonal therapy before or during this study.

The control group consisted of 14 patients who underwent operative hysteroscopy due to uterine synechiae (nine patients), uterine septum (three patients) and endometrial polyp (two patients). This study was approved by our institutional Medical Research Council. The blood samples were taken pre-operatively,

and subsequently on the third post-operative day in all patients. To minimize hormonal influence and to observe the immediate effect of loss of endometrium on circulating levels of IGFBP-1, we shortened the time interval between surgery and the second blood sampling to three days. All blood samples were drawn between 08 : 00 and 11 : 00 A.M. in the fasting state to minimize the effect of diurnal variation. The sera were separated immediately and stored at −70 +Y until assayed.

Assays

The level of IGFBP-1 was measured in the serum samples using IGFBP-1 immunoenzymometric assay kit which used antihuman IGFBP-1 mouse monoclonal antibody (Medix Biomedica, Helsinki, Finland). This assay had an intra-assay and inter-assay coefficient variance of 2.5% and 6.4%, respectively, and a detection limit of 0.4 ng/ml. Serum estradiol and progesterone were measured using RIA kit (Diagnostic Product Corp., Los Angeles, CA, USA).

Endometrial ablation

The procedure was scheduled for the post-menstrual proliferative phase or anovulatory cycles in 13 patients and six patients in luteal phase. All of the control subjects were in proliferative phase. The phase of menstrual cycle was postoperatively defined by clinical history, hormonal assay and histologic findings.

The instrument used for endoscopic resection of the endometrium was a gynecologic resectoscope (Richard Wolf, Bonn, Germany), which has 24 Fr. outer sheath and a 90-degree angle wire loop electrode. Electric energy was provided by a Valley-lab Force-2 electrosurgical generator (Valley-lab Inc., Boulder, CO, USA), with power settings at 30−50 watts of cutting current. The uterine cavity was distended by 32% dextran contained in a hand-held 50 ml syringe through a side channel of the resectoscope. The total volume of dextran never exceeded 500 ml (average; 375 ml). We used the technique of shaving the endometrium from the cornual portion and the fundal surface down to the level of internal os with a thickness of approximately three to four mm. A ball electrode was used for adequate hemostasis. Sessile and pedunculated myomas were morcellated together with endometrium.

A pediatric foley catheter was placed in the uterine cavity after the procedure in every patient for hemostasis for up to 24 hours. All tissue specimens were sent to the tissue pathology laboratory for immediate frozen or permanent section to rule out endomerial malignancy. All patients tolerated the procedures without any significant complications. All patients took Gonadotropin Releasing Hormone (GnRH) analogue or progesterone for 1 week after the operation.

Statistical analysis

Wilcoxon signed rank test was used to assess the difference in pre-operative and post-operative values of serum IGFBP-1. The correlation between IGFBP-1 and estradiol and progesterone was assessed by Spearman rank correlation test. Probability <0.05 was considered significant.

RESULTS

During the follow-up period of three months, amenorrhea developed in 13 patients (76.5%), hypomenorrhea in two patients and no changes in menstrual flow in two patients (two patients were lost during follow-up). We evaluated the adequacy of endometrial eradication by thorough pathologic examination. The surgical specimens revealed endomyometrium showing adequate depth of surgical resection

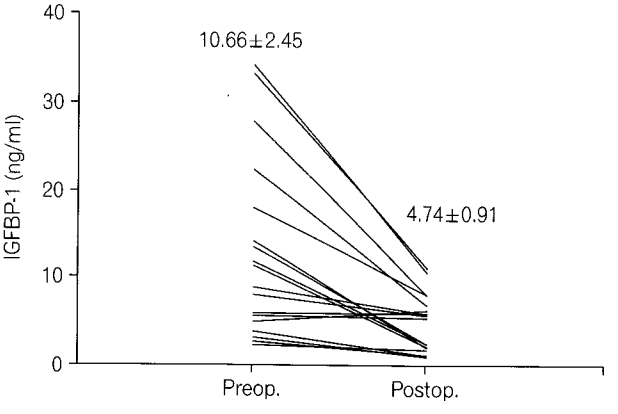

Fig. 1. Changes in circulating levels of IGFBP-1, before and after endometrial ablation. Numerical represents mean ±SEM. Pre-operative serum IGFBP-1 levels were significantly higher than post-operative day 3 ($p<0.05$).

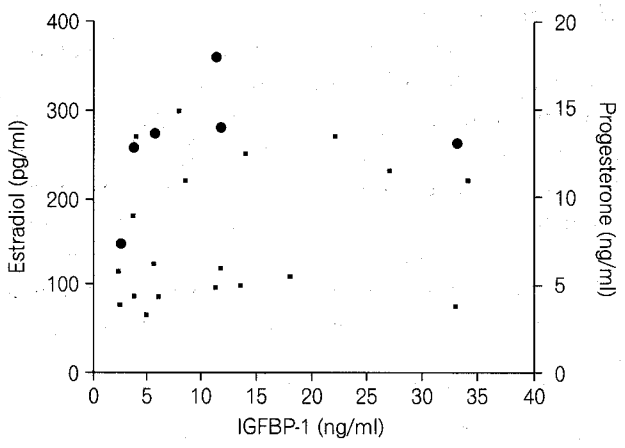

Fig. 2. The relation between the serum estradiol level (+q) or progesterone level (+l) and the preoperative IGFBP-1 level. There was no correlation between the parameters ($p > 0.05$) Spearman rank correlation.

Serum levels of IGFBP-1 in the control group did not alter significantly after the operation (from 8.04 $\pm$2.92 ng/ml to 7.50$\pm$2.88 ng/ml, mean$\pm$SEM, $p > 0.05$). In the study group, the pre-operative serum IGFBP-1 was 10.66$\pm$2.45 ng/ml (mean$\pm$SEM) and the levels fell to 4.74$\pm$0.91 ng/ml on post-operative day three ($p < 0.05$) (Fig. 1). The post-operative serum IGFBP-1 levels decreased significantly during the proliferative phase as well as the secretory phase.

There was no apparent difference in the extent of decrease in this protein between two phases of menstrual cycle. No correlation between the levels of estradiol or progesterone and that of IGFBP-1 was observed (Fig. 2).

DISCUSSION

Insulin-like growth factors have been associated with a family of binding proteins in serum, amniotic fluid and other body fluids, as well as in conditioned media from a variety of cell types.[7-9] The circulating IGFBPs are considered to regulate the endocrine effects of growth factors, and also to modulate the local actions of the IGFs in an autocrine and/or paracrine fashion. These binding proteins are unsaturated,[10] GH-independent,[11] and present diurnal variation.[12]

IGFBP-1 is secreted by the endometrium[13] and liver,[14] and it is also detected in human preovulatory follicular fluid, luteal cells of hyperstimulated preovulatory follicle, and corpora lutea.[15] Recently, IGFBP-1 mRNA has been detected in human luteinized granulosa cells.[16]

Estrogen is also presumed to modulate its synthesis in the liver, ovary[5] and endometrium.[17] Most serum IGFBP-1 is known to be derived from the liver, but part of it comes from the ovarian follicle and uterus.

Suikkari et al. have found out that there is a significant decrease in serum 34 kd IGFBP after hysterectomy, one week post-operatively, which them returned to the preoperative level at five weeks after hysterectomy, suggesting that the serum level of this protein did not follow the cyclic changes in levels of the major reproductive hormones.[6] This result seems to be in contrast with the reports that the synthesis of this protein takes place in secretory/decidulaized endometrium.[18-20] We chose endometrial ablation in favor of hysterectomy because we tried to focus on the contribution of entometrium excluding myometrium. We observed a considerable decrease in the circulating levels of this protein three days post-operatively. We can postulate that the endometrium is significantly related to maintaining serum IGFBP-1 levels.

Since the half-life of serum IGFBP-1 is approximately seven to eight minutes,[21] the post-operative three-day value was the expression of new products after the operation. The limit of our study is a lack of long-term results. Our patients started to take GnRH analogue or progesterone one week after the operation for the inhibition of endometrial growth. Hence, late post-operative changes of this protein may not have been observed.

In our study, two patients who did not respond to therapy showed minimal or no change in IGFBP-1 level after the operation. We believe, as a result of incomplete surgery, that the remaining endometrium could produce IGFBP-1 even after surgery. This finding could provide additional evidence of our hypothesis.

The discrepancy between in vivo and in vitro synthesis of IGFBP in the endometrium remains to be explained. Immunohistochemistry and in situ hybridization localized IGFBP-1 and its mRNA in the uterine luminal epithelium and the stromal glandular tissue in rats and in the epithelium of glands deep in the stroma of baboons.[17] In man, IGFBP-1 staining has also been reported in stromal cells.[17] An increase in the abundance of this binding protein has been

seen in the luteal phase of the menstrual cycle and in human decidual tissue.[17] The data available to date has indicated that, the synthesis of IGFBP-1 seems to be confined to the endometrium. Since there has been no report that the myometrium produces IGFBP-1, one can postulate there is no difference between endometrial ablation and hysterectomy regarding the production of this protein.

The endometrial production of IGFBP-1 has been thought to be minimal compared to production in the liver. From this study, we can conclude that endometrium produces a considerable amount of IGFBP-1 and significantly affects its circulation level regardless of menstrual cycle.

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