Human endometrial proteins (1)
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Summary. Human endometrium synthesizes a number of proteins. Two of the major proteins are the low molecular weight insulin-like growth factor-binding protein (IGF-bp25) and endometrial protein PP14 (placental protein 14). Both proteins have been cloned from human decidual cDNA library and their complete amino acid sequences have been deduced. IGF-bp25 is found in various tissues and body fluids including secretory and decidualized endometrium, amniotic fluid, liver, follicular fluid and luteinized granulosa cells of preovulatory ovarian follicles. Clinical studies have shown that there is no systematic variation in the circulating levels during normal menstrual cycle, whereas in hyperstimulated cycles the levels are higher when there are many preovulatory follicles and immediately after follicle aspiration for in vitro fertilization (IVF). Some women with polycystic ovarian disease have a subnormal level of IGF-bp25 in serum. The other protein, PP14, is synthesized by secretory and decidualized endometrium, and it is also abundant in amniotic fluid. PP14 is mainly released by secretory endometrial glands during the last week of ovulatory cycles. There is a consistent variation in serum PP14 levels during normal menstrual cycle. The levels are lowest at the time of ovulation and rise steeply during the last week of luteal phase and peak at the onset of menstruation. Administration of micronized oral progesterone to normally ovulating infertile women brings about elevation in their serum PP14 levels during late luteal phase. In postmenopausal women cyclical estrogen-progesterone replacement causes elevation of serum PP14 level, but this does not take place in hysterectomized postmenopausal women. During ovarian hyperstimulation for IVF the circulating PP14 levels show a similar type of variation as in normal ovulatory cycles. Nadir is seen at the time of follicle aspiration. The higher the estrogen level is in the follicular phase, the higher is the subsequent serum PP14 level in late luteal phase indicating that estrogen priming is important for the subsequent protein secretion by the endometrium. It may become possible in future to assess endometrial function by a blood test based on the circulating PP14 concentration.

Proteins of the human endometrium.

A variety of proteins have been isolated from the human endometrium (Table 1). This paper will review our studies on two of them, namely the small molecular weight insulin-like growth factor-binding protein (IGF-bp25), previously

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known as PP12 (placental protein 12), and endometrial protein PP14 (placental protein 14). Both are abundant in secretory/decidulized endometrium in which their synthesis has been demonstrated (Rutanen et al., 1986; Julkunen et al., 1986a).

### TABLE 1

*Human endometrial proteins* (after Seppälä et al., 1987a).

<table>
<thead>
<tr>
<th>Name</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>17β-hydroxysteroid dehydrogenase</td>
<td>Tseng and Gurpide, 1979</td>
</tr>
<tr>
<td>Placental protein 12*</td>
<td>Rutanen et al., 1986</td>
</tr>
<tr>
<td>Endometrial protein 14*</td>
<td>Bell, 1986</td>
</tr>
<tr>
<td>Alpha-1 pregnancy-associated endometrial globulin*</td>
<td>Bell, 1986</td>
</tr>
<tr>
<td>Insulin-like growth factor-binding protein*</td>
<td>Koistinen et al., 1986</td>
</tr>
<tr>
<td>Placental protein 14**</td>
<td>Julkunen et al., 1986</td>
</tr>
<tr>
<td>Progestogen-dependent endometrial protein**</td>
<td>Joshi et al., 1980</td>
</tr>
<tr>
<td>Endometrial protein 15**</td>
<td>Bell, 1986</td>
</tr>
<tr>
<td>Alpha-2 pregnancy-associated endometrial globulin**</td>
<td>Bell, 1986</td>
</tr>
<tr>
<td>Pregnancy-associated plasma protein-A</td>
<td>Sjöberg et al., 1984</td>
</tr>
<tr>
<td>Placental protein 5</td>
<td>Bützow et al., 1986</td>
</tr>
<tr>
<td>Endometrial proteins 1-17</td>
<td>Bell, 1986</td>
</tr>
</tbody>
</table>

* the names are likely to be synonyms;
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### Insulin-like growth factor-binding protein.

Insulin-like growth factors IGF-I and IGF-II are bound to specific binding proteins in serum. The major IGF-bp in blood has a molecular weight of about 150 kD (Baxter et al., 1986) and it is growth hormone-dependent. The smaller IGF-bp has a molecular weight of 25.3 kD as deduced from its complete cDNA sequence (Julkunen et al., 1988a). IGF-bp25 is not growth hormone dependent, and its levels in serum are inversely correlated to those of serum insulin (Suikkari et al., 1988a). Tissues in which synthesis of IGF-bp25 takes place include secretory endometrium (Rutanen et al., 1986) and the liver (Julkunen et al., 1988a). Preovulatory follicles contain high concentration of IGF-bp25 and, within the follicle, the protein is localized to luteinized granulosa cells (Seppälä et al., 1984), which may actually synthesize this protein.
Clinical conditions in which the circulating IGF-bp25 levels are elevated include pregnancy and trophoblastic disease (Rutanen et al., 1982), primary liver cancer (Rutanen et al., 1984), ovarian cancer (Iino et al., 1986a) and diabetes (Suikkari et al., 1988a). Subnormal levels have been observed in patients with insulinoma (Suikkari et al., 1988a) and polycystic ovarian disease (Suikkari et al., 1988b). During normal menstrual cycle the circulating IGF-bp25 levels show no systematic variation (Suikkari et al., 1987), whereas during ovarian hyperstimulation for IVF the levels rise as the follicles grow, and decline after follicle aspiration (Seppälä et al., 1988a). It is obvious that this elevation cannot derive from secretory endometrium, whereas multiple ovarian follicles are a more likely source. On the other hand, during pregnancy the high IGF-bp25 levels in amniotic fluid and serum probably derive from decidualized endometrium (Rutanen et al., 1985). In preeclampsia the levels are higher than in normal pregnancy indicating increased decidual secretion (Iino et al., 1986b).

Endometrial protein PP14.

PP14 is synthesized by secretory and decidualized endometrium as evidenced by experiments on incorporation of labeled methionine to immunoreactive PP14 by endometrial explants in tissue culture (Julkunen et al., 1986b), and by the detection of PP14 mRNA in the endometrium (Julkunen et al., 1988b). In SDS gel electrophoresis the molecular weight of PP14 is 28 kD, and the protein contains 17% carbohydrate (Bohn et al., 1982). There is amino acid sequence homology between PP14 and ß-lactoglobulins of various species (Huhtala et al., 1987; Julkunen et al., 1988b) and between PP14 and a family of retinol-binding proteins (Seppälä et al., 1988b).

PP14 may be used as a marker for endometrial differentiation, as it is synthesized by well differentiated secretory glands, not so much by the stroma. The serum PP14 concentration has the potential to become a marker of endometrial function. PP14 appears to be progesterone-regulated (Julkunen et al., 1986b,c). Evidence that a considerable proportion of circulating PP14 is uterus-derived comes from our studies in which PP14 mRNA was found in the secretory endometrium but not in other tissues (Julkunen et al., 1988b), and the presence or absence of the uterus was found to be critical for the serum PP14 levels to become elevated in response to estrogen-progestogen replacement in postmenopausal women (Seppälä et al., 1988b). We have observed that, after a similar priming with estradiol valerate, the levels during estrogen plus a conventional dose (0.25 mg) of levonorgestrel are higher than those during the same estrogen plus 10 mg medroxyprogesterone acetate (Seppälä et al., 1988b). Also the mode of drug delivery appears to be important. Sustained administration of danazol on patients with endometriosis suppresses rather than elevates the serum PP14 levels (Than et al., 1987). These results indicate that the measurement of endometrial secretory products in blood may tell about endometrial responses to exogenous hormones. Cyclically elevated progestogen levels appear to be critical for subsequent elevation of serum PP14 levels in late luteal phase. During the last week of luteal phase the serum PP14 concentration doubles in
every three days (Julkunen et al., 1986a; Seppälä et al., 1988a). No similar elevation is seen in anovulatory cycles. Infertile ovulatory women given micronized oral progesterone have higher luteal phase PP14 levels than the same women taking placebo indicating that it is possible to increase the endometrial secretory activity by exogenous progesterone (Seppälä et al., 1987b). Whether this has bearing to subsequent implantation is an obvious question that remains to be answered. Endometrial secretory activity is also influenced by the magnitude of estrogen priming in the follicular phase, irrespective of the subsequent luteal phase progesterone levels. This was evidenced by our finding (to be published) of a positive correlation between follicular phase estradiol and luteal phase PP14 levels.

During pregnancy the circulating PP14 levels show a similar pattern as those of chorionic gonadotropin (hCG). Very high PP14 levels have been found in amniotic fluid, whereas the hCG level is low (Julkunen et al., 1985). It has been suggested that PP14 has an immunosuppressive effect in human reproduction (Bolton et al., 1987).

These and the various other ongoing clinical studies indicate that we are learning about new biochemical ways to assess endometrial responses to endocrine stimuli.


Des études cliniques il ressort qu’il n’y a pas de variations systématiques dans les niveaux circulants pendant le cycle menstruel normal, tandis qu’après stimulation folliculaire les niveaux sont plus élevés quand il y a beaucoup de follicules préovulatoires et même après aspiration des follicules en vue de pratiquer la FIV. Quelques femmes souffrant d’ovaires polykystiques ont des niveaux sérigraphes subnormaux de IGF-bp25. L’autre protéine PP14 est synthétisée par l’endomètre sécrétoire ou décidéalisé et est également présente en abondance dans le liquide amniotique. La PP14 est principalement libérée par les glandes endométriales en phase sécrétoire pendant la dernière semaine des cycles ovulatoires. Il existe une variation nette des niveaux sérigraphes de PP14 pendant le cycle menstruel ; les niveaux sont les plus bas au moment de l’ovulation et s’élèvent fortement pendant la dernière semaine du cycle, le pic se situant au moment de la menstruation. L’administration orale de progestérone micronisée à des femmes stériles bien qu’ovulantes, augmente leur taux sérique en fin de phase lutéale. Chez la femme postménopausée une thérapie œstro-progestative de substitution provoque une élévation de la PP14 sèrique, mais cette élévation n’a pas lieu si la femme est hystérectomisée. Pendant l’hyperstimulation ovarienne en cas de FIV, la PP14 sérique varie comme au cours d’un cycle normal. Le minimum est observé au moment de l’aspiration des follicules. Plus est élevé le niveau d’estradiol pendant la phase folliculaire, plus le niveau de PP14 est élevé en fin de phase lutéale ; ceci montre l’importance de l’action protéique ultérieure de l’endomètre. Il semble possible dans le futur d’estimer le fonctionnement de l’endomètre par la connaissance du niveau sérique de la PP14.
References


