Placental protein 14 (PP14) is the major glycoprotein synthesized by late secretory endometrium and gestational decidua. The control mechanisms of PP14 production are uncertain but might include progesterone or an ovarian factor. It has been suggested that PP14 might be produced by the ovary itself. The aim of the present study was to evaluate if the ovary is a major source of PP14. We measured PP14 and also insulin-like growth factor binding protein-1 (IGFBP-1), another protein produced in large amounts by the secretory endometrium though not specific to that tissue. The samples included sera from the ovarian vein in one subject, sera of three women affected with Rokitansky syndrome (absent uterus) and follicular fluid samples collected during oocyte recovery in 46 in-vitro fertilization patients. PP14 was undetectable in the sample collected from the ovarian vein at the mid-luteal phase and was absent or at very low concentrations in most of the follicular fluid samples. Furthermore, the predominantly uterine origin was confirmed by the inability to detect any PP14 in sera throughout the menstrual cycle from patients with congenital absence of the uterus (Rokitansky syndrome). In conclusion this study shows that the ovary is not a major source of PP14. 

Key words: glycodelin/placental protein 14

Introduction

Many proteins originally isolated from the human placenta have also been found in different tissues of non-pregnant women and in follicular fluid (Seppala et al., 1984a, b). Placental protein 14 (PP14) is the major glycoprotein synthesized by late secretory endometrium and gestational decidua (Julkunen et al., 1990). The exact biological significance of PP14 is uncertain, but measurement of PP14 in serum has been proposed as a test of endometrial function (Stabile et al., 1994). The control mechanisms of PP14 production are also uncertain, but might include progesterone (Joshi et al., 1980; Seppala et al., 1987) or an ovarian factor. It has been suggested that PP14 might be produced by the ovary itself. PP14 has been found in serous ovarian cyst fluids (Ritinnen, 1992). In addition, no rise in PP14 concentrations has been observed in pregnancies in which the maternal ovaries are absent or inactive, e.g. Turner’s syndrome (Critchley et al., 1990; Li et al., 1992), or premature ovarian failure (Critchley et al., 1992). In in-vitro fertilization (IVF) pregnancies there is a rise in PP14 following implantation only if the ovaries have not previously been down-regulated (Arthur et al., 1995), though some authors have reported that PP14 secretion is not compromised by pituitary down-regulation in infertile women with functional ovaries (Miettinen et al., 1994). Finally, there is no rise in serum PP14 concentrations during the menstrual period in anovulatory women, including those receiving oral contraceptive agents (Wood et al., 1989).

The aim of the present study was to evaluate further the possible origin of PP14 from the ovary. We measured PP14 and also insulin-like growth factor binding protein-1 (IGFBP-1), another protein produced in large amounts by the secretory endometrium though not specific to that tissue (Julkunen et al., 1990). The samples included sera from the ovarian vein in one subject, sera of three women affected with Rokitansky syndrome (absent uterus) and follicular fluid samples collected during oocyte recovery in 46 patients undergoing IVF treatment.

Materials and methods

Three groups of patients were studied: (i) one woman undergoing hysterectomy for benign disease in the mid-luteal phase of the cycle, on day +8 post-ovulation (ovulation had been detected earlier by ultrasound). Samples were collected from a peripheral vein and the ovarian vein of the ovary containing the corpus luteum; serum was stored at –20°C; (ii) 46 women undergoing IVF cycles at the Reproductive Unit of the Department of Gynecology and Obstetrics, Florence University. Their ages ranged from 27–35 years (mean 32.6), and day 3 follicle-stimulating hormone (FSH) values were <10 mlU/ml. Ovarian stimulation was performed by individually adjusted hFSH (Metrodin®, 75 IU/ampoule; Serono, Rome, Italy; 3–6 ampoules daily). Thirty patients were pre-treated with the long acting gonadotrophin-releasing hormone (GnRH) analogue triptorelin (Decapeptyl® 3.75 Depot; IPSEN Biotech, Milan, Italy) administered in the mid-luteal phase of the previous cycle (group 2A). In the other 16 patients ovarian stimulation was performed only with hFSH (group 2B). All cycles were monitored by measurement of 17 β-estradiol and ultrasound; human chorionic gonadotrophin (HCG; Profasi HP®, Serono; 10 000 IU) was administered when there were at least two follicles >16 mm in diameter. During oocyte recovery, performed 36 h later, follicular fluids were collected and stored at –20°C; (iii) three women, aged 19, 24 and 26 years, affected by the Rokitansky syndrome. The Rokitansky syndrome usually presents with primary amenorrhoea and is due to agenesis of the Mullerian ducts; thus the patients do not have a uterus or Fallopian tubes and the vagina...
appears as a blind sac. The karyotype is usually normal. In our three patients the habitus was normal female, the karyotype was 46XX, circulating steroid patterns were normal, ultrasound showed ovaries but no uterus and repeated basal body temperature charts showed normal ovulatory cycles. During the study cycle ovulation was monitored by serial ultrasound; blood samples were collected in the preovulatory phase (2–4 days before ovulation) and every 3–4 days for 2 weeks in the post-ovulatory period (on day +4, +7, +11 and +14). Progesterone values >7 ng/ml were considered to confirm ovulation suggested by ultrasound. Serum samples were stored at −20°C.

In all cases women gave appropriate informed consent for these studies.

PP14 was measured by radioimmunoassay as described by Howell et al. (1989) and Chard and Olajide (1994); IGFBP-1 was determined as described by Wang et al. (1991).

Results
In the patient undergoing hysterectomy, PP14 was undetectable (<2 µg/l) in both ovarian and peripheral vein samples. The IGFBP-1 values were 18 and 19 µg/l. In 30 women undergoing oocyte recovery after pituitary down-regulation, PP14 was undetectable (<1 µg/l) in follicular fluid in 19 subjects and was present in small amounts (10–16 µg/l) in the remaining 11 subjects. In the 16 women without down-regulation, PP14 was undetectable in 13 subjects and present in small amounts (15–16 µg/l) in the remaining three subjects. Concentrations of IGFBP-1 in follicular fluid ranged from 63–1000 µg/l; there was no difference between women with and without down-regulation. In the three subjects with Rokitansky syndrome, serum PP14 was undetectable and IGFBP-1 values were within the normal range but without cyclic variations.

Discussion
Our data demonstrate that a direct origin of PP14 from the ovary is highly unlikely. Specifically, PP14 was undetectable in a sample collected from an ovarian vein at the mid-luteal phase and was absent or at very low concentrations in most of the follicular fluid samples. Furthermore, the predominantly uterine origin was confirmed by the inability to detect any PP14 in sera throughout the menstrual cycle from patients with congenital absence of the uterus (Rokitansky syndrome). Our data concerning follicular fluid samples agree with those of Andersen (1993) who examined 128 follicular fluids collected at oocyte retrieval and found mean values of PP14 to be 74% of serum concentrations. On the contrary, our data contrast with those of Chryssikopoulos et al. (1996) who examined 35 samples collected at oocyte retrieval. Mean PP14 concentrations were 55.9 ± 5.4, 25.4 ± 6.4 and 27.7 ± 7.6 µg/l respectively for pregnant women, for patients with oocyte fertilization but without clinical pregnancy and for patients without oocyte fertilization. We have no explanation for this discrepancy.

The present findings virtually exclude the possibility of an ovarian origin of PP14. Nevertheless, the apparent clear relationship between serum values of PP14 and the presence of a functioning ovary (Critchley et al., 1990, 1992; Li et al., 1992) implies some sort of mechanism linking the ovary and the endometrium. At one time it was believed that progesterone might be an important factor, based on observations that PP14 concentrations during the menstrual phase are higher in women with higher progesterone concentrations (Seppala et al., 1994). However, there are a number of pieces of contradictory evidence: (i) progesterone does not stimulate PP14 production by decidual tissue in vitro (Ren and Braunstein, 1990); (ii) there is a substantial gap (6 days) between the luteal rise in progesterone and the rise in PP14; (iii) there is no fall in PP14 concentrations following administration of the progesterone receptor antagonist, mifepristone (Howell et al., 1989); (iv) there is a rapid fall in PP14 concentrations after 10 weeks of pregnancy, when progesterone concentrations continue to rise; and (v) PP14 concentrations are subnormal throughout pregnancy in mothers with Turner’s syndrome (Critchley et al., 1990), or whose ovaries have been down-regulated (Anthony et al., 1991; Johnson et al., 1993a, b) even though endogenous progesterone concentrations show a normal increase.

Though progesterone itself does not seem to be involved, it is still attractive to speculate that PP14 could be under the control of a factor from the ovary. Serum oestradiol concentrations on day 9 of the cycle are correlated with the subsequent serum PP14 concentration on days 21–23 (Seppala et al., 1989). This emphasizes the importance of priming in the follicular phase to the subsequent maturation and secretory capacity of the endometrium in the luteal phase. Another possible factor is relaxin, though there is evidence both for (Stewart et al., 1997) and against (Critchley et al., 1994) control of PP14 concentrations by the administration of relaxin. Waites and Bell (1989) also suggested that PP14 secretion might be regulated by local factors from the endometrial stroma.

In conclusion, this study shows that the ovary is not a major source of PP14.

References
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