Human Reproduction vol.8 no.11 pp.1928–1932, 1993

Function of the corpus luteum, the endometrium and the trophoblast after treatment of tubal pregnancy by prostaglandin $F_{2\alpha}$

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The activity of the corpus luteum, the endometrium and the trophoblast was studied after local medical treatment of 31 women with tubal pregnancy. We measured the serum concentration of progesterone, the secretory endometrial protein placental protein 14 (PP14), and human chorionic gonadotrophin (HCG) before and after treatment by injection of prostaglandin $F_{2\alpha}$ into the site of the gestation and into the corpus luteum. There was no significant difference in the pre-treatment serum progesterone and serum PP14 concentrations of 26 women who were treated successfully and of five women, who were operated on after failure of the treatment. After the prostaglandin treatment the serum progesterone and PP14 concentrations decreased simultaneously with the serum HCG concentration or remained at a low, constant concentration. We conclude that measurement of serum progesterone and PP14 cannot be used for selection of patients for treatment by prostaglandin $F_{2\alpha}$ or for monitoring the effect of the treatment. The injection of prostaglandin into the ovary has either no effect on the activity of the corpus luteum or induces only a partial luteolysis.

Key words: ectopic pregnancy/human chorionic gonadotrophin/progesterone/prostaglandin

Introduction

The serum progesterone concentration in ectopic pregnancy is usually below that in normal pregnancy (Stovall *et al.*, 1989; Ruge *et al.*, 1992). Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) acts as a luteolytic agent (Hahlin *et al.*, 1987). It has, however, not been clarified to what extent the treatment of ectopic pregnancy by injection of $PGF_{2\alpha}$ into the corpus luteum results in a reduction of progesterone secretion. Another open question is whether the success of prostaglandin treatment can be predicted from the progesterone concentrations before or the change in progesterone concentration after treatment.

The secretory endometrial protein placental protein 14 (PP14) is synthesized in the endometrium during the luteal phase. Although it is the most abundant protein produced in the endometrium, its biological function is obscure. Its concentration may be regulated by the corpus luteum. Women without a functioning ovary have a low serum PP14 concentration, which is normalized by hormonal replacement therapy. If they become pregnant after in-vitro fertilization (IVF), however, they continue to have a low non-pregnant concentration of PP14 in spite of hormonal substitution. In ectopic gestation the serum concentration of PP14 is lower than in normal pregnancy, but higher than during the mid-luteal phase in non-pregnant women (Ruge *et al.*, 1992). It is not known if there is a relationship between the serum PP14 concentration and the outcome of prostaglandin treatment of ectopic pregnancy.

We have studied the serum concentration of progesterone, PP14 and human chorionic gonadotrophin (HCG) in 31 women treated for tubal pregnancy by laparoscopically guided injection of $PGF_{2\alpha}$ into the site of gestation and into the corpus luteum. The concentrations before treatment and the response to the procedure are related to the outcome.

Materials and methods

Patients (n = 31) were treated by local injection of $PGF_{2\alpha}$ as previously described (Vejtorp *et al.*, 1989). The patient characteristics are shown in Table I.

During laparoscopy the tube was grasped by an atraumatic forceps and 0.75–1.5 mg $PGF_{2\alpha}$ in 3–6 ml isotonic saline was injected into the oviduct at the site of the conceptus. A similar dose was injected subcapsularly into the ovary which contained the corpus luteum. The injection was stopped if the swelling of the oviduct became pronounced or if fluid leaked back through the puncture channel in the ovary.

After the first 17 patients, the treatment was only used if the HCG concentration was <2000 IU/l, as the failure rate was unsatisfactorily high at concentrations higher than this.

The serum concentrations of HCG, progesterone and PP14 were generally measured three times in the first week after treat-

Table I. Characteristics of 31 patients treated by local injection of prostaglandin $F_{2\alpha}$ for tubal pregnancy

Age (years; median and range)	29 (20–40)
Previous ectopic pregnancy (no.)	4
Gestational age (weeks; median and range)	7 (4–10)
Diameter of oviduct at the implantation site (cm; median and range)	1.5 (0.5–2.5)
Localization of pregnancy (no.)	
Cornual	1
Isthmic	7
Ampullary	23

ment, twice in the next week and then weekly until the concentration of HCG was <20 IU/l. If the HCG concentration remained at the initial level or increased, the treatment was considered a failure and the patient was taken for surgery.

HCG was measured by an immunoenzymometric assay having a detection limit of 1 IU/l (IRP 75/537), and an interassay coefficient of variation on 5.2% (x = 306 IU/l). Progesterone concentration in serum was determined by a radioimmunoassay (Farmos Diagnostica, Finland). The detection limit was 0.5 nmol/l and interassay coefficient of variation was 4.2% (x = 41 nmol/l, n = 15). The radioimmunoassay for PP14 determination has been described in detail elsewhere (Ruge *et al.*, 1992).

Results

Serum concentrations of progesterone, PP14 and HCG before treatment

Progesterone and HCG

At the time of treatment the median progesterone concentration was 15.9 nmol/l (range 3.4–100) in 26 women who were successfully treated by prostaglandin and 35.8 nmol/l (range 6.5–54, NS, Mann–Whitney test) in five women, who were operated on after lack of effect of the treatment. The individual serum concentrations of progesterone and HCG according to the effect of the treatment are shown in Figure 1.

Two of 18 (11%) women who had a progesterone concentration <25 nmol/l needed operative treatment after failed prostaglandin treatment, compared to three of 13 (23%, NS), who had a progesterone concentration of ≥25 nmol/l (Figure 1). At a progesterone concentration <50 nmol/l, four of 26 (15%) women were operated on, compared to one of five (20%, NS) who had concentrations ≥50 nmol/l.

The concentration of progesterone at the time of treatment correlated significantly with the concentration of HCG measured simultaneously (Figure 1, P = 0.012, Spearman's rank correlation test).

The HCG concentration before treatment was increasing in 14 of the 31 women. In this group the median of the last progesterone concentration before treatment was 13.8 nmol/l (range 5.4–64) compared to 12.3 nmol/l (3.1–61.8, NS) in four women who had decreasing HCG concentrations. The HCG was 27.3 nmol/l (4.1–100) in 13 women, who had only one measurement of HCG before treatment.

PP14

The median PP14 concentration in 26 women who were treated successfully was 0.15 mg/l (range 0.07–0.62), which was similar to the median concentration of 0.17 mg/l (range 0.07–0.28) in the five women who were operated on after failure of the $PGF_{2\alpha}$ injection.

Serum concentrations of progesterone, PP14 and HCG after treatment

Concentrations after successful prostaglandin treatment

Of the 26 women who were treated without operation, 14 (54%) had a progesterone concentration before treatment of >10 nmol/l. In these women the median serum concentrations of PP14 and HCG decreased in a nearly parallel course after the treatment (Figure 2). In 12 women the last pre-treatment progesterone concentration was <10 nmol/l. The progesterone concentration in these women did not change significantly after

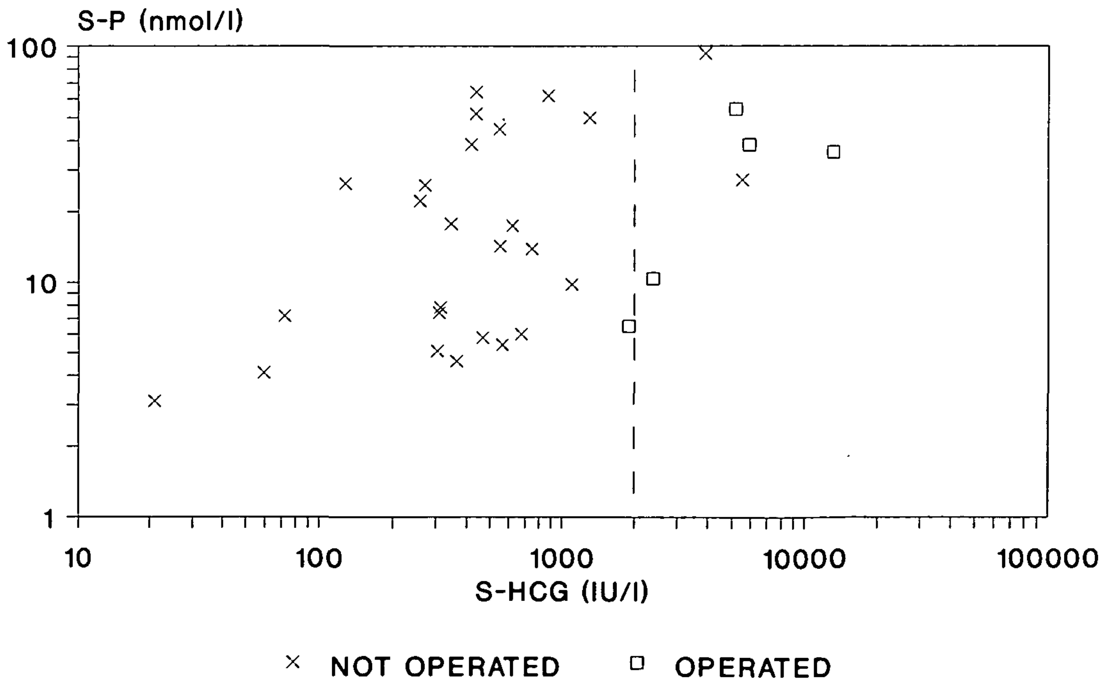

Fig. 1. Serum concentrations of progesterone (S-P) and human chorionic gonadotrophin (S-HCG) before local treatment by prostaglandin $F_{2\alpha}$ of ectopic pregnancy in women who were either treated successfully or were operated on after failure of the treatment.

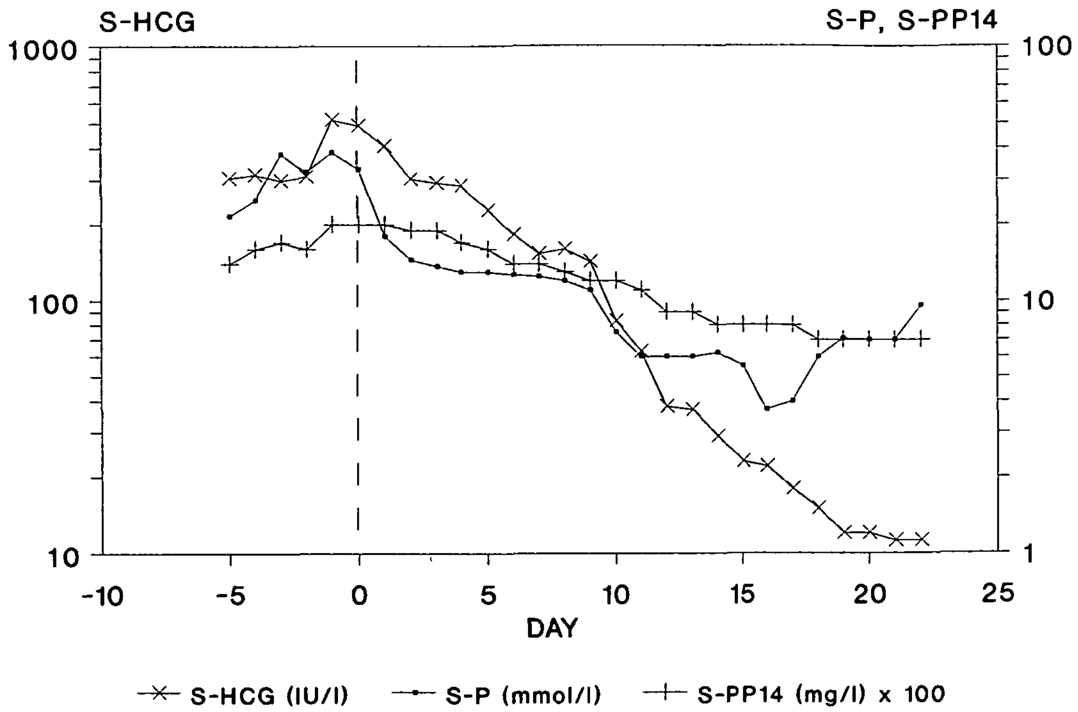

Fig. 2. Median serum concentrations of human chorionic gonadotrophin (S-HCG), progesterone (S-P) and placental protein 14 (S-PP14) after local treatment by prostaglandin $F_{2\alpha}$ of ectopic pregnancy at day 0 in 14 women, who had a S-P concentration >10 nmol/l at the time of treatment.

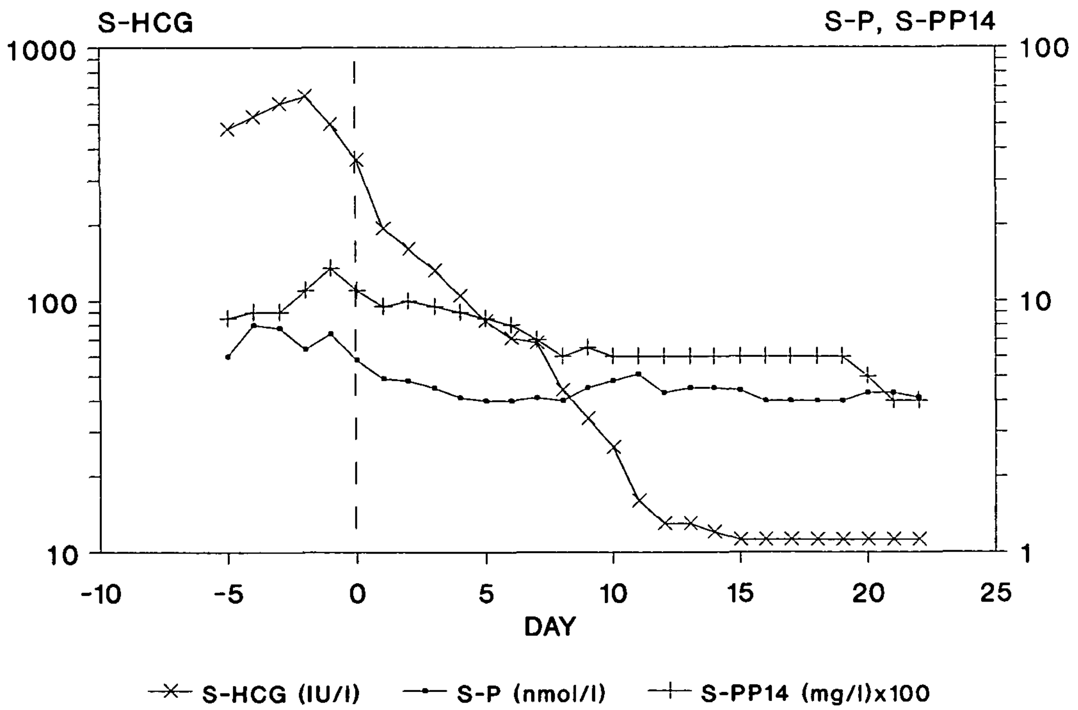

Fig. 3. Median serum concentrations of human chorionic gonadotrophin (S-HCG), progesterone (S-P) and placental protein 14 (S-PP14) in 12 women, who had a S-P concentration <10 mol/l at the time of treatment.

the treatment (Figure 3). The PP14 concentration showed a small but statistically significant decrease from the pretreatment concentration to the last measured concentration ($P < 0.01$, Wilcoxon matched pairs test).

Concentrations after failed prostaglandin treatment

One out of five women who were operated on after failed prostaglandin treatment had a low, constant progesterone concentration of approximately 7 nmol/l during five days in spite

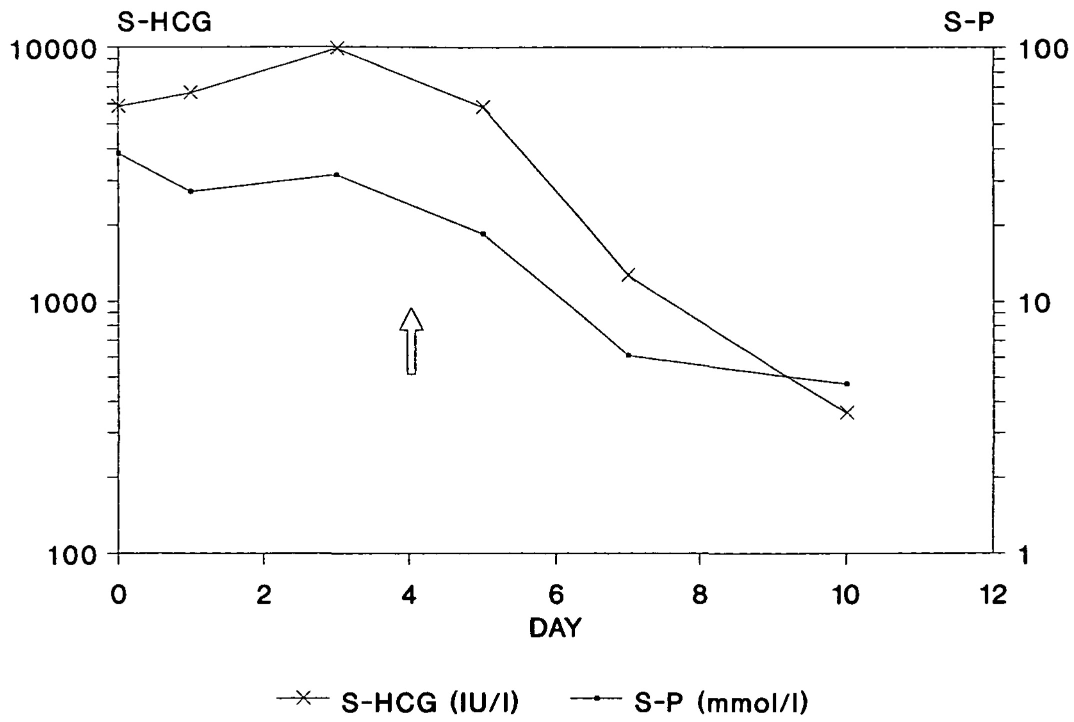

Fig. 4. Serial determinations of serum concentration of human chorionic gonadotrophin (S-HCG) and progesterone (S-P) in a woman, who was operated at day 4 after failure of treatment by prostaglandin $F_{2\alpha}$. Arrow indicates day of operation.

of an HCG concentration of 1900 IU/l and an initial rupture of the tube. Two women had decreasing and two increasing progesterone concentrations before the operation. The PP14 concentration after the $PGF_{2\alpha}$ injection but before operation for treatment failure was decreasing in two and persisted at a constant level in three women.

In one woman, who was treated by tubal resection, the measurements of progesterone and HCG 6 days after the operation showed a simultaneous decrease in the concentrations of the two hormones (Figure 4).

Late increase of progesterone concentration

Measurement of the progesterone concentration continued for at least 20 days after treatment in 15 women and for 30–53 days in seven women. A late increase in the progesterone levels to 25–37 nmol/l was observed in four women on days 20–30 and in two women on days 32 and 53. The concentration of HCG at the time of the increase was <10 IU/l in four women, whereas two had concentrations of 12 and 144 IU/l, respectively.

Discussion

This study concerns the effect of $PGF_{2\alpha}$ on the serum concentration of progesterone produced in the ovary or in the trophoblast, PP14 produced by the endometrium and perhaps also by the tubal endothelium and HCG produced by the trophoblastic tissue. We measured the serum concentrations before and after treatment of tubal pregnancy by injection of $PGF_{2\alpha}$ into the site of the gestation and into the corpus luteum.

The HCG concentration before the treatment of ectopic pregnancy by $PGF_{2\alpha}$ is a good predictor for the effect of the procedure (Vejtorp *et al.*, 1991). At concentrations >2000 IU/l the success rate is severely reduced. In contrast we found no significant difference between the progesterone concentration before treatment in women whose ectopic pregnancy was interrupted by $PGF_{2\alpha}$ and those who had a tubal pregnancy which continued in spite of the $PGF_{2\alpha}$ injection (Figure 1).

The progesterone concentration before treatment was lower than during normal intra-uterine pregnancy. Thus, in 84% of the women the serum concentration was <50 nmol/l, i.e. lower than the 10th percentile of the concentration in normal early pregnancy (Ruge *et al.*, 1992). Furthermore, it was demonstrated that the progesterone concentration was correlated with the HCG concentration.

In early intra-uterine pregnancy the ovary is the predominant site of progesterone synthesis. There is no correlation between the concentrations of progesterone and HCG, whereas the rate of increase of HCG concentration correlates with that of progesterone concentration (Kratzer and Taylor, 1990). Thus, the rate of increase of the concentration of HCG, but not the concentration itself directs the activity of corpus luteum.

In ectopic pregnancy, the unfavourable site of implantation limits the growth of the trophoblast and the increase of HCG concentration. The slow increase of HCG may result in insufficiency of the corpus luteum. That progesterone secretion in ectopic pregnancy nevertheless originates from the ovary is in accordance with the gradual decrease of progesterone concentration, which we found after complete removal of a tubal pregnancy (Figure 4).

The aim of injecting $PGF_{2\alpha}$ into the ovary is to obtain luteolysis. After luteoectomy before the 9th week of gestation the progesterone concentration decreases within one day to less than the half of the initial concentration. This is followed by an increase in intrauterine pressure and abortion (Csapo *et al.*, 1972). If luteoectomized patients are treated with progesterone, the pregnancy continues (Csapo *et al.*, 1973).

In non-pregnant women an injection of $PGF_{2\alpha}$ locally into the corpus luteum causes a decrease of >30% in progesterone concentration, which can be demonstrated within 0.5 h after the injection (Bennegård *et al.*, 1991).

In ectopic pregnancy, tissue slices from the corpus luteum have been studied as an in-vitro model. The addition of $PGF_{2\alpha}$ to the medium decreased the production of progesterone which had been stimulated by HCG to 80% of the initial level. This effect was obtained at an HCG concentration of 10^5 IU/l in the medium, i.e. at a concentration which is relatively high compared to the plasma concentration in ectopic pregnancy (Hahlin *et al.*, 1987).

In this study we found a slow decrease of the progesterone concentration or a low constant level after injection of $PGF_{2\alpha}$ into the corpus luteum and into the implantation site of ectopic gestations (Figures 2 and 3).

The half-life of HCG in serum after delivery increases from ~9 to 37 h during the first 3 days after childbirth (Midgley and Jaffe, 1968) and is in the same order of magnitude following surgical management of tubal pregnancy (Holtz, 1983). After removal of the corpus luteum and the feto-placental unit, the half-life of progesterone in serum increases from 6 min in studies initiated in the first 5 min period to 95 min after that time (Fylling, 1970). As a consequence of the large difference in the half-life of progesterone and HCG after a complete cessation of production, it seems probable that a prostaglandin-induced luteolysis would be detectable by an early decrease of the progesterone concentration. It is therefore questionable whether the prostaglandin injection in the ovary in this study has any effect on the treatment result.

Resumption of ovulation within 30 days after treatment was shown in four of seven women by an increase of the progesterone concentration. Similarly, it was demonstrated that 72% of patients recommence ovulation within 30 days after surgical treatment of an ectopic gestation (Spirtos *et al.*, 1987).

The pretreatment level of S-PP14 correlates significantly to the progesterone concentration in women who have an ectopic gestation (Ruge *et al.*, 1992). The association may be an expression of the effect of progesterone on the endometrium, which is the main site of the synthesis of PP14. In normal intrauterine pregnancy, PP14 concentration is independent of progesterone concentration. This is possibly due to a local stimulating factor from the gestation on the secretion of PP14.

The PP14 concentration was not predictive for the result of local prostaglandin treatment of ectopic gestation. This agrees with the lack of predictive value of the progesterone concentration for the outcome and the correlation between the progesterone and PP14 concentrations found in the study by Ruge *et al.* (1992) and confirmed in our own study (unpublished data). After treatment, the measurement of PP14 did not contribute to the evaluation of the effect of $PGF_{2\alpha}$.

It is apparent from this study that the measurement of serum progesterone concentration before treatment of ectopic pregnancy by local injection of $PGF_{2\alpha}$ cannot be used for selection of patients to this treatment. The function of corpus luteum is already reduced before treatment, probably owing to a previously diminished rate of increase of HCG, and the injection of $PGF_{2\alpha}$ does not induce a dramatic decrease of the concentration. As a consequence, the injection of prostaglandin in the ovary, may be avoided and an improved effect can possibly be obtained by injection of the total dose of $PGF_{2\alpha}$ into the site of the gestation. A definite answer to this problem, however, can only be obtained by a randomized study. The measurement of the PP14 serum concentration, which may contribute to the diagnosis of ectopic pregnancy, cannot be used as a guideline for selection of patients or for monitoring the effect of the prostaglandin treatment.

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Received on November 30, 1992; accepted on July 20, 1993