INHIBITION OF LACTATION BY PROSTAGLANDIN E_2

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SUMMARY

Prostaglandin E_2 was given orally to twenty puerperal women during the fourth and the fifth day after delivery. The milk secretion disappeared in all cases within 48 hours from the beginning of treatment and the prolactin plasma levels showed a significant decrease ($P<0.001$) already during the Prostaglandin E_2 administration.

The results can be explained by a Prostaglandin E_2 and prolactin decrease inhibitory effect on breast metabolism.

INTRODUCTION

The inhibiting action of Prostaglandins on milk secretion during puerperium, is a relatively recent finding: this particular property of Prostaglandin $F_{2\alpha}$ ($PgF_{2\alpha}$) was observed for the first time by Batta *et al.* ([1]) in the nursing rats and by Fioretti *et al.* ([2]) in the puerperae.

The mechanism of action is not yet clear: Batta *et al.* have ascribed the inhibition of milk secretion to the great production of oxitocin, induced by the $PgF_{2\alpha}$, with consequent constriction of the galactophora ducts. On the other hand, Fioretti *et al.* have explained the effects as due to a simultaneous decrease in prolactin plasma levels and to a modification in mammary metabolism. This substance resulted to be rapid and efficacious but with some limits: as a matter of fact, in a certain number of patients, $PgF_{2\alpha}$, administered intravenously, caused some side-effects (nausea, vomiting, diarrhoea), which were a limiting step to its unconditioned use.

On the ground of this results, PgE_2 was given orally to not nursing women, studying the effects on milk secretion, on prolactin plasma levels and mostly the rapidity of action.

In particular, we have studied its clinical use on the basis of the side effects observed and, of the eventual modifications in the control blood tests.

MATERIAL AND METHODS

A group of 20 puerperae, having a milk secretion in act, with different parity (from 0 to 4), aged between 19 and 28 years old, not disposed to nursing for medical or personal reasons, were treated with 8 mg of PgE_2 (divided in four doses of 2 mg each) during the fourth day after delivery and with 4 mg (in one dose) during the fifth day.

Before treatment, the patients had a spontaneous and rich milk secretion, with turgidity of the breast; on this parameters, serial controls

were carried out every 12 hours during the first two days of treatment, and one after 7 days and after one month respectively.

The prolactin plasma levels were determined on blood drawings collected every 30 minutes during the administration on the fourth day after delivery; further controls were performed after 4, 24 hours and 7 days from the beginning of treatment. Prolactin plasma levels were also determined in a control group of 20 puerperae.

Blood was centrifugated and plasma stored at −20°C till the moment of dosage.

Biodata kits were used for the radioimmunological determination of prolactin.

The statistical analysis of the results was carried out using a "t paired" test.

In all the patients was evaluated the eventual appearance of side effects or modifications in the blood and functional tests, performed before and after treatment with PgE_2 (hemochrome, glycemia, azotemia, GOT and GPT, heart rate, sistolic and diastolic blood pressure, albuminuria).

On the fifth day after delivery, two groups, of 6 puerperae each, treated with estrogens and PgE_2 respectively, underwent an oral glucose tolerance test, after a three days hyperglycemic diet (according to the indications of the Italian Society of Diabetology).

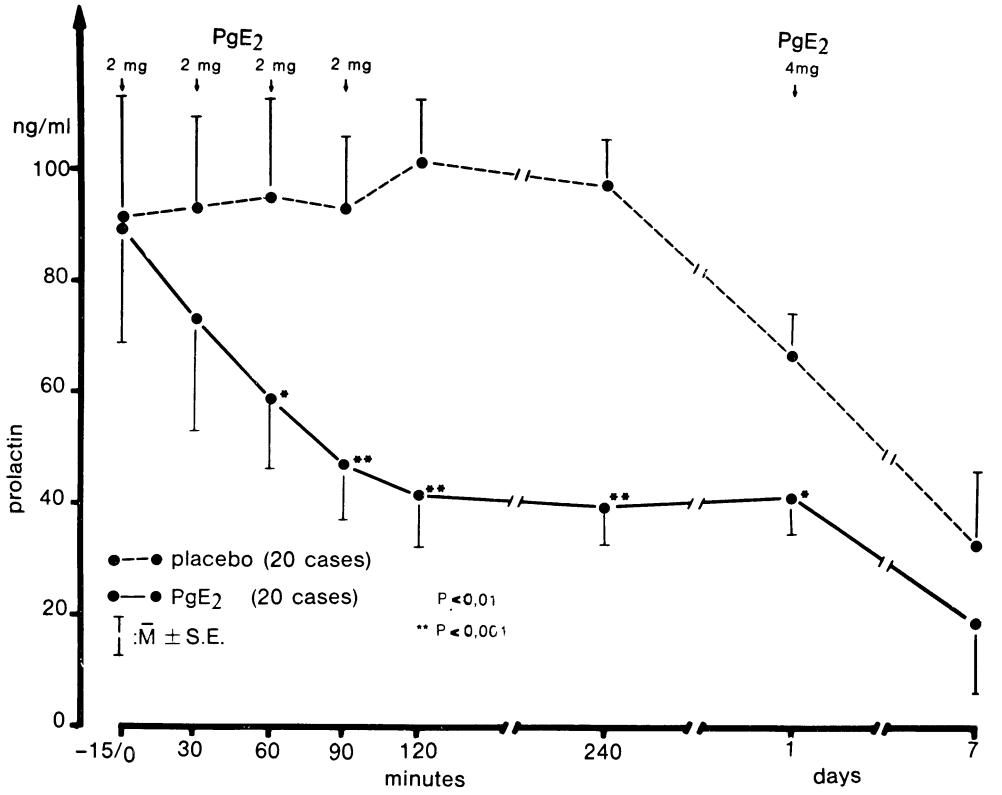

Fig. 1. — Modifications of prolactin plasma levels in nursing women (20) treated with Prostaglandin E_2 during the fourth and fifth day after delivery. They show a rapid and significative decrease in prolactin in comparison with the control group.

RESULTS

Milk secretion and breast turgidity had a contemporaneous involution, showing a progressive and constant decrease

at the controls performed after 12, 24 and 36 hours from the beginning of treatment; 48 hours later there was a milk secretion only by squeezing, and the turgidity was completely absent.

No relapses in milk secretion were observed after 7 days and after one

levels were practically the same as those found at the 240 minutes control, whilst 7 days later they were ulteriorly decreased (23.4±23.1 ng/ml) (fig. 1).

The statistical analysis has pointed out a significative decrease in prolactin levels in the patients treated with PgE_2

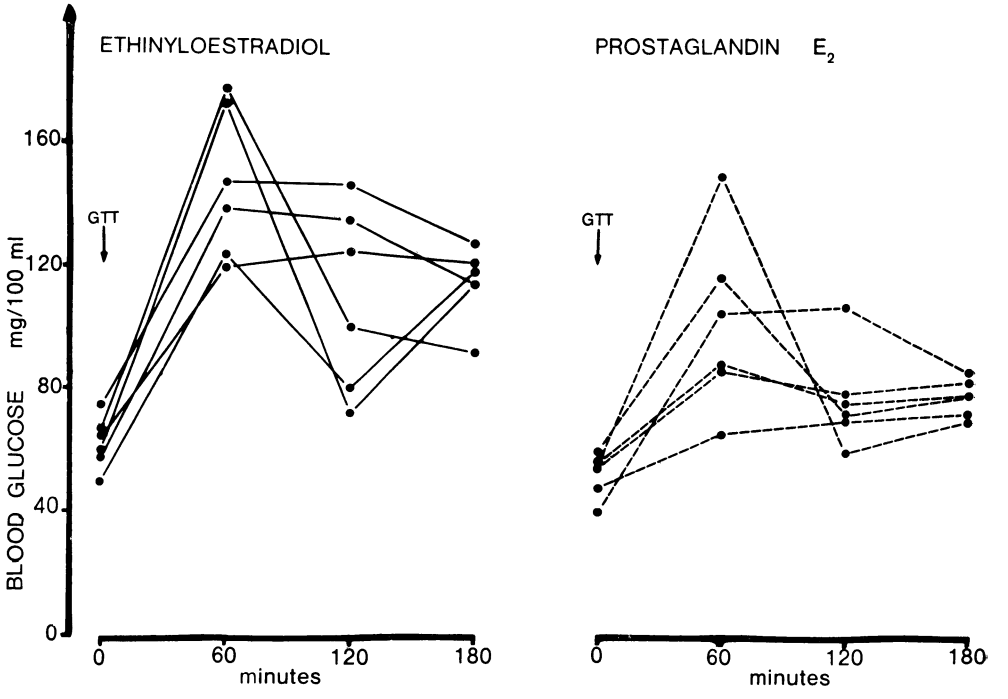

Fig. 2. — Oral glucose tolerance test, performed during the fifth day after delivery to two groups of puerperae treated with ethynil-estradiol (n. 6) and prostaglandin E_2 (n. 6). The diabetogenic effect of estrogens is reconfirmed by the glycemic answer of "borderline" type of 3 patients treated with ethynil-estradiol, whilsth no alteration of the curve was noticed after the PgE_2 treatment.

month. Prolactin plasma levels were decreased in comparison with the basal levels (91.4± 23.5 ng/ml) already after 30 minutes (73.7±20.0 ng/ml), 60 (58.8±12.9 ng/ml), 90 (47.2±9.1 ng/ml), 120 (42.5±7.9 ng/ml) and 240 minutes from the beginning of treatment with PgE_2 (40.8±7.1 ng/ml).

After 24 hours the prolactin plasma in comparison with the basal values and with the levels in the control group observed at 60, 90, 120, 240 minutes and 24 hours from the beginning of treatment.

Seven days later prolactin levels in the two groups of puerperae, were practically the same.

Prolactin concentrations in the control group were unchanged in comparison with

the basal values, having a mild and physiological decrease after 24 hours and after 7 days.

No side effects occured in the patients and, the blood and functional tests carried out before and after PgE_2 treatment, were normal.

While in the 6 puerperae treated with PgE_2 and undergone an oral glucose tolerance test (GTT) the glycemic curve had a normal trend, in 3 of those treated with ethynil-estradiol the curve had a pre-diabetic trend of « borderline » type (fig. 2).

DISCUSSION

According to the results obtained, PgE_2 seems to be able to inhibit puerperal milk secretion. Its clinical effects are clear and regular. On the other hand, it is not clear the mechanism of PgE_2 blocking the rise of the milk: this prostaglandin decreases the plasma levels of prolactin, probably inhibiting the hypophisarian secretion; however it presumably has an effect also on the mammary gland, inhibiting directly the galactopoietic metabolism.

The importance ascribed to the high levels of prolactin during pregnancy and puerperium for the rise of the milk, is well known ([3, 4]); but the block of milk secretion cannot be ascribed only to their rapid decrease, since the same administration of PgE_2 during the first and second day after delivery does not block the rise of the milk, even if it causes a decrease in prolactin plasma levels.

It can be presumed that PgE_2 has a double role: it could inhibit locally the metabolism of the mammary gland, probably through prostaglandin receptors, modifying at an intracellular level the quantity of cyclic nucleotides (cAMP, cGMP), physiological regulators of cells metabolism ([5, 6]). Always at a local level PgE_2 could cause a constriction of the mammary vessels ([7]), slowing the metabolic activity and blocking the galactopoiesis.

Besides the direct action of PgE_2 on the mammary gland, there is an inhibition of the synthesis of lactose and milk proteins, due to the sudden decrease of PRL plasma levels ([8]).

The mechanism of action of PgE_2 in decreasing the prolactin plasma concentrations, is not quite clear: it can be presumed that PgE_2 influences the hypophysarian cell directly or by the hypothalamic mechanisms which modulate the secretion. The second hypothesis is supported by the results of recent experiences on animals and humans: Fioretti *et al.* ([9]) have reported that the $PgF_{2\alpha}$ treatment blocks in nursing women the prolactin release, due to a sucking stimulus mediated by the hypothalamus ([10, 11, 12]). The same AA. ([13]) have also observed that the administration of $PgF_{2\alpha}$ to nursing rats increases the dopamine concentration in the medial eminence and decreases simultaneously the prolactin plasma levels.

Nasi *et al.* ([14]) report that PgE_2 can lower the prolactin plasma levels both in normoprolactinemic women and in those affected by disfunctional hyperprolactinemic amenorrhea but not in cases of hyperprolactinemia due to a hypothalamic PRL-secreting adenoma.

This result could strengthen the hypothesis that PgE_2 could modify the prolactin secretion not acting on the hypophysarian cells but, presumably, stimulating at hypothalamic level the production of the prolactin inhibiting factor (PIF), identified, since many years, with dopamine.

The oral glucose tolerance test of the two groups of patients treated with ethynil-estradiol or with PgE_2, confirms that the administration of estrogens during puerperium, can bring to a pre-diabetic condition ([16]); nevertheless a pathological effect of PgE_2 on the carbohydrates metabolism was not noticed.

The comparison between the PgE_2 treatment and the $PgF_{2\alpha}$ one, points out how both inhibit the lactation and how PgE_2 does not cause side effects.

Three of the patients treated with PgE_2 came again to our observation for a second delivery; they had a regular milk secretion proving the transitory action and the lack of noxious effects of PgE_2 on the mammary gland.

In conclusion, the short time of administration, the rapidity of action, the lack of a relapse in milk secretion, point out the use of PgE_2 as alternative to the methods still used to inhibit the lactation.

Nevertheless we think that further investigations are necessary to clarify the mechanism of action by which PgE_2 inhibits the milk and prolactin secretions.

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