RELATIONSHIPS BETWEEN PROLACTIN AND FOLLICLE-
STIMULATING HORMONE DURING EARLY PREGNANCY
AND THE PUERPERIUM

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SUMMARY

This investigation studies the relationship between the concentrations of prolactin and FSH
in the serum during pregnancy and the puerperium. A single dose of 5 mg bromocriptine
during early pregnancy induced a profound fall in the serum level of prolactin with a sub-
stantial rise 20 h later. During the initial reduction in the concentration of prolactin, no
alteration was noted in the level of FSH but during the subsequent increase in the prolactin
concentration, there was a significant \( P<0.05 \) decrease in the concentration of FSH. During
week 1 of the puerperium, the concentrations of FSH and prolactin were significantly
lower in lactating women than in women who were not breast feeding, but there was no
significant difference between the concentrations of FSH in women who had suppressed
lactation with bromocriptine and in those whose lactation was suppressed by non-hormonal
methods. When the concentration of FSH was measured every 10 min during a 30 min
breast feed, there was a marked but short-lived rise in the serum concentration of prolactin
but no change in the level of FSH. These results suggest that an increase in the serum level of
prolactin in pregnancy can have a suppressive effect on the production of FSH. Although
acute suckling-induced hyperprolactinaemia in the puerperium has no such effect, the
maintenance of lactation in the long term does suppress the concentration of FSH in the
serum.

INTRODUCTION

The normal physiological rise in the concentration of prolactin in the serum during pregnancy
may explain the cessation of ovulation that occurs at this time. The clinical observation that
amenorrhea post partum is related to the duration of breast feeding suggests that the
physiological increase in the concentration of prolactin during the postnatal period may
exert a powerful influence on normal ovulation. This action may be mediated at the ovary
(McNatty, Sawyers & McNeilly, 1974), or may be occurring at the level of the hypothalamic-
pituitary system, resulting in interference with the normal secretion of the gonadotrophins.
As the hyperprolactinaemia during pregnancy is physiological and not caused by any func-
tional or morphological disorder of the hypothalamus or pituitary gland, it was decided that
pregnancy and the puerperium would be good models for the study of any relationship that
may exist between the concentrations of prolactin and follicle-stimulating hormone (FSH)
in the serum. Because of problems of cross-reactivity, the concentration of luteinizing
hormone cannot be measured in serum from pregnant women, but the recent develop-
ment of more specific assays has allowed the measurement of FSH in the presence of human
chorionic gonadotrophin.
The purpose of this study was to investigate the effect of hyperprolactinaemia and artificial suppression of prolactin in early pregnancy and the puerperium on the concentration of FSH in the serum.

MATERIALS AND METHODS

*Prolactin suppression in early pregnancy*

Suppression of the secretion of prolactin in early pregnancy was achieved in five healthy women in the first trimester of pregnancy who were to undergo therapeutic abortion for non-medical reasons and who volunteered to take part in the study. The pregnancies were all normal and the women had had normal regular menstrual cycles before pregnancy with no history of gynaecological or endocrinological disease. The length of gestation ranged from 12 to 15 weeks and the women were aged between 22 and 26 years. Each woman received 5 mg bromocriptine (2-bromo-5α-ergocryptine; Parlodel, Sandoz Products Ltd) orally before the mid-day meal and blood was collected immediately before and 3, 6, 12 and 20 h after the tablets were given. Patients were kept in bed to diminish the side-effects of the tablets.

*Prolactin suppression in the puerperium*

Fifteen puerperal women were studied during the first 7 days post partum. They had undergone uneventful pregnancies with normal spontaneous vaginal deliveries and were divided into two groups: five women were lactating successfully and ten women wished to feed their infants artificially. Of the second group, five women received no therapy for suppression of lactation and the five others received 5 mg bromocriptine on day 1 post partum and then 2·5 mg for the subsequent 12 days of the puerperium. Daily blood samples were obtained and all subjects had a normal and uneventful puerperium.

*Suckling-induced hyperprolactinaemia*

Ten puerperal lactating women were studied on day 7 post partum during suckling. They had all undergone normal pregnancies and vaginal delivery of infants at term. No drug treatment was given during the period of study. Normal lactation had begun on day 2 post partum and an adequate milk flow had been established. All had agreed to be studied whilst nursing their babies. One hour before the time of the 10.00 h feed, an indwelling cannula was placed in a superficial vein in the forearm of the mother. Blood samples were obtained immediately before suckling, after changing the baby from one breast to the other (10 min from the start) and at the end of the feed (30 min from the start). The last sample was taken 1 h after the completion of feeding.

*Assay of FSH*

Serum concentrations of FSH were measured in duplicate by a double-antibody radioimmunoassay. The reference preparation MRC 68/39 was used as a standard and MRC 71/333 was used for preparing the tracer. The antiserum was raised by Dr W. R. Butt and was denoted M39. The intra- and interassay coefficients of variation were 4·8 and 6·4% respectively.

*Assay of prolactin*

Serum prolactin was measured by a homologous radioimmunoassay method using a commercially available kit supplied by Eurotipe Services Ltd. Human prolactin extracted from amniotic fluid was used as standard and human pituitary prolactin (Calbiochem, U.S.A.) labelled with 125I was used as the tracer. The limit of detection of the assay system lay between 2·2 and 180 ng/ml. The average intra- and interassay coefficients of variation were 7·8 and 12% respectively.
Statistical tests

Values are given as means ± s.d.; Student's t-test for paired data was used to determine the significance of the observed differences.

RESULTS

Effect of prolactin suppression in early pregnancy on serum FSH

The basal concentration of prolactin in the circulation before treatment was found to be within the range normally seen in pregnant women in the first trimester (21.5 ± 9.4 (s.d.) ng/ml; Hwang, Guyda & Friesen, 1971). A significant decline in the serum concentration of prolactin occurred 3 h after the administration of bromocriptine (P<0.01) with maximum inhibition occurring after 6 h (3.9 ± 1.8 ng/ml). The concentration then increased gradually, reaching the basal value after 12 h and a significantly higher concentration (107.9 ± 62.6 ng/ml, P<0.05; Fig. 1) after 20 h.

In contrast to the reduction in the concentration of prolactin no significant change was observed in the mean concentration of FSH for 12 h. However, after 20 h, there was a significant decrease in the serum level of FSH (P<0.05) and significant correlation was found between the percentage increase in the concentration of prolactin and the percentage decrease in the concentration of FSH in the serum of every subject (r = 0.893, P<0.05; Fig. 1).

Effect of prolactin suppression in week 1 of the puerperium on serum FSH

During the first 7 days of the puerperium, there were no significant changes in the concentrations of FSH in the serum irrespective of whether the women were breast-feeding their infants or not. Also the concentrations of FSH in the circulation of the women receiving bromocriptine therapy varied in a similar manner to the values observed in the women receiving no drugs. The mean concentration of FSH in the serum of subjects who had stopped lactating
without therapeutic suppression was not significantly different from the concentration in the group receiving bromocriptine. However, the mean concentration of FSH in the breastfeeding group was significantly lower than the concentration in women who were not lactating ($P<0.025$; Fig. 2).

Fig. 2. Concentrations of FSH in the serum during week 1 of the puerperium in five non-lactating women receiving bromocriptine (a), five non-lactating women receiving no treatment (b) and five lactating women (c).

Fig. 3. Mean ($\pm$ s.d.) percentage changes in the concentrations of FSH (---), prolactin (-----) and prolactin (-----) in the serum of ten lactating women during suckling on day 7 post partum. The period of suckling lasted 30 min from time 0.
Effect of suckling-induced hyperprolactinaemia on serum FSH

The basal concentrations of prolactin in the circulation of mothers before feeding were found to be within the normal range for the puerperium (123 ± 54 ng/ml). A highly significant (P < 0.0005) increase in the concentration of prolactin occurred as suckling began and reached a peak of 438 ± 691 ng/ml by the end of the 30 min feeding period. Thereafter the concentration declined rapidly and had almost returned to the basal value 1 h after the cessation of breast-feeding. No significant change was observed in the serum concentration of FSH at any time during the suckling period (P ≥ 0.4–0.1; Fig. 3).

DISCUSSION

In rats, suckling post partum is known to stimulate the release of prolactin and inhibit the secretion of gonadotrophins (Amenomori, Chen & Meites, 1970; Ford & Melampy, 1973; Hammons, Velasco & Rothchild, 1973; Moudgal, Maneckjee & Muralidhar, 1976). In man, however, the precise interaction between prolactin and the secretion of gonadotrophins remains far from clear.

The initial observations of non-consistent changes in the concentration of prolactin during the normal menstrual cycle (Jaffe, Yuen, Keye & Midgley, 1973), in contrast to the major peaks in the concentrations of pituitary gonadotrophic hormones, may indicate that there is no interaction between the secretion of gonadotrophins and prolactin by the pituitary gland under normal circumstances. Even in patients suffering from the pathological condition of hyperprolactinaemia, the levels of gonadotrophins have been shown to be normal (Franks, Murray, Jequier, Steele, Nabarro & Jacobs, 1975). However, Tyson, Khojandi, Huth, Smith & Thomas (1975) were the first to suggest that the cyclical secretion of gonadotrophins is disrupted by increased secretion of prolactin and is restored by its suppression.

The first part of the present study involved the reduction of the relatively high level of prolactin found in the circulation during early pregnancy to the concentration normally found in non-pregnant women. This treatment should have altered any inhibitory effect of prolactin on the secretion of gonadotrophins. Bromocriptine is known to inhibit the secretion of prolactin by the pituitary gland in the non-pregnant hyperprolactinaemic patient (Varga, Lutterbeck, Pryor, Wenner & Erb, 1972) and during the puerperium (del Pozo, del Brun, Varga & Friesen, 1972). The present study has shown that bromocriptine will also inhibit the secretion of prolactin during early pregnancy; the level of prolactin was reduced by 80% within 6 h of taking the drug. The significant increase in the concentration of prolactin after 20 h suggests the presence of a biphasic response of the pituitary gland to the inhibitory action of bromocriptine in early pregnancy. No such observation has been reported in human pregnancy before. After reducing the serum concentration of prolactin to the range normally found in untreated non-pregnant women, the level of FSH in the serum was not significantly altered. However, when the concentration of prolactin reached a maximum, an increase of more than 400% compared with the basal value 20 h after the administration of bromocriptine, the concentration of FSH was shown to be significantly decreased. This suggests that pituitary secretion of gonadotrophins during pregnancy may be more responsive to an increase in the concentration of prolactin in the circulation than it is to a short-term reduction in this concentration.

It has been stated that nursing elicits an increase in the pituitary secretion of prolactin associated with a simultaneous inhibition of gonadotrophin release (Meites, 1966; Reichlin, 1974). The data of Faiman, Ryan, Zwirek & Rubin (1968), Fuchs, Beling, Frandsen, Josimovich, Moller, Saunders & Saxena (1971) and Reyes, Winter & Faiman (1972) suggest that the recovery of pituitary secretion of FSH after delivery is not dependent on breast-feeding, and Bonnar, Franklin, Nott & McNeilly (1975) found that the concentrations of FSH
in both lactating and non-lactating women were identical in spite of an increase in the plasma concentration of prolactin in women who were breast-feeding. Meanwhile, Crystle, Powell & Stevens (1970) and Said & Wide (1973) reported that the level of FSH was significantly lower in women who were breast-feeding than in non-lactating subjects and Katsuyoshi, Mitsunori & Toshiko (1974), Seki, Seki & Okumura (1974) and Nader, Kjeld, Blair, Tooley, Gordon & Fraser (1975) showed that, in puerperal women, a reduction in the concentration of prolactin after treatment with bromocriptine caused an increase in the basal level of FSH. The results are therefore still of a controversial nature. The present data support the finding of most investigators that there are unchanging low serum concentrations of FSH during the first 7 days post partum in both lactating and non-lactating women. Suppression of the serum concentration of prolactin by bromocriptine seems not to alter the day-to-day variations in the level of FSH, compared with the non-treated group. However, the significantly lower mean serum concentrations of FSH in the nursing mothers compared with values in those who did not breast feed is in favour of an inhibitory action of high levels of prolactin on the pituitary secretion of FSH during the puerperium.

The neurogenic-hormonal response to suckling was recognized experimentally long ago (Selye, 1934). In the present studies, as in previous reports (Frantz & Kleinberg, 1970; Hwang et al. 1971; Tyson, Friesen & Anderson, 1972; Noel, Suh & Frantz, 1974; Jeppson, Nilsoen, Rannevik & Wide, 1976), suckling caused an increase in the plasma concentration of prolactin with a maximum at the end of the suckling period and a return to pre-suckling values after 90 min. The short releases of prolactin that occur after suckling are caused by the initiation of neuronal impulses to the hypothalamus which stimulate hypothalamic neurotransmitters and these in turn mediate the release of prolactin (Zacur, Foster & Tyson, 1976). It has not been clearly indicated in the literature whether it is the neural stimulus of suckling or the increased secretion of prolactin that is responsible for the inhibition of gonadotrophin release in animals. However, Lu, Chen, Hwang, Grandison, Marshall & Meites (1976) provided strong evidence that the suckling stimulus rather than the increased secretion of prolactin was the main cause of the reduction in the release of pituitary gonadotrophins. It has been suggested by Meites (1966) and Minaguchi & Meites (1967) that this mechanism operates in man and it is also believed that interaction may be through a short-loop feedback effect of the secretion of prolactin on the hypothalamus.

In the present study, despite the increase in the serum concentration of prolactin during suckling, there was no significant change in the concentration of FSH during a 90 min observation period. This is in agreement with the data of Jeppson et al. (1976) and Soria, Zarate, Canales & Villalobos (1976).

In summary, this study has shown firstly the presence of a biphasic response of prolactin to suppression with bromocriptine in early pregnancy. Suppression of the serum concentration of prolactin at this time was not associated with any change in the concentration of FSH but the very large increase in the concentration of prolactin which occurred 20 h after administration of bromocriptine was accompanied by a significant reduction in the level of FSH. However, during the puerperium, when there was continuous suppression of prolactin with bromocriptine, no biphasic response was noted and there was no significant change in the serum concentration of FSH during the period of study. Nevertheless, in the lactating women, when the concentration of prolactin is known to be high, there was a significant reduction in the overall mean concentration of FSH even though no further decrease in this concentration was noted during the act of breast-feeding itself. It would thus appear that the suppression of the serum concentration of FSH by hyperprolactinaemia is more closely related to the duration of the hyperprolactinaemia than to the actual concentration of prolactin present in the serum at any particular time.

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REFERENCES


