Oral administration of TRH in puerperal women:
effect on insufficient lactation,
thyroid hormones and on the responses of TSH
and prolactin to intravenous TRH

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Abstract. Thirteen puerperal women with insufficient
lactation were treated with thyrotrophin releasing hor-
mones (TRH) 20 mg twice daily for two weeks. Intra-
venous (iv) TRH stimulation tests were done before the
TRH therapy and within 3–5 h after the last dose of oral
TRH. Plasma samples were assayed for prolactin (Prl),
thyrotrophin (TSH), triiodothyronine (T3) and thyroxine
(T4) by radioimmunoassays, and the lactational response
was objectively monitored in 11 women. Oral TRH
treatment was associated with significantly (P < 0.05)
depressed Prl levels (23.0 ± 7.9 μg/L vs. 61.4 ± 26.2,
mean ± SEM), no change in TSH levels (3.7 ± 0.4 IU/L vs.
4.0 ± 0.4) but significantly (P < 0.01) elevated T3 (2.17 ±
1.14 nmol/l vs. 1.83 ± 0.09) and T4 (131.6 ± 7.9 nmol/l
vs. 96.6 ± 5.8) levels. Oral TRH entirely blocked the
TSH response and significantly (P < 0.01) blunted the
Prl response to iv TRH stimulation. No improvement in
lactation was observed.

Prolactin (Prl) is evidently necessary for the initiation
and maintenance of human lactation. This is
based upon the observations of high Prl levels in
fully lactating women (Rolland et al. 1975; Tyson et
al. 1976; Zárata et al. 1976), a Prl surge in maternal
blood during and after nursing (Tyson et al. 1972;
Gautvik et al. 1973; Noel et al. 1974a; Jeppson et
al. 1976) and diminished or absent lactation in
women whose Prl levels are initially low (Tyson et
al. 1976; Zárata et al. 1976) or artificially suppressed
by bromocriptine treatment (Brun del Re et al.
1973). Thyrotrophin releasing hormone (TRH), in
addition to its stimulatory effect on thyrotrophin
(TSH) secretion, is well known also to stimulate the
Prl release (Jacobs et al. 1971; Bowers et al. 1971).
Consequently, some investigators have tried treat-
ment with oral TRH for the improvement of
puerperal lactation (Tyson et al. 1975, 1976; Zárata
et al. 1976; Canales et al. 1977). In these studies,
however, the lactational results have been contra-
dictory and the effect of TRH on the pituitary-
thyroid axis has not been explored thoroughly. We
therefore designed this study to determine the
effect of long-term oral TRH treatment on insuffi-
cient lactation as well as on TSH, Prl and thyroid
hormone secretion in puerperal women.

Patients and Methods

Thirteen puerperal women volunteered for this study
after being fully informed of its purpose and course.
Their age ranged from 23 to 41 years with a mean of
28.8. Nine women who has delivered once or twice
before had breastfed their infants for 1–6 months. The
course of the present pregnancy was normal in all
women, resulting in the birth of infants with a birth-
weight of 2780–4250 g. Lactation started normally and
was sufficient for an infant’s need for 2–9 weeks, but
thereafter milk secretion gradually became diminished to
the extent that supplemental alimentation became neces-
sary. The women entered our trial 3–10 weeks (mean 6.3
weeks) after delivery.

Administration of TRH

On the first study day, all the women were studied with
an iv TRH stimulation test 5–6 h after the last nursing.
The test was done at 13.00 h with the insertion of a small infusion set. After 30 min, the first blood sample (5 ml) was collected into a heparinized tube through this set, and 200 μg of synthetic TRH (Hoffman LaRoche, Basle, Switzerland) was then injected as a rapid bolus. Thereafter, blood specimens were taken at 20 and 60 min. On study days 3 and 4, the women recorded their basal milk secretion (see later). On days 5–19, each woman took 20 mg of TRH orally twice a day, and within 3–5 h after the last dose of oral TRH and within 4–6 h after the last nursing, the women were re-tested with iv TRH stimulation.

**Monitoring the lactational response**

The women breastfed their infants for 30 min five times daily during the whole study period of 19 days. The lactational response was monitored in two ways in 11 women. Firstly, the infants were weighed before and after the first and last nursing on days 3 and 4 (before TRH) and on the 5th and 10th days during TRH intake. The weight gain indicated the amount of milk which was secreted during a particular nursing. Secondly, the amount of supplemental alimination was weighed daily before and during oral TRH treatment.

**Assays**

Plasma was separated by centrifugation and stored frozen at −20°C until assayed. PRL and TSH were assayed by radioimmunoassays using CEA-IRE-Sorin kits (Commisariat à l'Energie Atomique des Produits Biomédicaux, B.P. No. 21-91190, Gif-sur-Yvette, France). Triiodothyronine (T3) and thyroxine (T4) were also measured by radioimmunoassays (Farmos Diagnostica, Turku, Finland). All determinations were performed in duplicate and each hormone in the same batch of assay. The paired t-test and regression analysis were employed for the statistical treatment of the results.

**Results**

**Pituitary-thyroid hormones**

The individual and mean hormonal concentrations are given in Fig. 1 and Table 1. The mean PRL level decreased ($P < 0.05$) during the study period of two weeks, whereas the TSH level was not different from the pre-treatment concentration. Serum T3 level was $18.5\%$ and T4 level $36.6\%$ higher ($P < 0.01$) at the end of oral TRH treatment than before TRH intake.

Each woman responded with marked PRL and TSH elevations to the iv TRH stimulation before the start of oral TRH (Fig. 2). The maximal PRL increment was $114.7 ± 17.0$ μg/l (mean ± SEM) and that in TSH level $12.3 ± 2.2$ IU/l. Because the last sample was taken 60 min after the iv TRH bolus, no rise in T3 and T4 concentrations could be demonstrated.

![Graph showing hormonal levels](image)

**Fig. 1.**

Individual levels of prolactin (PRL), thyrotrophin (TSH), triiodothyronine (T3) and thyroxine (T4) before oral TRH treatment and within 3–5h after the last dose of two weeks' treatment with oral TRH. Note the logarithmic scale for PRL. The dotted lines indicate the normal range for non-pregnant women.
Table 1.
Basal levels (mean ± SEM, range) of prolactin (Prl), thyrotrophin (TSH), triiodothyronine (T3) and thyroxine (T4) before and at the end of two weeks administration of oral TRH, 40 mg daily in 13 puerperal women with insufficient lactation. * = P < 0.05; ** = P < 0.01 and *** = P < 0.001, indicate the significances of the differences.

<table>
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<th>Before</th>
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<tr>
<td>Prl (μg/l)¹</td>
<td>61.4 ± 26.2 (1.8–263.9)</td>
<td>* 23.0 ± 7.9 (1.1–75.8)</td>
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<tr>
<td>TSH (IU/l)²</td>
<td>4.0 ± 0.4 (2.5–6.6)</td>
<td>3.7 ± 0.4 (1.0–5.6)</td>
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<td>T₃ (nmol/l)³</td>
<td>1.83 ± 0.09 (1.50–2.35)</td>
<td>** 2.17 ± 1.14 (1.46–3.22)</td>
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<tr>
<td>T₄ (nmol/l)⁴</td>
<td>96.6 ± 5.8 (69.5–136.4)</td>
<td>***131.6 ± 7.9 (102.5–188.7)</td>
</tr>
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</table>

¹ Normal range for non-pregnant women 1.5–30.0 μg/l
² Normal range for non-pregnant women 2.1–8.1 IU/l
³ Normal range for non-pregnant women 1.2–2.6 nmol/l
⁴ Normal range for non-pregnant women 65–155 nmol/l

When the iv TRH stimulation tests were repeated at the end of oral TRH treatment, the TSH response was abolished and the Prl response blunted (Fig. 2). The maximal Prl increment was 57.8 ± 12.3 μg/l only, which is significantly less (P < 0.01) than before the start of oral TRH.

Lactational response
The basal milk secretion was not correlated with the basal Prl level (r = 0.157, P > 0.05) or with the Prl response to the first iv TRH bolus (r = 0.080, P > 0.05). Oral TRH treatment caused no significant changes in the milk secretion or in the need for supplemental alimentation (Fig. 3).

Side-effects of TRH
Seven women (53.5%) complained of nausea and 2 women (15.3%) of flushing during oral TRH intake, whereas these symptoms did not occur in any of the women before and after TRH treatment. Flushing, nausea and/or desire to void were reported during 22 of 26 iv TRH stimulation tests. There were no changes in blood pressures or in pulse rate in any of the women.

Discussion
A single dose of oral TRH induces significant rises in Prl and TSH levels in non-pregnant women (Staub et al. 1971, 1978; Haigler et al. 1972; Snyder & Utiger 1973; Rabello et al. 1974) and also in puerperal women (Tyson et al. 1976; Kivinen et al. 1978). From earlier studies in non-puerperal subjects it is known that the TSH and Prl responses disappear gradually after repetitive oral doses of TRH (Rabello et al. 1974; Zárate et al. 1974; Lasso et al. 1976; Frey & Haug 1977; Staub et al. 1978) or during constant iv infusion of TRH (Noel et al. 1974b; Bremner et al. 1977). It is likely that a
similar phenomenon takes place also during the puerperium, because prolonged administration of TRH did not result in chronic TSH or PRL rises in puerperal women in the present study. The decreased TSH response is thought to be due to the negative feedback mechanism, because repeated oral doses of TRH raise the levels of T3 and T4 in non-pregnant (Staub et al. 1971; Snyder & Utiger 1973; Rabello et al. 1974; Frey & Haug 1977) and puerperal subjects, as evident from this study. The TSH response to oral TRH, however, was also blunted in hypothyroid patients with low or undetectable T3 and T4 levels (Frey & Haug 1977; Staub et al. 1978). Therefore, negative feedback cannot be the only explanation. TRH might also regulate the number or affinity of its own receptors directly in the pituitary or stimulate the release rather than de novo synthesis of TSH, leading to a transitory depletion of TSH stores. None of the women developed clinical hyperthyroidism. This agrees with the results from normal women or men (Rabello et al. 1974; Lasso et al. 1976; Frey & Haug 1977; Staub et al. 1978) or from puerperal women (Zárate et al. 1976; Canales et al. 1977). Tyson et al. (1976), however, reported two puerperal women who developed hyperthyroidism after being treated with 80 mg of TRH daily.

All women responded with consistent PRL and TSH elevations to iv injection of TRH before the start of oral TRH. Oral TRH treatment for two weeks entirely abolished the TSH response to iv TRH and significantly blunted the PRL response. The disappearance of the TSH response could be due to the elevated levels of T3 and T4, as suggested before (Snyder & Utiger 1973; Shenkman et al. 1973; Frey & Haug 1977). Apparently, oral TRH does not completely deplete the pituitary PRL stores, because a significant PRL response to iv TRH stimulation was maintained in this study of puerperal women as has also been found in normal women (Frey & Haug 1977).

In the present study, there was a mild increasing trend in the milk amount in some women during oral TRH intake. This may be due to the more regular nursings during the study, because, as is well known, suckling per se stimulates and maintains milk secretion. We did not, however, see any significant improvement in lactation. Previously, oral TRH treatment has failed to improve full lactation in puerperal women (Tyson et al. 1976; Zárate et al. 1976). Insufficient lactation was, however, improved when 20 mg of oral TRH was given twice daily (Tyson et al. 1976), or lactation was successfully re-initiated with 80 mg of TRH daily in

Fig. 3.
Individual (○) and mean (●) (± SEM) milk productions and the needs of supplemental alimentations for the infants before and during oral TRH treatment in 11 women. There are no significant changes.

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all women whose lactation was temporarily stopped with bromocriptine (Canales et al. 1977). Our present study indicated objectively that the effect of orally administered TRH on insufficient lactation is negligible. Other agents like metoclopramide, which stimulates the Prl secretion at the hypothalamic level, might prove more useful for the improvement of lactation without causing thyroid stimulation (Guzman et al. 1979).

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References


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