Circadian thyrotropin variations are preserved in normal pregnant women*

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Serum thyrotropin (TSH) concentration circadian rhythm is abolished in many endocrine and non-endocrine diseases. In the present study we have measured serum TSH concentration over 24 h every 2 h in second and third trimester pregnant women. During the 24-h period, serum free thyroxine and free triiodothyronine concentrations did not change significantly. In contrast, serum TSH concentrations demonstrated significant circadian variations both in the second and third trimester pregnant women (p < 0.02 and p < 0.005, respectively). In summary, second and third trimester pregnancy is associated with a normal circadian TSH rhythm.

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Considerable evidence has accumulated indicating that serum thyrotropin (TSH) concentrations undergo circadian changes, the highest values occurring late at night or early in the morning (1–4).

Such circadian variations are reduced or abolished in many pathological conditions, such as primary thyroid diseases or thyroid hormone overtreatment (5–8), hypothalamic-pituitary disorders (9–11), severe non-thyroidal illness (12–16) and depression (17).

The first trimester of pregnancy is characterized by a slight increase in serum free thyroxine (FT₄) and free triiodothyronine (FT₃) concentrations associated with a decrease in serum TSH values attributed to stimulation of thyroid function by the increased serum human chorionic gonadotropin (hCG) concentrations (18). Conversely, in the second and, more so, in the third trimester a decrease in serum FT₄ and FT₃ values has been reported, usually in pregnant women from areas with mild iodine deficiency (18, 19), possibly as a result of desaturation of circulating thyroxine-binding globulin (TBG).

This study was undertaken to investigate serum TSH circadian variations in pregnant women during the second and third trimesters of pregnancy.

Materials and methods

Eleven euthyroid pregnant women were enrolled in this study after giving informed consent. Six women aged 26 ± 2 years (mean±SEM) had a gestational age of 21.2 ± 1.5 weeks; five women aged 25 ± 2 years had a gestational age of 36.6 ± 0.8 weeks. They were admitted to the Division of Gynecology, Ospedale S Maria, Borgotaro, Italy for obstetric evaluation, which was found to be normal. They were otherwise healthy.

An iv catheter was inserted into the antecubital vein and kept patent with heparin. During the day the women were allowed to walk and had meals at their usual time; they slept from 23:00 h to 07:00 h. Blood was drawn during sleep without interrupting sleep.

Blood samples were obtained every 2 h. Serum was kept at −20°C until assayed.

Serum TSH, FT₄ and FT₃ concentrations were measured by chemiluminescence (Kodak Clinical Diagnostics, Cinisello Balsamo, Italy). Normal ranges in pregnant women are as follows: TSH, 0.2–2.9 mU/l; FT₄, 8.5–20.6 pmol/l; FT₃, 3.4–7.9 pmol/l. All samples were analyzed in the same run to avoid interassay variation. The intra-assay coefficients of variation of control samples with hormone concentrations similar to the values of the pregnant women were as follows: TSH, 8.0%; FT₄, 4.8%; FT₃, 9.3%. All values were expressed as mean ± SEM. Serum TSH concentrations were also reported as the percentage deviation from the 24-h mean concentration for each pregnant woman.

Statistical analysis was carried out by one-way*The study was presented in part at the XXV National Meeting of the Italian Society of Endocrinology, Rome, 22–25 May 1994, and at the 76th Annual Meeting of the American Endocrine Society, Anaheim, CA, 15–18 June 1994.
analysis of variance (1-way ANOVA) to evaluate serum thyroid hormone concentrations during a 24-h period within the same group of pregnant women, and by 2-way ANOVA to compare hormonal values in the two groups of pregnant women; paired and unpaired Student’s t-tests were used to compare thyroid hormone and TSH values within each group and between the two groups of women, respectively.

Results

Mean serum FT₄ concentrations at 08:00 h were 16.4 ± 1.4 pmol/l in the second trimester and 16.3 ± 1.1 pmol/l in the third trimester (p = NS); similarly, no differences were found in mean serum FT₃ levels (4.9 ± 0.4 pmol/l in the second trimester vs 5.4 ± 0.3 pmol/l in the third trimester; p = NS). No significant variations were observed in FT₄ and FT₃ values and FT₃/FT₄ ratios during the 24-h period of observation (Table 1). Furthermore, FT₄ and FT₃ patterns and FT₃/FT₄ ratios during the 24-h period did not differ significantly in the two groups of pregnant women (Table 1). However, the mean of all FT₄ values of third trimester pregnant women was significantly lower (p < 0.05) than that of all values of second trimester pregnant women: 16.0 ± 0.2 and 17.1 ± 0.4 pmol/l, respectively. In contrast, the mean of all FT₃ values of third trimester pregnant women was significantly higher (p < 0.05) than that of second trimester pregnant women: 5.1 ± 0.1 and 4.9 ± 0.1 pmol/l, respectively. Similarly, the mean of all FT₃/FT₄ ratios was higher (p < 0.0001) in third trimester than that in second trimester pregnant women.

The mean serum TSH value in the morning (08:00 h) in the women in the second trimester was significantly lower than in the third trimester (0.5 ± 0.1 vs 1.3 ± 0.5 mU/l; p < 0.005; Table 1). Serum TSH concentrations demonstrated significant circadian variations both in the second and in the third trimester pregnant women (p < 0.02 and p < 0.005, respectively) and the 24-h values were significantly different (p < 0.04; Table 1). The mean of all TSH values of the third trimester pregnant women was significantly higher (p < 0.0001) than that of the second trimester: 1.0 ± 0.1 and 0.5 ± 0.01 mU/l, respectively.

Circadian TSH variations were also apparent both in second and in third trimester women when TSH values were expressed as a percentage deviation from the 24-h mean (p < 0.009 and p < 0.0001, respectively; Fig. 1).

Discussion

Circadian serum TSH variations occur in normal subjects (1–4) and appear to be, at least in part, under dopaminergic control (20), although this is a matter
of controversy (21, 22). The TSH secretory rhythm is abolished by an excess of circulating free thyroid hormones, either of exogenous or endogenous origin (5, 6, 8). In addition, alterations of the TSH circadian rhythm, and in particular the loss of nocturnal TSH surge, appear to predict the possible subsequent occurrence of hyperthyroidism in patients with non-toxic goiter (7). An impaired circadian TSH rhythm is also found in hypothyroidism (9, 10) and in several non-thyroidal endocrine and non-endocrine disorders (11–13).

Pregnancy is a condition associated with profound changes in the hormonal milieu. In this study we investigated whether pregnancy is associated with variations in the TSH circadian rhythm. We found that euthyroid women in the second and third trimester of pregnancy maintained an essentially normal circadian TSH rhythm, as assessed by a 24-h period of observation. In keeping with a previous report by Pacchiarotti et al. (19), serum TSH values in the second trimester were significantly lower than in the third trimester.

The 24-h levels of serum FT$_4$ and FT$_3$ in the present series did not differ significantly in the different periods of pregnancy. However, the mean of all FT$_4$ values of third trimester pregnant women was lower than that of second trimester pregnant women. In contrast, the mean of all FT$_3$ values and FT$_3$/FT$_4$ ratios of third trimester pregnant women was higher than that of second trimester pregnant women. This finding obtained in pregnant women residing in an area of mild iodine deficiency (24) suggests a subtle thyroid insufficiency due to iodine deficiency, as reported previously by Glinoer et al. (25).

The reduced serum TSH concentrations observed in third trimester pregnant women might be due to a decrease of T$_4$ within the pituitary gland. Thyroxine rather than T$_3$, via the intrapituitary T$_4$ to T$_3$ deiodination, is the major regulator of pituitary TSH secretion (26).

We have reported previously that serum prolactin (PRL) is elevated during pregnancy (27). This increase in serum PRL levels did not affect the serum TSH circadian variation, in keeping with the observation that the TSH rhythm is preserved in patients with pituitary PRL-secreting microadenomas (28). Although it is known that endogenous cortisol hypersecretion (2) and the administration of pharmacological doses of synthetic glucocorticoids (2) abolish the nocturnal TSH surge, the increased adrenocorticotrophic function found in pregnant women (29) apparently does not influence substantially the TSH rhythm.

The present study, carried out in euthyroid women in the second and third trimester of pregnancy, is in agreement with and expands previous observations by Pekonen et al. (30), who reported that pregnant women in the first trimester have a normal nocturnal serum TSH surge. In conclusion, pregnancy, even if it is accompanied by small changes in serum TSH and thyroid hormone levels, is associated with a normal circadian TSH rhythm.

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