Thyroid function during early pregnancy is similar in euthyroid women and in women with subclinical hypothyroidism treated with thyroid hormone

De Geyter C, Steimann S, Muller B, Kranzlin ME, Meier C. Pattern of thyroid function during early pregnancy in women diagnosed with subclinical hypothyroidism and treated with l-thyroxine is similar to that in euthyroid controls. Thyroid 2009;19:53-9.

SUMMARY

BACKGROUND Subclinical hypothyroidism (SCH) is defined as an elevation of serum thyrotropin (TSH) above the normal reference limit with normal serum free thyroxine (FT_4) or free triiodothyronine (FT_3) levels. When SCH occurs in pregnancy, there is an increased risk for miscarriage in both the first and second trimesters; however, there is uncertainty concerning how thyroid function during early pregnancy in women with SCH might differ from that in euthyroid pregnant women. The aim of this study was to determine the extent of thyroid secretory capacity and the regulation of thyroid function in women with SCH receiving levothyroxine ($L\text{-}T_4$) during early pregnancy as compared with pregnant euthyroid controls.

METHODS This cohort study was performed at Women's Hospital of the University of Basel, Switzerland, where thyroid function is routinely assessed in women undergoing an infertility workup during which ovulation was induced with 10,000 IU of human chorionic gonadotropin (hCG). Pregnant women with SCH—defined as a consistently elevated serum TSH greater than 4.5 μIU/ml in the presence of normal serum FT_4 and FT_3 levels—who agreed to participate in this prospective study had weekly serum samples collected until the 12th week of gestation for measurement of TSH, thyroglobulin, total T_4, FT_4, FT_3, estradiol, progesterone, hCG, and prolactin. Serum TSH was normalized with $L\text{-}T_4$ (50 μg/day) in women with SCH before infertility treatment and the establishment of pregnancy and was maintained until the 12th week of gestation. The control group comprised previously infertile pregnant women with normal thyroid function, defined as TSH levels ranging from 1 to 4 μIU/ml. This group took no medication other than folic acid and also had weekly serum samples taken during pregnancy until the 12th week of gestation.

RESULTS The study group comprised eight pregnant women with SCH taking $L\text{-}T_4$ and eight euthyroid controls in whom the clinical characteristics were not otherwise significantly different from those of the study group. The shortest interval between the beginning of treatment with $L\text{-}T_4$ and conception was 42 days and the longest was 3 years 10 months. Two women, one in each group, had a miscarriage at the 10th week of pregnancy. All the others delivered healthy children after uncomplicated pregnancies. Throughout the observation period, TSH levels remained higher among women with SCH taking $L\text{-}T_4$, as compared with euthyroid controls (Figure 1). Serum TSH levels in both groups increased during early pregnancy and reached peak levels at 6 weeks, with the most prominent differences occurring between study subjects and controls during weeks 6, ($P<0.06$) 7, ($P<0.03$) and 8 ($P<0.05$).) (Figure 1). Two of the eight patients diagnosed with SCH had TSH levels exceeding 4.5 μIU/ml during weeks 6 and 7 of their pregnancy. After week 7, serum TSH levels declined, reaching stable levels at week 9 and remaining parallel in the two groups thereafter (Figure 1). The amount of change in TSH, as compared with the TSH values at week 5, was comparable in the two study groups, except during week 12 when the drop in TSH was significantly greater in women with SCH as compared with the euthyroid group ($P<0.01$) (Figure 2).

Although the TSH levels were significantly higher among women with SCH as compared with euthyroid controls, the self-limited estrogen-induced increment of TSH during early pregnancy was

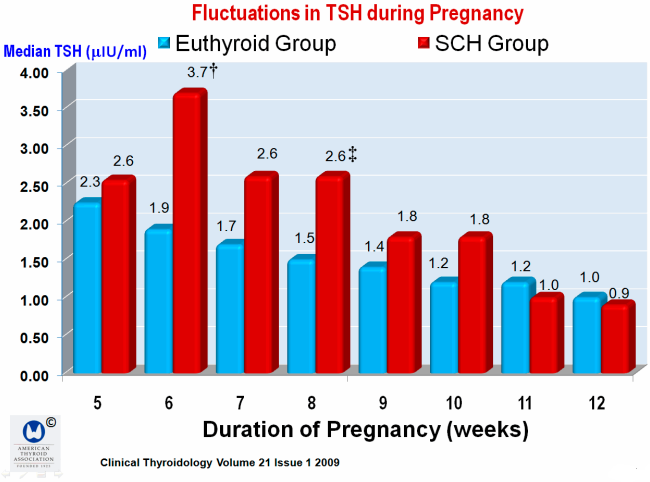

Figure 1. The fluctuations in TSH levels during pregnancy peak at month 6. *P<0.06. †P<0.006. ‡P <0.05. All P values are for comparisons of women with SCH and euthyroid controls. The figure was adapted from Figure 1a of De Geyter et al.

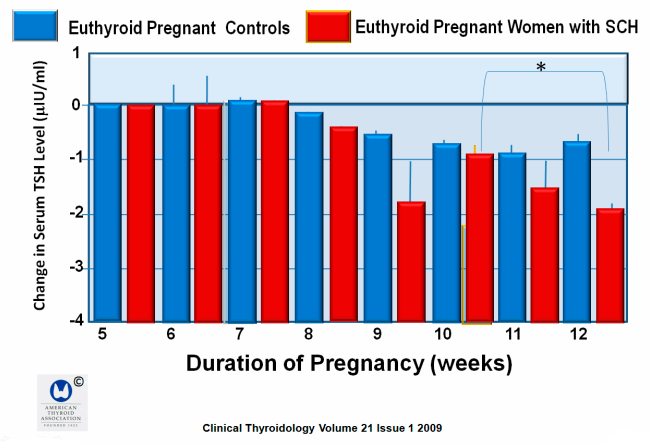

Figure 2. The TSH changes in months 5 to 12. TSH levels were calculated by subtracting the TSH level at week 5 in euthyroid controls and in women with subclinical hypothyroidism (SCH) taking $L\text{-}T_4$ (50μg). The height of each column represents the median value ±95%. The values were comparable in the two groups except during week 12 when the decline in the TSH was significantly greater in women with SCH compared with that in euthyroid women *P<0.01.

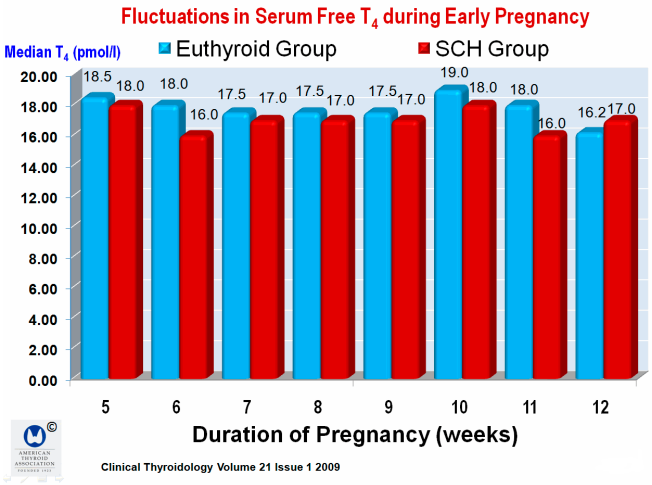

Figure 3. Fluctuations in Serum FT_4 in euthyroid and subclinically hyothyroid pregnant women Minor fluctuations in serum free T_4 and T_3 (T_3 not shown) occurred throughout pregnancy, without significant differences between euthyroid pregnant controls and women with SCH treated with L-T_4 during weeks 5 to 12 of gestation.

similar in the two groups. Serum hCG levels increased progressively during early pregnancy until week 9, remaining stable thereafter. In contrast, serum FT_4 and FT_3 remained unchanged throughout the sampling period both in women with SCH and in euthyroid controls (Figure 3). Prolactin levels increased in early pregnancy and continued to increase throughout pregnancy; however, by weeks 11 and 12 the levels were significantly lower in women with SCH treated with L-T_4 ($P<0.03$).

CONCLUSION The pattern of thyroid function during early pregnancy followed similar changes in euthyroid controls and women with SCH treated with 50 μg of L-T_4.

COMMENTARY

An evidence-based review by Stagnaro-Green confirmed that hypothyroidism and autoimmune thyroid disease in euthyroid women are associated with preterm delivery (1). This is of enormous concern, considering that preterm delivery, defined as birth occurring at or before 37 weeks of gestation, is the leading cause of perinatal fetal morbidity and mortality in the United States (2). Moreover, the rate of preterm delivery has been increasing significantly in the past two decades, rising from 8.8% of live births in 1989 to 10.2% in 1997, a relative increase of 15.6% (3), to about 12 to 13% in 2008 (2). Subclinical hypothyroidism, which appears to be an important component of this change, has been associated with miscarriage in both the first and second trimesters (1,4). A retrospective study by Casey et al. (5) found that among 17,298 pregnant women who presented for prenatal care to the University of Texas Southwestern Medical Center Parkland Hospital, 404 (2.3%) had SCH, a group whose pregnancies were 3 times as likely to be complicated by placental abruption (relative risk, 3.0) and an almost twofold rate of preterm birth (relative risk, 2.8). However, there is evidence that this might be avoided with L-T_4 therapy. Negro et al. (1) performed a prospective study in which 984 euthyroid women in the first trimester of pregnancy were screened for thyroid peroxidase antibodies (TPOAb). Of the 115 (12%) that were TPOAb-positive, 50% were treated with L-T_4 during pregnancy and 50% had no therapeutic intervention. The miscarriage rates were 3.5% in euthyroid woman who were TPOAb-negative and 2.4% (P = not statistically significant) in euthyroid women who were TPOAb-positive but were treated with L-T_4, as compared with a 22% miscarriage rate in women who were positive for TPOAb and were not treated with L-T_4 ($P< 0.01$). Maternal thyroid deficiency during pregnancy results in neuropsychological development in children (6), and there is evidence that low maternal serum FT_4 concentrations during early pregnancy are associated with impaired psychomotor development that is apparent in infancy and at least until the age of 3 years (7,8).

Thus, a number of studies implicate thyroid dysfunction in the form of overt or SCH, with or without autoimmune thyroid disease, in the high preterm delivery rates in the United States.

De Geyter et al. suggest that the clinical situations presented in their study are different from those observed with primary hypothyroidism, which are characterized by profound thyroid abnormalities that render the thyroid gland unresponsive to the compensatory stimulatory action of hCG. In their study, both SCH and ovarian hyperstimulation (a consequence of the infertility treatment) were associated with an intermediate rise then a decline in circulating TSH with normal FT_4 levels. The authors thus conclude that although both SCH and ovarian hyperstimulation were associated with an intermediate rise in circulating TSH, the pattern of thyroid function during early pregnancy followed changes similar to those observed in euthyroid controls. As a result, the authors believe that "…it is conceivable that the numerous reports on pregnancy-related complications observed in women with SCH, such as miscarriage and late obstetrical complications are not caused by hypothyroxinemia, but rather by additional contributing factors, such as age and antithyroid antibodies." However, it is difficult to reach this conclusion with any certainty as there were a limited number of subjects (n = 16) in the study, which was too small to reach appropriate statistical power. It is further limited by the supplementation of L-T_4 in women the group with SCH, which the authors suggest may have reduced possible differences between the two groups.

This study underscores how difficult it is to study thyroid function very early in pregnancy. This is undoubtedly an important contribution, but the interpretation of the data in terms of the pathophysiology of SCH in pregnancy is not immediately evident.

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