Treatment of Primary Hypothyroidism During Pregnancy: Is There an Increase in Thyroxine Dose Requirement in Pregnancy?

Inder J. Chopra and Khansa Baber

We studied the dose requirements of thyroxine (T_4) and serum concentrations of thyrotropin-stimulating hormone (TSH) and free T_4 in 16 pregnant women with primary hypothyroidism due to autoimmune thyroid disease (ATD, n = 11) or thyroidectomy (n = 5). All patients had been advised by their obstetricians to take prenatal vitamins enriched with iron (~90mg/tablet) and calcium (~200 mg/tablet), known to inhibit absorption of T_4. We asked patients to take their vitamins 4 hours after ingesting T_4 in the morning. The mean T_4 dose of 0.10 ± 0.01 (mean ± SEM, mg/d) during pregnancy did not differ significantly from that (0.09 ± 0.005) before or after (0.10 ± 0.01) pregnancy. Similarly, mean serum TSH of 2.7 ± 0.28 mIU/L during pregnancy did not differ significantly from that before (2.2 ± 0.47) or after (3.2 ± 1.31) pregnancy. The mean serum free T_4 concentration during pregnancy (16 ± 0.97 pmol/L) was significantly ($P < .05$) lower than that (22 ± 1.5) before or after (23 ± 2.2) pregnancy and similar to that observed with our free T_4 measurement technique in normal (healthy) pregnant women. We next examined the data separately in patients with ATD and thyroidectomy. The mean T_4 dose (0.08 ± 0.009) and TSH (2.4 ± 0.29) during pregnancy in 11 ATD patients did not differ appreciably from those before (T_4 dose, 0.08 ± 0.0006; TSH, 2.7 ± 0.54) or after (T_4 dose 0.09 ± 0.0063; TSH, 4.1 ± 1.91) pregnancy. Similarly, the mean T_4 dose (0.12 ± 0.022, n = 5) during pregnancy in thyroidectomized patients was similar to that before (0.12 ± 0.017, n = 3) or after (0.12 ± 0.022) pregnancy. However, serum TSH increased significantly, albeit within the normal range, during pregnancy in thyroidectomized patients (3.2 ± 0.62, n = 5 *v* 0.41 ± 0.017, n = 3, $P < .05$) and it (1.3 ± 0.60) decreased significantly ($P < .05$) after pregnancy. Our data suggest that (1) the dose requirement of T_4 does not change systematically in pregnancy in most hypothyroid women. There may occur a modest increase in T_4 dose requirement during pregnancy in some thyroidectomized patients; (2) diminished absorption of T_4, possibly related to ingestion of exogenous agents (eg, iron, calcium, vitamins), may have contributed to previous suggestions of substantial increased T_4 requirement in pregnancy; (3) ingestion of T_4 dose absorption-inhibiting agents some 4 hours away from T_4 markedly diminishes or obviates their effect in many patients. Although many hypothyroid patients may not require an adjustment in their T_4 dose during pregnancy, it is prudent to monitor all such patients carefully as the consequences of inadequate therapy may be very important.

HYPOTHYROIDISM occurs in about 6 per 1,000 pregnancies. It has been linked to a number of complications in the mother and the developing fetus.[1,2] The complications that correlate best with reduced thyroid status are pregnancy-induced hypertension and low birthweight.[1,2] Incorrect or inadequate treatment of maternal hypothyroidism has been shown associated with increased frequency of perinatal mortality and congenital and developmental anomalies.[3] There has been much debate about the management of pregnant women with hypothyroidism. Some investigators have recommended routinely increasing the dose of thyroxine (T_4) in treated hypothyroid women by 25% to 50% when pregnancy is first confirmed.[2] Others suggest some (unspecified) increases or no change in the requirement of T_4 in pregnant hypothyroid patients.[4-8]

It is customary in the United States to administer prenatal vitamins during pregnancy and unless advised otherwise, pregnant hypothyroid patients frequently take their T_4 and prenatal vitamins at nearly the same time of the day. Prenatal vitamins are highly enriched with iron and calcium, both of which are potent inhibitors of the absorption of T_4.[9,10] However, this information was not known until after the description of increased T_4 requirement in pregnancy.[5] It is possible that the increased requirement for T_4 observed in pregnant hypothyroid patients in many cases was related in part at least to iron/calcium-related reduced absorption of T_4. In this study, we specifically requested our patients to take their T_4 soon after awakening in the morning and to take their iron, calcium, magnesium, and/or vitamins not until several hours after ingestion of T_4; these various agents are known inhibitors of the absorption of T_4 from the gastrointestinal tract. Our studies have indeed shown that there is little or no change in T_4 dose requirement during pregnancy in most of hypothyroid patients.

MATERIALS AND METHODS

Since 1996, we studied prospectively 16 women (age 23 to 43 years) with primary hypothyroidism. They were all followed in the clinical practice of one of us (I.J.C.) at the University of California, Los Angeles (UCLA). The underlying etiology of hypothyroidism was chronic or Hashimoto's thyroiditis, 9 cases; treated Graves' disease, 3 cases (status post-treatment with antithyroid drugs, 2 cases; and thyroidectomy, 1 case); thyroid nodule(s) status after subtotal thyroidectomy, 2 cases; and thyroid cancer, status after total thyroidectomy, 2 cases.

The original diagnosis of hypothyroidism was based on clinical presentation, decreased free T_4 or free T_4 index, and/or elevated serum thyrotropin-stimulating hormone (TSH). Fourteen of 16 patients studied were hypothyroid prior to pregnancy and all but one of them were euthyroid on maintenance dose of L-thyroxine (T_4). One of the 14 who

From the Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, University of California, Los Angeles, Center for Health Sciences, Los Angeles, CA.

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Address reprint requests to Inder J. Chopra, MD, UCLA Center for Health Sciences, Division of Endocrinology, Diabetes and Hypertension, 900 Veteran Ave, Suite 24-130, Warren Hall, Los Angeles, California 90095-7073.

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Table 1. Mean T_4 Dose and Mean Serum Free T_4 and TSH Concentrations in Treated Hypothyroid Women Before, During, and After Pregnancy

		Before Pregnancy			During Pregnancy			After Pregnancy		
Group	Case No.	Mean T_4 Dose (mg/d)	Mean TSH (mIU/L)	Mean FT_4 (pmol/L)	Mean T_4 Dose (mg/d)	Mean TSH (mIU/L)	Mean FT_4 (pmol/L)	Mean T_4 Dose (mg/d)	Mean TSH (mIU/L)	Mean FT_4 (pmol/L)
I	1	0.088	2.3	23.0	0.088	1.9	15.0	0.088	1.4	23.0
	2	0.088	3.2	19.0	0.088	1.3	19.0	0.088	0.02	32.0
	3	0.075	2.3	13.0	0.075	2.0	18.0	0.075	5.8	15.0
	4	—	7.1	—	0.050	4.2	12.0	0.05	2.3	18.0
	5	0.088	0.4	14.0	0.088	1.0	17.0	0.067	1.6	14.0
	6	0.066	2.3	26.0	0.050	1.8	15.2	0.05	3.5	22.0
	7	—	—	—	0.12	4.7	14.1	0.12	3.3	25.0
	8	0.075	2.8	22.0	0.075	2.4	17.3	0.075	2.7	15.0
	9	0.083	1.3	24.0	0.075	0.89	12.4	—	—	—
	Mean	0.080	2.71	20.20	0.080	2.24	15.60	0.080	2.58	20.50
	SEM	0.004	0.77	2.13	0.008	0.48	0.81	0.008	0.61	2.15
II	10	0.05	1.3	30.8	0.058	3.3	9.7	0.1	20.5	18.0
	11	—	—	—	0.090	3.9	17	0.1	1.3	28.0
	Mean	—	—	—	0.074	3.6	13.3	0.093	10.9	23
	SEM	—	—	—	0.016	0.31	3.56	0.009	9.6	5.11
III	12	0.10	0.6	22.7	0.12	3.2	14.1	0.102	1.1	23.1
	13	0.10	3.1	21.1	0.12	3.1	14.1	0.11	3.9	21.8
	14	0.11	3.1	18.6	0.13	2.5	14.1	0.13	0.1	23.1
	15	0.112	0.45	28.6	0.116	3.3	17.4	0.108	0.08	24.4
	16	0.15	0.39	27	0.204	3	27	0.2	0.03	48.7
	Mean	0.11	1.53	23.6	0.138	3.02	17.3	0.13	1.04	28.2
	SEM	0.003	0.84	1.2	0.004	0.22	0	0.007	1.1	0.43
All patients	Mean	0.09	2.19*	22.3*	0.10	2.66	15.8	0.10	3.18	23.40
	SEM	0.005	0.47	1.47	0.01	0.28	0.97	0.01	1.31	2.22

Abbreviations: T_4, thyroxine; TSH, thyrotropin-stimulating hormone; FT_4, free T_4.

*Normal range: TSH, 0.3 to 4.7 mIU/L; FT_4, 9 to 29 pmol/L.

were hypothyroid prior to pregnancy was taking only herbal preparations in a hope of a "natural" cure of her hypothyroidism (case no. 4, Table 1). She started taking T_4 therapy immediately after the diagnosis of pregnancy. The remaining 2 patients studied became hypothyroid after they had total thyroidectomy during the second trimester of pregnancy. One of these had developed propylthiouracil-induced agranulocytosis (case no. 10) and the other had surgery for a Hurthle cell neoplasm (case no. 7).

All patients had been advised by their obstetrician to take during pregnancy prenatal vitamin tablets enriched with iron, calcium, and folate (each tablet contained about 90 mg elemental iron and 200 mg elemental calcium). We asked patients to take their T_4 on an empty stomach early in the morning and to take their vitamins approximately 4 hours after ingestion of T_4. This was done prior to pregnancy and it was further discussed and reinforced at the first visit after the diagnosis of pregnancy. Besides vitamins, patients were not taking any drugs known to alter thyroid function. All patients delivered normal full-term babies.

Patients were studied at 2- to 3-month intervals during and at 3- to 4-month intervals before and after pregnancy. Two or more data points were available for each period study (vide infra). The dose of T_4 was adjusted when serum TSH was 4.8 mU/L or higher (normal range, 0.3 to 4.7 mU/L). Whenever possible, we have compared T_4 doses during pregnancy with those required in the 9 months prior to pregnancy and/or the 9 months after the delivery. This could be done in 11 of 16 cases. In 2 cases, postpartum observation was for 1.3 and 3 months. The remaining 3 cases started T_4 treatment during pregnancy (vide supra) and in them, we have compared the T_4 dose during pregnancy with that required in 3 to 6 months after delivery. We have examined the mean T_4 dose, the mean serum free T_4, and the mean serum TSH values prepartum, in each of 3 trimesters of pregnancy and postpartum. The study was approved by the Institutional Review Board (IRB) at UCLA.

Methods

Serum T_4, triiodothyronine (T_3), free T_4 index, free T_4 by dialysis, free T_3 by dialysis TSH, and antithyroid antibodies were measured by respective assays at the Clinical Laboratories of the UCLA Medical Center. Serum TSH was measured using a second generation 2-site immunoradiometric assay.

Statistical Analyses

Data are expressed as mean ± SEM. Changes in serum free T_4 and TSH values during and after pregnancy were examined using paired *t* test. Student's *t* test for unpaired data was used to compare mean T_4 doses among groups of patients. Analysis of variance (ANOVA) by repeated measures was also used to compare data among groups.

RESULTS

The mean age of 16 patients studied was 38.5 years (range, 31 to 43) and the mean duration of hypothyroidism at the beginning of pregnancy was 2.9 years (range, 0.16 to 7.0, n = 14). Thirteen of 16 patients were receiving maintenance dose of T_4 before pregnancy (Table 1). Three patients (no. 4, 7, and 10,

Table 2. Changes in Mean T_4 Dose, Mean Serum TSH, and Mean Serum Free T_4 ConcentrationDuring and After Pregnancy in T_4-Treated Hypothyroid Women

		Change During Pregnancy			Change After Pregnancy		
Group	Patient No.	Mean T_4 Dose (mg/d)	Mean TSH (mIU/L)	Mean FT_4 (pmol/L)	Mean T_4 Dose (mg/d)	Mean TSH (mIU/L)	Mean FT_4 (mol/L)
I	1	0	−0.4	−7.7	0	−0.54	8.2
	2	0	−1.9	−0.64	0	−1.3	14.2
	3	0	−0.27	5.1	0	3.8	−2.6
	4	—	—	—	0	−1.8	6.4
	5	0	0.6	2.8	−0.021	0.56	−2.8
	6	−0.016	−0.52	−10.4	0	1.72	6.6
	7	—	—	—	−0.002	−1.5	11.2
	8	0	−0.39	−4.6	0	0.29	−1.9
	9	−0.008	−0.38	−11.92	—	—	—
	Mean	−0.003	−0.47	−3.91	−0.003	0.15	4.91
	SEM	0.003	0.28	2.48	0.003	0.67	2.33
II	10	−0.008	2.1	−21.1	0.027	17.2	8.2
	11	—	—	—	0.013	−2.6	11.5
	Mean	—	—	—	0.02	7.3	9.85*
	SEM	—	—	—	0.007	4	1.65
III	12	0.019	2.6	−8.6	−0.017	−2.1	9.0
	13	0.021	−0.02	−7.1	−0.008	0.75	7.7
	14	0.022	−0.6	−4.5	−0.004	−2.4	9.0
	15	0.004	2.83	−11.7	−0.008	−3.2	6.97
	16	0.054	2.58	0	−0.004	−2.9	21.7
	Mean	0.024*	1.48	−6.38*	−0.0082	−1.97	10.9*
	SEM	0.009	0.74	1.97	0.004	0.71	2.73
All patients	Mean	0.01	0.48	−6.18*	0.00	0.40	7.56*
	SEM	0.005	0.43	1.96	0.0025	1.302	1.66

*$P < .05$.

Table 1) started T_4 treatment during pregnancy. Patient no. 4 tried iodine-rich kelp and herbs to heal herself until she was pregnant. Patient no. 7 was diagnosed with Hurthle cell neoplasm in the second trimester of pregnancy and total thyroidectomy was performed at 22 weeks of gestation. Patient no. 10 was on propylthiouracil treatment for Graves' hyperthyroidism, but it had to be stopped because of agranulocytosis; she underwent thyroidectomy near the end of the second trimester of pregnancy.

Table 1 lists the data on thyroid function tests and T_4 dose before, during, and after pregnancy. Based on changes in their T_4 dose, patients were grouped in 3 groups. Group I consisted of 9 patients (9/16, 56.3%), who required no change in their dosage of T_4 during pregnancy. They did not demonstrate a significant change in the serum free T_4, serum TSH, or T_4 dose during pregnancy (Tables 1 and 2). Serum TSH and free T_4 were normal before, during, and after pregnancy in 7 of 9 patients in group I. One patient (case no. 2, group I) showed no increase in her T_4 dose during pregnancy but her serum TSH was suppressed (0.02 mIU/L) and free T_4 was elevated postpartum on the same T_4 dose (0.08 mg/d); she thus required a reduced T_4 dose postpartum than before or during pregnancy. Another patient (case no. 3, Table 1) demonstrated elevated serum TSH (5.8 mIU/L) and normal serum free T_4 levels postpartum while taking 0.075 mg of T_4 daily; her serum TSH and free T_4 were normal both before and during pregnancy on the same dose (0.075 mg/d) of T_4. She thus needed more T_4 postpartum than before or after pregnancy. Group II consisted of 2 women (2/16, 12.5%) in whom T_4 dose increased during pregnancy and remained increased or increased further during the postpartum period. The remaining 5 patients were in group III (5/16, 31.2%); these patients required some increase in their T_4 dose during pregnancy but the dose was decreased postpartum to or towards prepartum levels. The mean increase in T_4 dose during pregnancy in these 5 patients was 20% (20 μg/d; range, 4% to 36%, 4 to 54 μg/d, $P < .05$). The T_4 mean dose decreased 4% to 14% (mean, 7%) after delivery in these patients (Table 2). Three patients in group III (cases no. 14 to 16, Table 1) had suppressed TSH (<0.1 MIU/L) postpartum when the dose of T_4 was not yet sufficiently decreased. The mean serum TSH decreased and the mean serum free T_4 increased significantly ($P < .05$) postpartum in group III patients. When data in all patients were examined together, the mean serum TSH and mean T_4 dose during pregnancy did not differ significantly from the corresponding prepartum or postpartum values (Tables 1 and 2). However, the mean serum free T_4 by dialysis decreased significantly during pregnancy and increased postpartum to levels comparable to prepartum levels (Tables 1 and 2).

We next classified our patients according to the etiology of their hypothyroidism, ie, autoimmune thyroid disease (ATD, 11 cases) or thyroid ablation (thyroidectomy, 5 cases). Tables 3 and 4 show mean T_4 dose, mean serum TSH, and mean serum free T_4 values in these 2 groups. Patients in whom hypothy-

Table 3. Mean T_4 Dose and Serum Free T_4 and TSH Concentrations Before, During, and After Pregnancy in T_4-Treated Hypothyroid Women With Differing Etiologies of Hypothyroidism

		Before Pregnancy			During Pregnancy			After Pregnancy		
Etiology of Hypothyroidism	Patient No.	Mean T_4 (mg/d)	Mean TSH (mIU/L)	Mean FT_4 (pmol/L)	Mean T_4 (mg/d)	Mean TSH (mIU/L)	Mean FT_4 (pmol/L)	Mean T_4 (mg/d)	Mean TSH (mIU/L)	Mean FT_4 pmol/L
Group (ATD)	1	0.088	2.3	23.0	0.088	1.9	15.0	0.088	1.4	23.0
	2	0.088	3.2	19.0	0.088	1.3	19.0	0.088	0.02	32.0
	3	0.075	2.3	13.0	0.075	2	18.0	0.075	5.8	15.0
	4	—	7.1	—	0.050	4.2	12.0	0.05	2.3	18.0
	6	0.066	2.3	26.0	0.050	1.8	15.2	0.05	3.5	22.0
	8	0.075	2.8	22.0	0.075	2.4	17.3	0.075	2.7	15.0
	9	0.083	1.3	24.4	0.075	0.89	12.4	—	—	—
	10	0.05	1.3	30.8	0.058	3.3	9.7	0.085	20.5	18.0
	12	0.1	0.6	22.7	0.120	3.2	14.1	0.102	1.1	23.1
	13	0.1	3.1	21.1	0.120	3.1	14.1	0.11	3.9	21.8
	14	0.11	3.1	18.6	0.130	2.5	14.1	0.13	0.1	23.1
	Mean	0.08	2.67	22.10	0.080	2.42	14.60	0.09	4.13	21.1
	SEM	0.0006	0.51	1.5	0.009	0.29	0.83	0.0063	1.91	1.58
Group B (thyroidectomy)	5	0.088	0.4	14.0	0.088	1	17.0	0.067	1.6	14.0
	7	—	—	—	0.12	4.7	14.1	0.12	3.3	25.0
	11	—	—	—	0.09	3.9	17.0	0.1	1.3	28.0
	15	0.112	0.45	28.6	0.116	3.28	17.4	0.108	0.075	24.4
	16	0.15	0.39	27.0	0.204	2.97	27.0	0.2	0.03	48.7
	Mean	0.12	0.41	23.2	0.12	3.17	18.5	0.12	1.26	28.0
	SEM	0.017	0.017	4.63	0.022	0.62	2.2	0.022	0.60	5.67

Abbreviation: ATD, autoimmune thyroid disease.
*$P < .05$.

Table 4. Changes in Mean T_4 Dose, Mean Serum TSH, and Mean Free T_4 Concentrations During and After Pregnancy in T_4-Treated Hypothyroid Women With Different Etiologies of Hypothyroidism

		Change During Pregnancy			Change After Pregnan		
Etiology of Hypothyroidism	Patient No.	Mean T_4 Dose (mg/d)	Mean TSH (mIU/L)	Mean FT_4 (pmol/L)	Mean T_4 Dose (mg/d)	Mean TSH (mIU/L)	Mean FT_4 (pmol/L)
Group A (ATD)	1	0	−0.40	−7.7	0	−0.54	8.2
	2	0	−1.9	−0.64	0	−1.3	14.2
	3	0	−0.27	5.1	0	3.8	−2.6
	4	—	—	—	0	−1.8	6.4
	6	−0.016	−0.52	−10.4	0	1.7	6.6
	8	0	−0.39	−4.6	0	0.29	−1.9
	9	−0.008	−0.38	−11.9	—	—	—
	10	−0.008	2.1	−21.1	0.027	17.2	8.2
	12	0.019	2.6	−8.6	−0.017	−2.1	9
	13	0.021	−0.02	−7.1	−0.008	0.75	7.7
	14	0.022	−0.6	−4.5	−0.004	−2.4	9
	Mean	0.00	0.02	−7.15*	0.00	1.60	6.48*
	SEM	0.003	0.42	2.2	0.003	1.8	1.61
Group B (thyroidectomy)	5	0	0.6	2.8	−0.021	0.56	−2.8
	7	—	—	—	−0.002	−1.5	11.2
	11	—	—	—	0.013	−2.6	11.5
	15	0.004	2.8	−11.7	−0.008	−3.2	6.97
	16	0.054	2.6	0	−0.004	−2.9	21.7
	Mean	0.02	2.00*	−2.97	0.00	−1.94*	9.71*
	SEM	0.017	0.71	4.45	0.004	0.69	3.95

*$P < .05$

roidism was due to ATD demonstrated no appreciable change in mean T_4 dose or mean serum TSH during pregnancy or postpartum (group A, Table 3). Similarly, the mean T_4 dose during pregnancy in patients who had thyroidectomy (group B, Table 3) was not statistically significantly different from that before or after pregnancy, but there were moderate increases in serum TSH values, within the normal range ($P < .05$), during pregnancy that decreased postpartum ($P < .05$) without a change in mean T_4 dose. Serum TSH was suppressed postpartum in 2 cases (no. 15 and 16, Tables 3 and 4). The mean serum free T_4 decreased or showed a tendency towards decrease during pregnancy and it increased to or towards prepartum values following delivery (Tables 3 and 4).

DISCUSSION

Several changes in thyroid physiology during pregnancy may impact on the availability of thyroid hormone to the mother and the fetus. Thus, there is an increase in serum concentration of thyroxine-binding globulin (TBG), which is associated with an increase in serum concentration of total T_4 and T_3. The studies have shown that this increase in serum TBG levels in pregnancy is a result of estrogen-induced increase in glycosylation of TBG that decreases its metabolic clearance.[11] Serum concentration of free T_4 and free T_3 levels have been measured in pregnancy by a variety of techniques and both normal and low high levels have been reported in term pregnancy.[12-14] We have had a substantial experience with measurement of free T_4 and free T_3 concentrations directly by radioimmunoassay following equilibrium dialysis. Using this technique, which we employed in the current study, free T_4 and T_3 concentrations are low normal in term pregnancy and other high TBG states and this decrease is not associated with any change in serum TSH, which remains clearly normal.[15,16] However, the situation may be different in the first trimester of pregnancy. Thus, several studies[14,17] have shown an increase in serum free T_4 concentration or free T_4 index at this time. Furthermore, Glinoer et al[17] showed that the increase in serum free T_4 concentration was associated with a decrease in serum TSH concentration transiently in the first trimester of normal pregnancy and suggested that these changes result from weak thyroid-stimulating effect of high serum human chorionic gonadotropin (HCG) levels in the first trimester of pregnancy. However, Liberman et al[14] observed moderate elevation of free T_4 index in the first trimester of pregnancy without suppression of serum TSH.[14] Thus, the contribution of high HCG levels to daily production rates of T_4 in pregnancy is probably minimal. This view is supported by studies demonstrating no appreciable change in circulating iodine concentrations during pregnancy[14] and those indicating that, when measured directly, T_4 production (turnover) rates is normal both early and late in pregnancy[18,19].

Pregnancy is also associated with substantial changes in thyroid hormone metabolism. Thus, placenta is enriched with an enzyme, the type 3 iodothyronine monodeiodinase (D3), which metabolizes T_4 and T_3 to reverse T_3 (rT_3) and 3, 3′-diiodothyronine (T_2), respectively, which have negligible TSH-suppressive or calorigenic activity.[20-22] The high D3 enzyme activity may enhance thyroid hormone metabolism and may thus increase the need for T_4 during pregnancy. However, data showing that metabolic clearance rate of T_4 is decreased and T_4 production (turnover) rate remains normal in pregnancy suggest that the net effect of the placental type 3 iodothyronine monodeiodinase is probably minimal in human pregnancy. Alternatively, it is possible that its effect is counterbalanced by that of high serum TBG decreasing free T_4 and/or metabolic clearance of T4.

In this study, we observed that as a group, our 16 pregnant treated hypothyroid women did not demonstrate a significant change in their T_4 dose during or after the pregnancy. Their mean serum TSH levels during or after pregnancy were similar to that before pregnancy. These data are consistent with those demonstrating normal daily production rates of T_4 during pregnancy[18,19] and those suggesting little or no change in T_4 requirement in pregnancy in a majority of T_4-treated hypothyroid women.[4,8] Several other studies, however, have shown a significant increase in T_4 dose requirement in pregnancy in T_4-treated hypothyroid women.[5-7] The basis for the differences in the results of these studies is not known but treatment with agents that inhibit absorption of T_4 and the timing of their administration may be important factors. In our study, we had requested patients to take their iron and calcium rich prenatal vitamins about 4 hours after ingestion of T_4. These agents are recommended to pregnant subjects routinely in our area and they are known inhibitors of T_4 absorption.[9,10] It is not known whether these agents were administered to patients in previous studies or whether the timing of their administration was adjusted to avoid interference with absorption of T_4. However, it is unlikely that these precautions were undertaken in previous studies, as they were all conducted and published[4-8] prior to the description of the effect of iron or calcium in reducing gastrointestinal absorption of T_4.[9,10] Our study is apparently the first one to make a systematic attempt to limit the effect of iron/calcium-rich prenatal vitamins on T_4 dose requirement of hypothyroid pregnant women.

Although the case could not be made for increased need for T_4 in pregnancy in a majority of our patients (11/16, 69%, groups I and II, Table 1), there were some (5/16, 31%) who did have their dose of T_4 increased during pregnancy and it decreased partially postpartum towards their prenatal T_4 dose. The basis for this observation is unclear but a number of factors may have contributed to it. Thus, (1) these patients may need more than the scheduled 4 hours of separation of prenatal vitamins from the dose of T_4; (2) patients may have ingested other unspecified agents, eg, soy products or fiber products that inhibit absorption of T_4; (3) T_4-binding agents may enhance fecal excretion of T_4 and interfere in its enterohepatic circulation. Enterohepatic circulation of T_4 is a process that plays a significant role in distribution and disposal of T_4[23,24]; (4) the gravid uterus may affect a variable alteration in absorption/distribution of T_4; (5) in some patients, there was postpartum exacerbation of thyroiditis and associated increased release of T_4[25];and (6) a combination of these factors may be involved.

It has been suggested that pregnancy-associated increased T_4 dose requirement is more marked in athyreotic patients than in patients in whom hypothyroidism is a result of autoimmune

thyroid disease.[2,7] Our data provided some, albeit modest, support for this suggestion. Thus, whereas we found no change in T_4 dose requirement in pregnant patients in whom hypothyroidism was a result of autoimmune thyroid disease, there was a modest (c.f. postpartum dose, 7%; range, 2% to 24%; 2 to 21 μg/d) increase in T_4 dose during pregnancy in 4 thyroidectomized patients (Table 4). However, the remaining thyroidectomized patient required a 14% more T_4 postpartum than during pregnancy (Tables 3 and 4). Serum TSH also increased modestly, within the normal range, during pregnancy in thyroidectomized patients. Overall, the mean reduction in T_4 dose requirement postpartum of 4% was not statistically significant. Others have also noted no change, increase or decrease in T_4 dose requirement in pregnant hypothyroid patients.[4,8] Thus, it is possible that these variable findings reflect random time-to-time variations in T_4 dose requirements that may occur in any group of hypothyroid patients. Overall, our data suggested that mean T_4 requirement does not change appreciably either in thyroidectomized patients or in those with autoimmune thyroid disease (Tables 3 and 4). We did observe, however, that thyroidectomized patients required more T_4 (0.12 ± 0.017 mg/d) than those with autoimmune thyroid disease (0.08 ± 0.0006 mg/d) (Table 3). Since a majority of our study subjects had some residual thyroid gland, which may speculatively be considered to increase thyroid hormone production even without an observed increase in serum TSH, a definitive study of the subject examined would perhaps be the one done on a homogeneous group of T_4-treated athyreotic patients.

Serum free T_4 decreased or had a tendency to decrease during pregnancy in nearly all groups of patients and it increased after delivery to or towards prenatal values. Using free T_4 by equilibrium dialysis and radioimmunoassay as the method for free T_4 measurement, we and others have observed similar reduction in free T_4 during pregnancy in normal subjects and other high TBG states.[12-17] However, individual serum free T_4 levels remained in the normal range in these and the present studies, and they were not accompanied by an increase in serum TSH concentration, which would have been the case if the observed decrease in serum free T4 concentrations had implied hypothyroidism rather than a high TBG state.

Some investigators have recommended increasing T_4 dose in hypothyroid pregnant women by 25% to 50% when pregnancy is first confirmed.[2] This was recommended because of observed increase in T_4 requirement by about 45 μg/d in some studies.[2,5,7] Our studies do not favor this recommendation. We feel that the key recommendation should indicate that patients take their prenatal vitamins and any additional calcium or iron 4 hours or more away from their T_4 dose. It seems that 4 hours is a sufficient time for T_4 to be absorbed in bloodstream and that administration of potential T_4-binding agents at that time has little influence on the efficacy of T_4 in most patients. We feel that it is prudent to measure serum TSH and free T_4 concentrations during pregnancy and for a few months postpartum at about 2-month intervals to ensure their maintenance in a euthyroid state. This recommendation is similar to those of evaluations recommended previously at 6 to 8 weeks[2,5] or at 6 weeks and 6 months of pregnancy[7] and is prudent since maintenance of euthyroid status in the mother is important to the well-being of both the mother and the fetus.[3,12,13,26]

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