

Thyroid Function Inside and Outside of Pregnancy: What Do We Know and What Don't We Know?

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A workshop entitled, "The Impact of Maternal Thyroid Diseases on the Developing Fetus: Implications for Diagnosis, Treatment, and Screening," was held in Atlanta, Georgia, January 12–13, 2004. This paper reports on the session that examined the prevalence of thyroid dysfunction in reproductive-age women and the factors associated with abnormal function. For this session the following papers were presented: "Thyroidal Economy in the Pregnant State: An Overview," "The Prevalence of Thyroid Dysfunction in Reproductive-Age Women—United States," and "Risk Factors for Thyroid Disease: Autoimmunity and Other Conditions." These presentations were formally discussed by invited respondents and by others in attendance. Salient points from this session about which there was agreement include the following: physiologic changes associated with pregnancy require an increased availability of thyroid hormones by 40% to 100% in order to meet the needs of mother and fetus during pregnancy. In the first trimester of gestation the fetus is wholly dependent on thyroxine from the mother for normal neurologic development. For the maternal thyroid gland to meet the demands of pregnancy it must be present, disease-free, and capable of responding with adequate stores of iodine. Thyroid autoimmunity is common and may contribute to miscarriages, as well as to hypothyroidism. With sufficient iodine nutrition, autoimmune thyroid disease (AITD) is the most common cause of hypothyroidism. As of 1994, iodine nutrition in the United States appeared to be adequate, but its continued monitoring is essential.

Introduction

THIS REPORT, the third of six reports in this issue of *Thyroid*, contains the summaries of several papers presented to a workshop held in Atlanta, Georgia, January 12–13, 2004, to address "The Impact of Maternal Thyroid Diseases on the Developing Fetus: Implications for Diagnosis, Treatment, and Screening." The workshop was sponsored jointly by the National Center on Birth Defects and Developmental Disabilities of the Centers for Disease Control and Prevention (CDC) and the American Thyroid Association, with support from CDC's National Center for Environmental Health. The purpose of this individual session was to examine the prevalence of thyroid dysfunction in reproductive age women and the factors associated with abnormal function. This session, titled "Thyroid Function Outside and During Pregnancy: What is Normal and What is Not?," was moderated by Dr. Gregory Brent. Presentations were provided by Drs. Glinoyer, Hollowell, and Smallridge, followed by invited discussions

by Drs. Reed Larsen and Alex Stagnaro-Green. Subsequent to the workshop, the authors identified salient points from their session about which there was agreement, and identified areas for which information was lacking or incomplete. The statements ending this session reflect the views of the presenters. The conclusions drawn by all of the workshop participants appear elsewhere in this journal as a summary of working group discussions.

"Thyroidal Economy in the Pregnant State: An Overview"—Dr. Daniel Glinoyer

This workshop addressed in detail what is known about maternal thyroid dysfunction and its effects on both the mother and the fetus. It is important first, however, to review normal maternal thyroid physiology as it transitions into and progresses through pregnancy. Not only are there major endogenous changes, but nutrition (especially iodine status) also contributes significantly to the health of the preg-

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The opinions and findings in this article are those of the authors and should not be construed as official policies or positions of the Centers for Disease Control and Prevention or the U.S. Department of Health and Human Services.

nant woman and her unborn child. This presentation also sets the stage for subsequent speakers by providing an overview of the etiology and incidence of maternal thyroid disorders.

At the outset of pregnancy, the preconception steady state of thyroid physiology is altered by five factors that increase the requirement for thyroxine (T₄) and the activity of the thyroid gland to produce more T₄. These factors include: (1) An increase in estrogen (E₂), which modifies the concentration of thyroid binding globulin (TBG) when E₂ reaches a level of approximately 500–1000 pg/mL; (2) a twofold to threefold increase of TBG from 250 to 740 nmol/L during the first half of gestation, which changes equilibrium of bound to free T₄, with the potential of decreasing free T₄; (3) increased human chorionic gonadotropin (hCG), produced by the placenta, which peaks at 8 to 10 weeks reaching 50,000–75,000 IU/L, and has a direct but transient stimulation effect on the thyrocytes (1); (4) the increasing need for iodine because of enhanced renal clearance, the iodine needs of the fetus, and increased thyroid hormone production (2–4); and (5) iodothyronine deiodinases, which alter the metabolism, distribution, and availability of T₄ during pregnancy for both mother and fetus (5) (Fig. 1).

In order to maintain normal levels of free T₄ needed by mother and fetus, the supply or production of T₄ must increase by approximately 50% above the preconception levels. This requires adequate iodine nutrition in mothers and normal functioning of the thyroid gland and of the other homeostatic mechanisms listed above. If there are insufficient preconception iodine stores or inadequate iodine nutrition in early pregnancy, iodine balance may become negative and may not be fully restored during the remainder of pregnancy even with iodine supplementation later (6). Therefore, in pregnancy it is important to establish that iodine nutrition is sufficient (7) (Fig. 2) and that other factors such as hypothyroidism or the treatment of hyperthyroidism

do not interfere with the required increase in thyroid hormone supply (8).

Worldwide, hyperthyroidism caused by Graves' disease is relatively uncommon in pregnancy, occurring in 1 to 2 in 1000 pregnancies. Hypothyroidism and thyroid insufficiency is evident by the 1% to 2% of pregnant women who already receive levothyroxine (LT₄), the 5% to 8% of pregnant women who have positive thyroid autoantibodies, the 2% to 3% of apparently healthy pregnant women who have elevated thyrotropin (TSH), and the 40% to 70% of pregnant women with elevated TSH and/or low-normal free T₄ who have thyroid autoantibodies. When iodine status is adequate, the most common cause of thyroid deficiency is autoimmune thyroid disease (AITD) (9,10).

Discussant: Dr. P. Reed Larsen reemphasized the importance of the increased thyroid hormone requirements during normal pregnancy. From the available data for the incidence of hypothyroidism during pregnancy in the United States (11), clinical hypothyroidism would affect as many as 16,000 of the 4 million pregnancies each year. If subclinical hypothyroidism were considered a risk, 72,000 pregnancies could be affected. Based on studies done in the early 1990s of women who were diagnosed with and treated for hypothyroidism before pregnancy, the magnitude of the increase in levothyroxine requirements is approximately 40% to 50% in athyreotic patients and about 20% to 30% for patients with Hashimoto's disease who can retain a certain functional reserve. The time at which the elevation in TSH first appears has not been precisely determined. Based on the studies of Mandel et al. (12), and Kaplan (13), an increase in TSH was documented in 25% of individuals in the first trimester and 37% in the second trimester. Preliminary data from a prospective study by Alexander et al. (14) at our institution suggests that the increased TSH, reflecting an increased LT₄ requirement, most often occurs during the first trimester. This is important since the first trimester is the

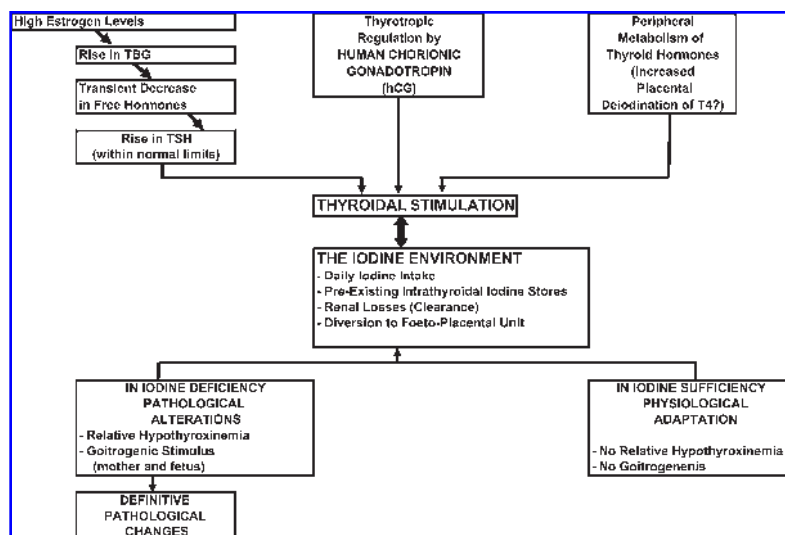


FIG. 1. From physiologic adaptation to pathologic alterations of the thyroidal economy during pregnancy. The figure illustrates the sequence of events occurring for the maternal thyroid gland, emphasizing the role of iodine deficiency to enhance the stimulation of the thyroidal machinery. (Adapted from Glinioer 1997 [1]).

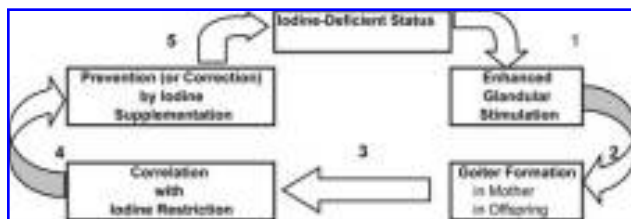


FIG. 2. The regulation of thyroid function in pregnant women with a restricted or deficient iodine intake, illustrating schematically the formation steps of a vicious circle, unless iodine supplementation is provided to avoid enhanced glandular stimulation. (Adapted from Glinioer 2001 [2]).

time when the fetus is wholly dependent on the maternal circulation for thyroid hormone.

“The Prevalence of Thyroid Dysfunction in Reproductive-Age Women—United States” —Dr. Joseph Hollowell

There are few thyroid studies focused on the young adult population. Overall the prevalence of hypothyroidism in the United States is not appreciably different from that mentioned earlier, namely, overt hypothyroidism is seen in about 0.3% to 0.7% of women of reproductive age and subclinical hypothyroidism in approximately 2.5%. Studies of pregnant populations in Maine on two occasions, by Klein et al. (15) in 1991 and by Allan et al. (11) in 2000 both using TSH 6.0 mU/L or more at 15 to 18 weeks' gestation as the indicator of hypothyroidism show a rate of 2.5% and 2.2%, respectively. Both studies showed that women with elevated TSH had chronic autoimmune thyroiditis as the main cause for the hypothyroidism.

A review of the NHANES III data for thyroid function showed that 2.5% of women age 15 to 44 years had TSH greater than 4.5 mIU/L. In this relatively younger age group, women 31 to 44 years of age had a higher rate of elevated TSH (3.5%) than women 15 to 30 years of age (1.5%). When antibodies were absent, the percent of women with elevated TSH was reduced. In the absence of antibodies, TSH was elevated in 1.0% of women 31 to 44 years of age and 0.6% of women 15 to 30 years of age. Of women with TSH greater than 4.5, 73% had positive thyroid peroxidase antibodies [TPOAb] and 46% had positive thyroglobulin antibodies [TgAb]. Of those with either one or both antibodies positive, 12.1% had elevated TSH.

There has been disagreement on whether iodine deficiency is an important contributor to thyroid insufficiency in the United States. The median urine iodine concentration in the United States decreased more than 50% from 320 $\mu\text{g/L}$ in 1971–1974 to 145 $\mu\text{g/L}$ in 1988–1994. When adjusted for creatinine excretion, the reduction was from 293 $\mu\text{g/g}$ creatinine in 1971–1974 to 125 in 1988–1994. Of the population, 11.7% had urinary iodine (UI) less than 50 $\mu\text{g/L}$. When adjusted for creatinine excretion, 7.5% had iodine less than 50 $\mu\text{g/g}$ creatinine (16). There was concern that this represented a continuing downward trend, but in 2000 the median UI was 161 $\mu\text{g/L}$ (17), slightly greater than that of 1988–1994, indicating that the decrease since 1971–1974 has not continued (Fig. 3). It is thought that the changes between 1971–1974

and 1988–1994 were the result of regulatory and educational efforts of the U.S. Department of Agriculture and the Food and Drug Administration on the uses of iodine in bread and for dairy sanitation. The urinary iodine concentrations in the U.S. population were within the definitions described by the World Health Organization (WHO) as showing adequate iodine nutrition for a population (18).

Some thyroidologists have been concerned that the 14.9% of U.S. women of reproductive age who had UI concentrations below 50 $\mu\text{g/L}$ may be at risk of iodine deficiency. When urine iodine concentration is corrected for creatinine concentration, the fraction less than 50 $\mu\text{g/g}$ creatinine is 8.2% of women 15 to 44 years of age. Adjusting iodine excretion by creatinine excretion corrects for changes in water clearance and lean body mass and has been shown to more likely represent the 24-hour excretion of iodine in a random spot urine sample than UI unadjusted for creatinine excretion (19). In a population with adequate nutrition it may be inappropriate not to adjust for creatinine excretion. NHANES provides a U.S. population survey and is not designed to make clinical or individual conclusions. Using the 1994 WHO definitions for iodine deficiency in a country, the U.S. population as a whole does not appear to be deficient in iodine.

In discussion: Dr. Gabriela Morreale de Escobar reported that most European women with inadequate iodine intake before pregnancy cannot compensate for double the need in pregnancy and that U.S. complacency about this is misguided. She believes that the NHANES III survey of urinary iodine percentiles, among all women of childbearing age, indicated that approximately 18% could be entering the danger range of iodine insufficiency. But of the group

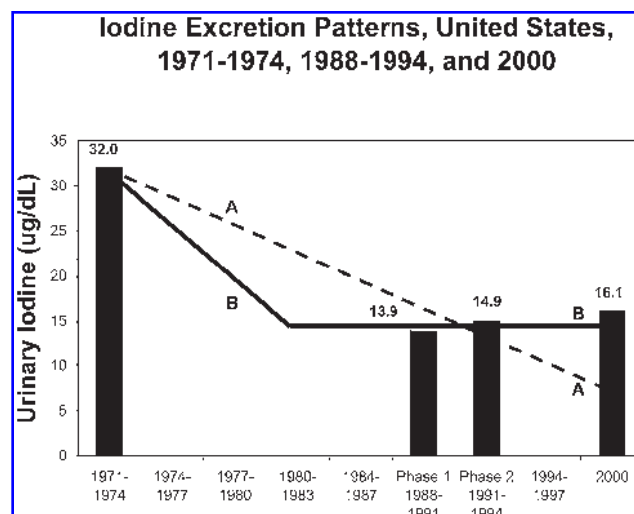


FIG. 3. The urinary iodine (UI) concentration in the United States population decreased from 1971–1974 (NHANES I) to 1988–1994 (NHANES III) (16). Within NHANES III, there was no difference between the median values of the first phase (1988–1991) and the second phase (1991–1994). A later survey from 2001, which had fewer samples for one year only shows the iodine nutrition for the U.S. population (UI median, 16.1 $\mu\text{g/dL}$) (17) not to be lower and possibly to be higher than in 1988–1994 (B). The data from 1988–1994 created the concern of a continuing trend (A), which has not materialized.

of pregnant women studied, approximately 25% had urinary iodine compatible with an iodine intake of less than 50% of the recommended dose in pregnancy. This supports routinely adding iodine to prenatal vitamin/mineral preparations such as those used for folic acid supplementation.

Comments: Dr. John T. Dunn,^a Executive Director of the International Council for the Control of Iodine Deficiency Disorders, emphasized the point that the most common cause of hypothyroidism in both the developed and undeveloped world is iodine deficiency. Even in the United States it may be of concern. Dr. Dunn felt that a compelling case could be made for every pregnant woman having supplemental iodine at 150 $\mu\text{g}/\text{d}$. Iodized salt probably cannot raise the levels sufficiently; because salt is restricted in pregnancy and raising the table salt iodine levels may create problems for the other 95% of the population.

Dr. Dunn proposed the following statement (for a group including himself, Drs. Francois Delange [ICCIDD], Bruno deBenoist [WHO], and Ian Darnton-Hill [UNICEF]): "Iodine nutrition needs to be included in any assessment of the impact of maternal thyroid status on the fetus. Efforts to promote optimal iodine nutrition in pregnancy are essential. Strong consideration should be given to including adequate iodine (150 μg or more daily) in all vitamin/mineral preparations used in pregnancy." The American Thyroid Association has endorsed a similar view.

"Risk Factors for Thyroid Disease: Autoimmunity and Other Conditions"—Dr. Robert Smallridge

Several risk factors predispose women to hypothyroidism during pregnancy, including AITD, type 1 diabetes mellitus, iodine deficiency, and thyroid ablation. Recent studies have suggested that AITD, independent of hypothyroidism, may have adverse effects, which include increased risk of miscarriages and recurrent miscarriages, fetal death, and possible effects on childhood cognition, and postpartum depression.

Thyroid autoimmunity is common. Reviewing 14 studies (20–33), 1530 of 14,148 pregnant women (10.8%; range, 6.2%–21.8%) were positive for TPO-Ab and/or Tg-Ab. The association of thyroid autoimmunity with hypothyroidism was strong, as the specificity of TPO-Ab was 0.91 for either a low normal free T_4 or elevated TSH.

Women with AITD appear to have an increased risk of miscarriages. In a total of 3814 women in 6 studies (27,29,30,33,34,36), 24% of antibody-positive women, versus 10.1% of antibody-negative women, had miscarriages. The positive and negative predictive values of TPO-Ab positivity were 0.24 and 0.90, respectively. A higher percentage of women with recurrent miscarriages were antibody positive (36.1% versus 16.8%).

AITD also poses the greatest risk to women for developing postpartum thyroid dysfunction (PPTD). In 18 studies, 10.0% of 12,574 women had positive TPO antibody postpartum. The sensitivity and specificity of thyroid antibody for developing PPTD were 0.71 and 0.94, respectively, with a relative risk of 29.8. Hypothyroidism was the most common

abnormality, occurring in 65% of women with PPTD (37). In three small studies (21,38,39), type 1 diabetes mellitus confers a threefold to fivefold increased risk of PPTD.

Thyroid autoimmunity may also increase the risk of postpartum depression. In three reports (22,40,41), the risk of depression increased on average from 30.0% to 46.3% in women with AITD, and in one randomized trial, LT_4 treatment did not reduce the frequency of depression in those women at greatest risk.

The observations cited above raise the question; should thyroid antibody testing be included in screening strategies? **Discussant:** Dr. Alex Stagnaro-Green pointed out that his thinking on the role of antibodies on pregnancy outcome had changed since his 1990 publication, when they thought fetal death rate was an epidemiological phenomenon or related to the minor elevations in TSH in 25% of patients. But when the latter were dropped from the analysis, statistical significance remained. Current work by Schoenfeld (42) and Davies and others (43), who immunized mice with thyroglobulin and allowed them to become pregnant, has shown a higher percentage of miscarriage compared to control groups.

Thyroid Function Inside and Outside of Pregnancy

What we know:

1. Physiologic changes associated with pregnancy require the thyroid gland to increase production or administration of thyroid hormones by 40% to 100% in order to meet the needs of mother and fetus during pregnancy.
2. The fetus requires T_4 for normal development of neurologic and perhaps other organ systems. In the first trimester of gestation the fetus is wholly dependent on the mother for thyroxine.
3. For the maternal thyroid gland to meet the demands of pregnancy it must be present, disease-free, and capable of responding with adequate stores of iodine.
4. In the United States, hypothyroidism of varying severity occurs from 0.4% to 2.5% of pregnancies, possibly putting 16,000 to 100,000 pregnancies and fetuses at risk.
5. With sufficient iodine nutrition, AITD is the most common cause of hypothyroidism.
6. Women with AITD and with positive thyroid antibodies are at higher risk for hypothyroidism during pregnancy and for postpartum thyroid disease.
7. Patients with a family or personal history of thyroid disease, goiter, type 1 diabetes mellitus, history of spontaneous abortion, or any symptoms suggesting hypothyroidism, are at higher risk for hypothyroidism.
8. Recent studies have suggested that AITD, independent of hypothyroidism, increase the risk of miscarriages, recurrent miscarriages, and fetal death.
9. Iodine nutrition for the U.S. population aged 6 to 74 years as measured by UI excretion changed between the National Health and Nutrition Examination Survey of 1971–1974 and 1988–1994 from 320 to 145 $\mu\text{g}/\text{L}$. Iodine excretion adjusted for creatinine excretion changed from 293 μg I/g creatinine in 1971–1974 to 125 in 1988–1994. The median UI in the most recent NHANES data (2000) was 161 $\mu\text{g}/\text{L}$.
10. In the United States 15.3% of women of reproductive age had UI less than 50 $\mu\text{g}/\text{L}$; and when adjusted for creatinine, 8.4% had less than 50 μg I/g creatinine.

^aDr. John T. Dunn died unexpectedly on April 9, 2004.

11. Monitoring iodine nutrition in the United States should continue.
12. In the NHANES III sample, no significant correlations were found between low UI among women of reproductive age (or others) and thyroid insufficiency as measured by TSH less than 4.5 or total TT_4 less than 4.5.
13. Less than one half of prenatal vitamin/mineral preparations contain iodine.

We do not know:

1. The prevalence of hypothyroidism in the first trimester of pregnancy;
2. The exact timing during pregnancy when increased T_4 production occurs or when increased dosage of LT_4 with pregnancy is required;
3. The mechanism by which elevated thyroid antibodies influence the outcome of pregnancy; Is thyroid autoimmunity an independent risk factor?
4. The impact of iodine nutrition in the U.S. population on the prevalence of hypothyroidism;
5. The prevalence of goiter in the United States—either within or outside of pregnancy;
6. Whether T_4 (free or total) or TSH would be the better method to detect thyroid deficiency during pregnancy in the United States;
7. Reference ranges by month of pregnancy in the United States for T_4 (free or total) or TSH, especially during the first trimester;
8. Cutoffs that would trigger further action;
9. Optimal time to test women in pregnancy;
10. Whether to include thyroid antibodies among screening tests.

Acknowledgments

The authors thank the scheduled discussants for the workshop, Dr. P. Reed Larsen and Dr. Alex Stagnaro-Green, for their important contributions and also Dr. John T. Dunn who presented the position of the ICCIDD, WHO, and UNICEF on positions of iodine supplementation. We also thank the other participants who provided important feedback, gave additional information, and added another dimension to this session. We recognize the able assistance of Micah Milton, Martha Brocato, and Marie Murray, who organized, recorded, and transcribed this session, making this summary effort much easier.

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