THYROID
Volume 15, Number 1, 2005

2004 Where Do We Go from Here?—Summary of Working Group Discussions on Thyroid Function and Gestational Outcomes

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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 points of agreement among the attendees based on the scientific rigor of material presented. At the end of the workshop, participants were divided into four smaller groups to discuss and determine areas of agreement on issues associated with thyroid insufficiency, identify research needs and gaps, and recommend research strategies and policy needs. Discussion included: problems for the mother and the pregnancy; neuropsychological/developmental performance in offspring of women with thyroid deficiency; issues of diagnosis and treatment for the pregnant women with overt and subclinical hypothyroidism; the issues involved with screening women who are pregnant or who are planning pregnancy; and the status of Iodine Nutrition in the United States. The group then identified research needs and gaps. The results of these discussions are outlined in the paper with recommended research strategies and public health action.

Introduction

THIS REPORT contains the summaries of several workgroups finalizing the proceedings of 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 purpose of this session was to examine scientific rigor of material presented earlier in the workshop in order to get a sense of which outcomes or proposals were backed by credible research and could be reasonably held to be valid as opposed to those points with conflicting or with less convincing evidence.

Attending this final session were scientists, clinicians, and advocates in the fields of thyroidology, obstetrics, pediatric endocrinology, adult endocrinology, internal medicine, psychology, public health, environmental health, epidemiology, nutrition, and immunology from North America and Europe.

Data were presented during the previous one and a half days on the following topics:

1. The physiology of pregnancy,
2. The incidence and prevalence of thyroid insufficiency and autoimmunity,
3. The outcomes of thyroid insufficiency for mother, fetus, and offspring,
4. The possibilities and limitations of detecting and treating thyroid insufficiency during pregnancy, and
5. The importance of a scientific basis for clinical and public health practice.

These summaries can be found in the preceding papers in this issue (1–5).

At the end of the second day of the workshop the attendees were divided into four smaller groups to discuss and determine areas of agreement on issues associated with thyroid insufficiency, identify research needs and gaps, and rec-

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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, the National Institutes of Health, or the U.S. Department of Health and Human Services.

ommend research strategies and policy needs. A set of questions was used to guide the discussions (Fig. 1).

Areas of Discussion

1. Health Outcomes
   a. Problems for the mother and the pregnancy
      i) There was general agreement that overt maternal hypothyroidism was associated with a number of adverse maternal and infant outcomes, including pregnancy-induced hypertension, placental abruption, spontaneous abortion, fetal distress, preterm birth, and low birth weight.
      ii) Fetal physiology in the presence of overt maternal thyroid deficiency.
         (1) The data presented were convincing that the fetus requires thyroxine for the normal development of neurologic and perhaps other organ systems.
         (2) Significant fetal thyroid hormone production and secretion does not begin until approximately 20 weeks' gestation.
         (3) In the first trimester of gestation the fetus is wholly dependent on thyroxine from the mother
   b. Neuropsychological/developmental performance in offspring of women with thyroid deficiency
      i) Published data consistently document a relationship between clinical or overt maternal hypothyroidism and problems with neuropsychological development of the offspring.
      ii) The data are for subclinical or milder hypothyroidism and adverse neurodevelopmental outcomes of offspring are suggestive, but have limited data.
         (1) In the Main population-based study:
            (a) Full-scale WISC IQs averaged 7 points lower among children born to mothers with undiagnosed thyroid deficiency during pregnancy, in comparison with control children.
            (b) More than twice as many of these children had IQ measurements more than 1 standard deviation below the control mean, and four times as many had IQs more than 2 standard deviations below.
         (2) In the Dutch study of euthyroid mothers (thyrotropin [TSH] not elevated) whose free thyroxine (FT_4) levels were below the tenth centile at 12 or 32 weeks' gestation:

Questions for Discussion in Small Group Setttings

Four small groups, each to address the overview issues:

1) The following three aspects of undetected and/or untreated maternal thyroid deficiency during pregnancy are under consideration in the small group discussions
   a. Problems for the mother, herself
   b. Fetal viability in the presence of maternal thyroid deficiency
   c. Neuropsychological/developmental performance in offspring of women with thyroid deficiency
2) Please rate the following for each of these aspects, on a scale of 1–5 (5 = strongest evidence for agreement.

	Problems for the mother	Fetal viability	Neuropsychological performance of offspring
a) Evidence supporting existence of problem			
b) Importance			
c) Detectability			
d) Treatability			

3) Assuming that maternal thyroid deficiency is detectable:
   a. When should testing be done?—during pregnancy?—before pregnancy?
   b Which test? What cutoffs?
   c. Is confirmatory testing indicated? What tests and what cutoffs?
   d. Is the condition a suitable candidate for population screening, or would testing be limited to clinical suspicion.
4) Is there sufficient evidence to suggest that treatment of *clinical* disease in pregnancy alters the poor pregnancy outcomes and the adverse child development outcomes? Is there a critical time window? What about for subclinical disease? What additional research is needed?
5) When maternal thyroid deficiency is identified:
   a. Which medication is recommended? Dose, timing, and monitoring
6) What financial costs or medical (complication) costs need to be considered?
   a. Financial cost of screening
   b. Undesirable effects with treating false positives
   b. Consequences of over- or under-treatment—Can consequences be minimized?
7) Do we have enough data to answer the above questions? If more reserach is needed, what types?
8) Is there sufficient evidence on maternal thyroid deficiency (e.g. outcomes, epidemiology, treatment) to warrant public health action? Is screening feasible? Is it time to make recommendations for public health and/or clinical practice?

FIG. 1. Questions used to guide small group discussions.

(a) The mental and psychomotor index scores averaged 8 points lower among children at 2 years of age in comparison to controls. For the 32-week group, IQ was lower at 5 years.
(i) At the workshop there was concern by some participants about the generalizability of the Dutch findings to the U.S. population and other populations, because of possible differences in iodine nutritional status.

c. The increased risk of adverse health outcomes in the mother, fetus, and infant were, in general, more consistent for overt hypothyroidism than subclinical hypothyroidism.
i) The observed consequences of thyroid insufficiency to the fetus and mother during pregnancy were more convincing than the evidence for the association with neuropsychological and developmental deficiency. Those concerned cited the possible influences of other unmeasured factors during and post gestation on neurodevelopment, such as, premature delivery or post-partum depression.

2. Diagnosis and Treatment

There was agreement for aggressive identification and treatment of thyroid insufficiency in pregnancy when the TSH was very high and hypothyroidism was overt.

a) In overt hypothyroidism (elevated TSH with low FT_4), there was overall agreement that treatment was essential for the duration of pregnancy using levothyroxine (LT_4) (approximately 2.0 μg/kg per day).
i) The pregnant woman should be followed by monitoring T_4 and TSH at 4- to 6-week intervals to keep the T_4 in the higher half and TSH in the lower half of the currently available reference ranges;
ii) There was general agreement that it would be unethical to withhold treatment of overt hypothyroidism for purposes of a clinical trial.
iii) If the pregnant woman had an abnormally high TSH and normal FT_4, one would want to recheck it, to clarify the thyroid status. There was disagreement among participants about the need for treatment under these circumstances.

b) Groups at greater risk for overt hypothyroidism require special attention and are. If not previously tested, testing should occur whenever symptoms or their risk factor is identified and if found to have overt disease, treatment should be initiated. If testing is normal, follow-up studies may be indicated at the discretion of the treating physician.
(1) Women already known to have thyroid disease, goiter, or ablation;
(2) Women who are taking thyroxine;
(3) Women with personal or family autoimmune thyroid disease;
(4) Women with type 1 diabetes mellitus; and
(5) Women whose TSH concentration is discovered to be elevated before or during pregnancy when tested for a clinical indication.

c) Subclinical hypothyroidism
(1) There is insufficient data available about the impact of treatment on pregnancy outcome or neurodevelopmental outcomes in exposed offspring.
(2) At this time there is no uniform agreement on what the TSH concentration should be to make a diagnosis of subclinical hypothyroidism, or the concentration that would necessitate treatment.
(3) Workshop participants disagreed on the need to treat women with subclinical hypothyroidism.
(4) There remains a disparity between the target serum TSH concentration for pregnant women with diagnosed hypothyroidism (lower half of normal range), and the dose to initiate thyroxine therapy in previously undiagnosed subclinical hypothyroidism. It is not known at this time if these differences in TSH levels are relevant for pregnancy outcomes.

3. Screening women who are pregnant or who are planning pregnancy

a) Implication for offspring:
(1) From the Maine population-based study it was extrapolated that an intelligence quotient that is 1 standard deviation or more below the mean might be avoided in 4600 children in the United States each year through the systematic detection and treatment of hypothyroidism in pregnancy. This would mean screening more than 4 million pregnant women each year to find and treat approximately 0.3% of them with overt hypothyroidism that would require treatment, although approximately half of them would already know they had thyroid disease or would be on treatment for thyroid disease. There was little agreement on the management of subclinical hypothyroidism, in the additional 2%.

b) Implications for the pregnant women themselves:
i) The Maine population-based study, upon following 80% of women with TSH above the 98th centile who were not known to be thyroid deficient during their pregnancy (n = 48), found that 64% were clinically hypothyroid 10 years later, compared to 4% of the control group. The average time to diagnosis was 5 years, and three of the women remained undiagnosed until the time of retesting 10 years later.
(1) One implication from this study is that pregnant women with elevated TSH values may deserve special attention, even when classified as having subclinical hypothyroidism.

c) Ideal screening time if screening is undertaken for hypothyroidism. It was pointed out that preconception screening would be difficult for many reasons and probably not satisfactory. Many participants believed that it would be more feasible to screen early in pregnancy—the first trimester if possible.

d) Thyroid tests for screening

Which thyroid tests should be used to detect thyroid insufficiency? One presenter earlier had addressed the use of:
i) TSH, which has good absolute value agreements between methods, not requiring method-specific TSH reference ranges.

(1) The nonpregnant TSH upper limit of 2.5 mIU/L can be used as a conservative upper guide for first trimester pregnancy screening.

ii) Total thyroxine (TT_4) with changes in pregnancy that are predictable across methods.

(1) TT_4 in the first trimester is increased by approximately 50% over nonpregnant values, and thereafter changes only slightly during pregnancy.

(2) TT_4 below 100 nmol/L (7.8 μg/dL) appears to be a reasonable indicator of hypothyroxinemia in pregnancy.

(3) TT_4 can be collected by the filter paper systems in use by newborn screening laboratories.

iii) Current FT_4E (estimate) methods, are sensitive to abnormal binding-protein states similar to those seen in pregnancy, and lack gestational reference values.

iv) Many participants believed that any screening in the United States should begin with TSH and then be followed up with T_4 and antibodies.

v) Most of the study groups concluded that until some of the research gaps are answered, it is premature to have population-wide screening for the U.S. pregnant or preconception population.

4. Iodine Nutrition in the United States

a) There was concern among some participants that, despite the NHANES III data showing the U.S. population with adequate iodine nutrition based on the 1994 World Health Organization (WHO) guidelines, some pregnant women and women of reproductive age in the United States may have marginal iodine nutrition from the standpoint of the newer recommendations of the Institute of Medicine (6) that pregnant women receive 220 μg of iodine per day. A few attendees felt strongly that iodine was enough of an issue to recommend iodizing all commercial salt for U.S. consumption. Many participants discussed and supported the need for iodine supplements of 150 μg for pregnant women from the time pregnancy is discovered and that vitamin/mineral capsules intended for prenatal use should all be manufactured to contain 150 μg of iodine. It was suggested that the American Thyroid Association (ATA) and the American College of Obstetrics and Gynecology (ACOG) examine this issue in more detail.

(1) ATA has recently issued a statement supporting the above use of iodine supplements during pregnancy (7).

5. Research Needs and Gaps

a) Screening issues

i) Whether adverse maternal, fetal, and infant outcomes are significantly increased in women with subclinical hypothyroidism, and to what degree;

ii) The persistence of the neurodevelopmental abnormalities seen in the Main and Dutch studies as those children age;

iii) Information leading to an optimal approach to screening for diagnosis and treatment of hypothyroidism in the population of pregnant women;

iv) Clinical validity of T_4 (free or total) or TSH for the initial screen to detect thyroid deficiency during pregnancy in the United States;

v) Method-specific, trimester-specific and possibly population-specific FT_4 reference ranges in the United States;

vi) Optimal cutpoints for TSH screening;

vii) Value of including thyroid antibodies in screening tests;

viii) Determine the prevalence of hypothyroidism in women of reproductive age and pregnancy, including the first trimester of pregnancy;

ix) The prevalence of goiter in the United States—either within or outside of pregnancy and the relationship to iodine nutrition and thyroid function;

x) Better methods to assess population (and possibly clinical) iodine status in the United States.

b) Treatment issues

(1) The effect of treatment of subclinical hypothyroidism on maternal, fetal, infant and developmental outcomes;

(2) Effect of treatment timing on outcomes during pregnancy or in offspring;

(3) The relative contribution of deficiency in T_4 transfer to the fetus during pregnancy as opposed to other factors, e.g., premature birth or maternal postpartum depression, etc., on the abnormal neurodevelopmental outcome in offspring;

(4) The exact timing during pregnancy when increased T_4 production occurs or when increased dosage of levothyroxine with pregnancy is required

(5) The TSH concentration at which treatment is necessary to avoid problems;

(6) Whether thyroid replacement beginning early in pregnancy will reduce or avoid problems with fetal development;

c) Pathologic mechanisms:

i) The mechanism by which elevated thyroid antibodies influence the outcome of pregnancy—directly or by altered thyroid function;

ii) Influence of iodine nutrition on thyroid analyte values or prevalence of hypothyroidism during pregnancy in the United States;

iii) Verification of the current status of iodine nutrition in women of reproductive age in the United States;

iv) Understanding of the relative importance of gestational hypothyroxinemia (low FT_4 with normal TSH) versus subclinical maternal hypothyroidism to the outcome of pregnancy and offspring in the United States.

6. Research Strategies

a) Clinical trials

i) Subclinical hypothyroidism

(1) The participants considered it important, ethical, and critical to conduct a randomized con-

trolled trial (RCT) in women with subclinical hypothyroidism, because the outcomes and benefits of treatment are uncertain.
(2) The study now being conducted in Wales by Dr. John Lazarus could be replicated in the United States.

ii) Overt hypothyroidism
(1) It was agreed that an RCT could not be done using individuals known to have overt hypothyroidism, because treatment of overt hypothyroidism is known to be beneficial.

iii) Screening issues
(1) To answer some of the above questions on screening, very large numbers of pregnant women would have to be recruited to achieve sufficient power for the studies.

b) Alternative suggestions
i) A nested case/cohort study linked to the planned National Children's Study in the United States of 100,000 pregnancies that would be evaluated and followed up until the offspring are age 21 years. This kind of study could include the influence of iodine nutrition as well as subclinical hypothyroidism on outcomes.
ii) A pilot study to determine feasibility of screening procedures to detect thyroid disorders during pregnancy and follow up abnormal test results, possibly using centralized or regional laboratories currently being used for newborn screening.

7. Public Health Action

a) Iodine Nutrition Policy
i) Develop a long term plan for positively maintaining adequate (not excessive) dietary sources of iodine for the U.S. population
(1) Continue to monitor iodine intake by:
(a) measuring urinary iodine concentrations in future NHANES
(b) Oversampling pregnant women and women of reproductive age.

b) Public Education
i) Educate women of reproductive age about the impact of overt hypothyroidism on pregnancy
ii) Educate women of reproductive age, who are at high-risk for thyroid disease, on the need for testing if they are pregnant or wish to become pregnant
iii) Educate clinicians caring for women of reproductive age on the role of iodine and the importance of thyroid health during pregnancy, on the need to test and monitor high-risk women, and on appropriate diagnosis, and treatment.
iv) Devise methods to reach women at the earliest stages of pregnancy with the above messages

Acknowledgments

The authors thank Drs. Daniel Glinoer, Gregory Brent, and Carole Spencer for their critical review and suggestion for this summary. We also thank the participants engaged in these discussions adding an important dimension to this session and report. 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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