Introduction

The Impact of Maternal Thyroid Diseases on the Developing Fetus: Implications for Diagnosis, Treatment, and Screening. Summary of Proceedings, Workshop Organization, Program, and Participants

Gregory Brent¹ and Coleen A. Boyle²

Introduction

Pregnancy is associated with dramatic changes in thyroid function and metabolism in the mother and in the developing fetus. These changes occur in a characteristic sequence and require maternal–fetal interactions at a number of levels. A wide range of clinical observations, clinical studies, epidemiologic investigations, and characterization of in vitro and in vivo models have pointed to the importance of maternal thyroid status on pregnancy outcomes and fetal development. In a number of clinical studies, maternal hypothyroidism has been associated with adverse pregnancy outcomes, as well as cognitive deficits in the offspring. The mechanism for these effects and the magnitude and duration of maternal hypothyroidism required to see adverse outcomes, however, are not established by current data.

The most prevalent condition worldwide impacting thyroid function in pregnancy and the developing fetus is iodine deficiency. The link between maternal iodine deficiency and mental retardation in the offspring has been known for more than 100 years. A variety of adaptations in pregnancy result in increased nutritional iodine requirements, a condition that makes pregnant women a susceptible population in areas of iodine deficiency or insufficiency. Much progress has been made to improve iodine nutrition, although many areas in the world still have inadequate iodine intake, especially during pregnancy. The assessment of iodine status and the implications of mild deficiency have a significant impact on decisions regarding iodine supplementation during pregnancy and appropriate population standards for iodine intake.

There has been an increasing awareness of the full spectrum of autoimmune hypothyroidism, including an early stage typically characterized by the presence of antithyroid (antithyroid peroxidase) antibodies, mild elevation of serum thyrotropin (TSH), and normal range serum free thyroxine concentration, referred to as subclinical hypothyroidism. Several studies have identified potential complications of pregnancy and fetal outcome in pregnant women with this profile. The changes in thyroid function with pregnancy, however, especially in the first trimester, may influence the accuracy of thyroid hormone assays as well as the expected normal range. The decision for the value of screening for thyroid disease in pregnancy is closely related to the ease of diagnosis of this condition, the optimal test to assess thyroid status, the clinical consequences of this profile, and the value of treatment. These issues were a major focus of the workshop.

The Centers for Disease Control and Prevention (CDC), National Center for Birth Defects and Developmental Disabilities (NCBDDD) in collaboration with the American Thyroid Association held a workshop on January 12–13, 2004 entitled “The Impact of Maternal Thyroid Disease on the Developing Fetus: Implications for Diagnosis, Treatment, and Screening.” This workshop was unique in a number of respects. The planning committee, speakers, and participants included endocrinologists, obstetricians, pediatricians, epidemiologists, neuroscientists, laboratory medicine specialists, and other experts from around the world. Considerable time was allocated for discussion and interaction with the hope of identifying areas of agreement, areas of disagreement, and data gaps to recommend future studies.

The goals of the workshop were to:

1. Assess the prevalence of thyroid dysfunction in reproductive age women and the factors associated with abnormal function;

¹American Thyroid Association and VA Greater Los Angeles Healthcare System/UCLA, Thyroid Division, 1 Los Angeles, California.
²National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

The opinions and findings in this paper 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.
2. Examine the evidence on thyroid dysfunction during pregnancy related to adverse fetal and child developmental outcomes;
3. Examine the ability to detect and treat maternal thyroid dysfunction; and
4. Examine the implications of the above for clinical and public health practice.

The intent of the conference was not to reach a consensus recommendation, but to present the most recent scientific data available, promote an open discussion across a range of relevant disciplines, and develop a strategy to address the remaining areas of uncertainty. A spirit of open intellectual exchange prevailed, recognizing the great progress that has been made in this field, but also making clear the many areas that require further investigation.

The workshop agenda, planning committee, poster session, and a list of invited speakers and other participants are included in Appendices A through D. The proceedings summaries (1–5) were developed by a writing committee and reviewed by the meeting participants.

References

Address reprint requests to:
Coleen A. Boyle, Ph.D.
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
1600 Clifton Road
Mailstop E-87
Atlanta, GA 30333
E-mail: cboyle@cdc.gov

Appendix A. Planning Committee
Hani Atrash, M.D. National Center on Birth Defects and Developmental Disabilities (NCBDDD), Centers for Disease Control and Prevention (CDC)
Coleen A. Boyle, Ph.D. NCBDDD, CDC
Gregory Brent, M.D. Secretary, American Thyroid Association (ATA)
James E Haddow, M.D. Foundation for Blood Research
Joseph G Hollowell, M.D. Department of Pediatrics, University of Kansas Medical Center
Stephen LaFranchi, M.D. Oregon Health and Sciences University
Cindy Lawler, M.D. National Institute of Environmental Health Sciences, National Institutes of Health (NIH)
Maureen Malee, M.D. Jackson Memorial Hospital, The University of Miami and American College of Obstetrics and Gynecology
Susan Mandel, M.D. Hospital of the University of Pennsylvania
Robert Smallridge, M.D. Mayo Clinic, Jacksonville
Barbara Smith, C.A.E. ATA
Catherine Y Spong, M.D. National Institute of Child Health and Human Development, NIH
Kevin Sullivan, Ph.D. Emory University and National Center for Chronic Disease Prevention and Health Promotion, CDC

Appendix B. Workshop Agenda
Scientific Workshop on Maternal Thyroid Disease:
“The Impact of Maternal Thyroid Diseases on the Developing Fetus: Implications for Diagnosis, Treatment, and Screening”
January 12–13, 2003
Renaissance Atlanta Hotel, Atlanta, Georgia

Monday—January 12, 2003
8:00 AM Welcome and Introductions
8:20 AM Workshop Goals, Format, and Rules
8:30 AM  Methods and Criteria Used for Evidence-Based Decisions in Public Health  
  **Moderator** Coleen Boyle  
  Paul Ladenson  
  James Haddow  
  Coleen Boyle  

9:45 AM  Thyroid Function Outside and During Pregnancy:  
  What is Normal and What is Not?  
  **Moderator** Gregory Brent  
  Normal Thyroid Function in Health Women:  
  Dynamics in Pregnancy, Etiology, and Incidence of Thyroid Disease  
  Prevalence of Thyroid Dysfunction in Reproductive Age Women—U.S. Population  
  Risk Factors for Thyroid Disease:  
  Autoimmunity and Other Conditions  
  Discussion  
  Daniel Glinoer  
  Joseph Hollowell  
  Robert Smallridge  
  Reed Larsen  
  Alex Stagnaro-Green  

11:20 AM  Open Discussion  

1:00 PM  Is Thyroid Inadequacy During Gestation a Risk Factor for Adverse Pregnancy and Developmental Outcomes?  
  **Moderators** James Haddow and Stephen LaFranchi  
  Jorge Mestman  
  Gabriella Morreale de Escobar  
  Victor Pop  
  Robert Klein  
  John Lazarus  
  Stephen LaFranchi, Kenneth Leveno, Joanne Rovet, Susan Waisbren  

3:45 PM  Discussion  

5:00 PM  Open Discussion  

6:00 PM  Poster Session  

**Tuesday—January 13, 2003**  
8:00 AM  Are Detection and Treatment of Thyroid Insufficiency In Pregnancy Feasible?  
  **Moderator** Susan Mandel  
  Carole Spencer  
  Susan Mandel  

9:00 AM  Discussion: Fetal Outcomes After Treatment of Maternal-Fetal Hypothyroidism—Timing  
  Robert Delong  
  Rosalind Brown  

10:00 AM  Open Discussion  

10:45 AM  Where Do We Go from Here—Discussions on Thyroid Function and Gestational Outcomes  
  Charge to Small Groups  
  Group 1 (Peachtree)  
  Facilitated by Stephen LaFranchi  
  Group 2 (?)  
  Group 3 (?)  
  Group 4 (Georgia Ballroom)  
  Coleen Boyle  
  Robert Smallridge  
  Catherine Spong  
  Coleen Boyle  

1:15 PM  Reports from Small Groups  

2:15 PM  Open Discussion  

2:30 PM  Wrap-up  

3:00 PM  Adjourn
Appendix C. Posters

Poster Presentations

A  PRACTICAL IMPLICATIONS OF THE INCREASED IODINE NEED DURING PREGNANCY
   Francois Delange, Bruno deBenoist, Ian Darnton-Hill, and John T. Dunn

B  CHILD GROWTH AND DEVELOPMENT: INTERVENTIONS IN IODINE DEFICIENCY IN
   NORTHWEST CHINA
   Robert Delong

C  MATERNAL ANTITHYROID DRUGS TO PREVENT FETAL HYPERTHYROIDISM
   Jody Ginsberg and Tammy McNab

D  EARLY MATERNAL THYROIDAL INSUFFICIENCY (EMTI) IS A TREATABLE AND PREVENTABLE CAUSE OF
   NEURODEVELOPMENTAL DEFICITS- IS IT TIME TO SCREEN?
   Steven H. Lamn, Cindy J. Goebel, Offie P. Soldin, Joseph G. Hollowell, and Arnold Engel

E  PUBLIC HEALTH APPROACH TO PREVENTING HYPOTHYROIDISM IN PREGNANCY–ADEQUATE IODINE
   NUTRITION
   Glen Maberly, Kevin Sullivan, and F. Van der Haar

F  EXPERIMENTAL EVIDENCE FAVORING THYROID SCREENING IN EARLY PREGNANCY
   Gabriella Morreale de Escobar and colleagues

G  FIRST TRIMESTER INCREASE OF CIRCULATING FT4, A PHYSIOLOGICAL RESPONSE TO ONSET OF PREGNANCY
   Gabriella Morreale de Escobar and colleagues

H  PREVALENCE OF POSTPARTUM THYROIDITIS: CLINICAL AND GEOGRAPHIC VARIATION
   Wanda Nicholson, Paul Ladenson, Robert Smallridge and colleagues

I  LOW CONCENTRATIONS OF MATERNAL THYROXIN DURING EARLY GESTATION: A RISK FACTOR OF
   BREETH PRESENTATION?
   Victor J.M. Pop

J  VISUAL DEVELOPMENT IN THE OFFSPRING OF WOMEN WITH TREATED HYPOTHYROIDISM DURING
   PREGNANCY
   Joanne Rovet

K  T4 AND T3 IN PREGNANCY REFERENCE RANGES USING ISOTOPE DILUTION TANDEM MASS SPECTROMETRY
   Offie Soldin and colleagues

L  THE THYROID AND PREGNANCY: A NOVEL RISK FACTOR FOR VERY PRETERM DELIVERY
   Alex Stagnaro-Green and colleagues

M  THYROID HORMONE (TH) ACTION IN THE FETAL RAT BRAIN AND EFFECTS OF ENDOCRINE DISRUPTERS ON
   TH SIGNALING
   R. Thomas Zoeller and colleagues

Appendix D. Speakers and Other Participants

Workshop Speakers and Participants

Marilee C. Allen, M.D.  Professor of Pediatrics
   The Johns Hopkins School of Medicine, Baltimore, Maryland

Hani Atrash, M.D.  National Center on Birth Defects and Developmental Disabilities (NCBDDD),
   Centers for Disease Control and Prevention (CDC), Atlanta, Georgia

Coleen A. Boyle, Ph.D.  NCBDDD, CDC, Atlanta, Georgia
Gregory Brent, M.D.  Secretary, American Thyroid Association (ATA), Professor of Medicine, VA Greater
   Los Angeles Health Care System, Los Angeles, California

Rosalind Brown, M.D.  Professor of Pediatrics, The Children’s Hospital, Harvard, Boston, Massachusetts
Jose F. Cordero, M.D.  Director, NCBDDD, CDC, Atlanta, Georgia
Gary Cunningham, M.D.  Professor of Obstetrics and Gynecology, University of Texas, Southwestern Medical
   Center, Dallas, Texas

Robert DeLong, M.D.  Professor of Pediatrics, Duke University Medical Center, Durham, North Carolina
John Dunn, M.D.  Professor of Medicine, University of Virginia, Charlottesville, Virginia
Thomas P. Foley, Jr, M.D.  Professor of Pediatrics, Univ of Pittsburgh, Pittsburgh, Pennsylvania
Jody Ginsberg, M.D.  University of Alberta, Edmonton, AB, Canada
Daniel Glinoer, M.D., Ph.D.  Department of Internal Medicine, University Hospital St. Pierre, Brussels, Belgium
James E. Haddow, M.D.  Foundation for Blood Research, Scarborough, Maine
Joseph G. Hollowell, M.D., M.P.H.  University of Kansas Medical Center, Kansas City, Kansas
Robert Z. Klein, M.D.  Department of MCH, Dartmouth Medical School, Lebanon, New Hampshire
Paul Ladenson, M.D.  Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland
Stephen LaFranchi, M.D.  Professor of Pediatrics, Oregon Health and Sciences University, Portland, Oregon
Stephen Lamm, M.D.  Consultants in Occupational and Environmental Health, Washington, D.C.
Cindy Lawler, M.D.  National Institute for Environmental Health Sciences, National Institutes of Health (NIH), Research Triangle, North Carolina
Kenneth Leveno, M.D.  Professor of Obstetrics and Gynecology, University of Texas, Southwestern Medical Center, Dallas, Texas
John Lazarus, M.D.  University of Wales College of Medicine, Cardiff, Wales
Glen Maberly, M.D.  Rollins School of Public Health, Emory University, Atlanta, Georgia
Maureen Malee, M.D.  Professor of Obstetrics and Gynecology, The University of Miami, Jackson Memorial Hospital, Miami, Florida
Susan Mandel, M.D.  Professor of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania
Jorge Mestman, M.D.  Professor of Medicine, University of Southern California, Los Angeles, California
Micah Milton, M.P.H.  NCBDDD, CDC
Marvin Mitchell, M.D.  New England Newborn Screening Program, Boston, Massachusetts
Gabriella Morreale de Escobar  Instituto de Investigaciones Biomédicas ‘Alberto Sols,’ Madrid, Spain
Victor J. M. Pop, M.D., Ph.D.  Department of Clinical Health Psychology, Tilburg, The Netherlands
Joanne Rovet, Ph.D.  Professor of Pediatrics, The Hospital For Sick Children, Toronto, Canada
Robert Smallridge, M.D.  Mayo Clinic, Jacksonville, Florida
Barbara (Bobbi) Smith, C.A.E.  Executive Director, ATA, Falls Church, Virginia
Carole Spencer, Ph.D.  Professor of Medicine, University of Southern California, Los Angeles, California
Catherine Spong, M.D.  Chief Pregnancy and Perinatal Branch, National Institute on Child Health and Human Development, NIH, Bethesda, Maryland
Alex S. Stagnaro-Green, M.D.  Newark, New Jersey
Kevin Sullivan, Ph.D.  Rollins School of Public Health, Emory University, Atlanta, Georgia
Susan Waisbren, Ph.D.  Professor of Pediatrics, The Children’s Hospital, Harvard, Boston, Massachusetts