

## 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 Brent<sup>1</sup> and Coleen A. Boyle<sup>2</sup>

### Introduction

**P**REGNANCY 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 (antithy-

roperoxidase) 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;

<sup>1</sup>American Thyroid Association and VA Greater Los Angeles Healthcare System/UCLA, Thyroid Division, 1 Los Angeles, California.

<sup>2</sup>National 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<sup>a</sup> and reviewed by the meeting participants.

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<sup>a</sup>Drs. Coleen Boyle, Gregory Brent, Daniel Glinoe, James Haddow, Joseph Hollowell, Paul Ladenson, Stephen LaFranchi, Susan Mandel, Robert Smallridge, Carole Spencer, and Catherine Spong.

**References**

1. Boyle CA, Ladenson P, Haddow JE 2004 Methods and criteria used for evidence-based decisions in public health. *Thyroid* 15:41–43.
2. Smallridge R, Glinoe D, Hollowell JG, Brent G 2004 Thyroid function inside and outside of pregnancy: What do we know and what don't we know? *Thyroid* 15:54–59.
3. LaFranchi S, Haddow JE, Hollowell JG 2004 Is thyroid inadequacy during gestation a risk factor for adverse pregnancy and developmental outcomes? *Thyroid* 15:60–71.
4. Mandel S, Spencer C, Hollowell JG 2004 Are the detection and treatment of thyroid insufficiency in pregnancy feasible? *Thyroid* 15:44–53.
5. Hollowell JG, Boyle CA, LaFranchi S, Smallridge RC, Spong CY 2004 Hypothyroidism in pregnancy—Where do we go from here? A summary of discussions on thyroid function and gestational outcomes. *Thyroid* 15:72–76.

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	<i>Jose Cordero</i>
8:20 AM	Workshop Goals, Format, and Rules	<i>Coleen Boyle</i>

8:30 AM	Methods and Criteria Used for Evidence-Based Decisions in Public Health Methods to Evaluate Scientific Evidence Criteria for Screening Considerations for Public Health Action	<i>Moderator</i>	<i>Coleen Boyle Paul Ladenson James Haddow Coleen Boyle</i>
9:45 AM	Thyroid Function Outside and During Pregnancy: What is Normal and What is Not? 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	<i>Moderator</i>	<i>Gregory Brent  Daniel Glinoyer  Joseph Hollowell  Robert Smallridge Reed Larsen Alex Stagnaro-Green</i>
11:20 AM	Open Discussion		
1:00 PM	Is Thyroid Inadequacy During Gestation a Risk Factor for Adverse Pregnancy and Developmental Outcomes? Adverse Pregnancy Outcomes Thyroid Physiology in the Fetus Dutch Data New England Data Prospective Study—Wales	<i>Moderators</i>	<i>James Haddow and Stephen LaFranchi Jorge Mestman Gabriella Morreale de Escobar Victor Pop Robert Klein John Lazarus</i>
3:45 PM	Discussion		<i>Stephen LaFranchi, Kenneth Leveno Joanne Rovet Susan Waisbren</i>
4:30 PM	Open Discussion		
6:00 PM	Poster Session		
<b><u>Tuesday—January 13, 2003</u></b>			
8:00 AM	Are Detection and Treatment of Thyroid Insufficiency In Pregnancy Feasible? Laboratory Reference Values in Pregnancy Criteria for Diagnosis and Treatment of Hypothyroidism in Pregnancy	<i>Moderator</i>	<i>Susan Mandel Carole Spencer  Susan Mandel</i>
9:00 AM	Discussion: Fetal Outcomes After Treatment of Maternal-Fetal Hypothyroidism—Timing		<i>Robert Delong Rosalind Brown</i>
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) Group 2 (?) Group 3 (?) Group 4 (Georgia Ballroom)	<i>Facilitated by</i>	<i>Coleen Boyle Stephen LaFranchi Robert Smallridge Catherine Spong Coleen Boyle</i>
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. Lamm, 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 BREECH 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

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|---------------------------|---|
| Marilee C. Allen, M.D.    | Professor of Pediatrics<br>The Johns Hopkins School of Medicine, Baltimore, Maryland  |
| Hani Atrash, M.D.         | National Center on Birth Defects and Developmental Disabilities (NCBDDD),<br>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<br>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<br>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 Glinoyer, 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